SPIRAL® MANUAL

Manual of Intensive Care Medicine

FIFTH EDITION

Richard S. Irwin
James M. Rippe

Wolters Kluwer Health | Lippincott Williams & Wilkins

MANUAL OF INTENSIVE CARE MEDICINE

Fifth Edition

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To Our Families

Diane, Rachel, Sara, Jamie, Rebecca, John, Andrew K., Andrew M., and Adam, Stephanie, Hart, Jaelin, Devon and Jamie

In Memoriam

The Editors note with great sadness the untimely passing of Dr. Ray Clouse. Dr. Clouse edited the Gastrointestinal section of this Manual from its inception and also the gastrointestinal section for our larger, hard covered Intensive Care Medicine textbook.

Dr. Clouse was a truly outstanding human being, physician, a great friend, and a superb editor. We will miss him greatly.

Richard S. Irwin, MD
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CONTENTS

II: CARDIOVASCULAR PROBLEMS AND CORONARY CARE

Section Editor—Akshay S. Desai

III: PULMONARY PROBLEMS IN THE INTENSIVE CARE UNIT

Section Editor—J. Mark Madison

V: INFECTIOUS DISEASE PROBLEMS IN THE INTENSIVE CARE UNIT

Section Editor – Daniel H. Libraty

VI: GASTROINTESTINAL AND HEPATOBILIARY PROBLEMS IN THE INTENSIVE CARE UNIT

Section Editor—Dominic J. Nompleggi

VII: ENDOCRINE PROBLEMS IN THE INTENSIVE CARE UNIT

Section Editor—Michael J. Thompson

X: SURGICAL PROBLEMS IN THE INTENSIVE CARE UNIT
Section Editor—Fred A. Luchette

XI: SHOCK AND TRAUMA
Section Editor—Arthur L. Trask

XIII: TRANSPLANTATION
Section Editor — Christoph Troppmann

XIV: RHEUMATOLOGIC AND IMMUNOLOGIC PROBLEMS IN THE INTENSIVE CARE UNIT
Section Editor — Paul F. Dellaripa

XV: PSYCHIATRIC ISSUES IN INTENSIVE CARE

Section Editor — John Querques

XVI: MORAL, ETHICAL, LEGAL ISSUES, AND PUBLIC POLICY IN THE INTENSIVE CARE UNIT

Section Editors — James M. Rippe and Richard S. Irwin

APPENDIX

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PREFACE

We are delighted to present the fifth edition of the *Manual of Intensive Care Medicine*. Previous editions have established this *Manual* as a leading source of information in the ever-evolving, diverse and complicated field of critical care and intensive care medicine. The practical format and user-friendly, portable size of the *Manual*, have made it a particularly valuable aid in the bedside practice of intensive care and a valuable reference for students, interns, residents, fellows and others practicing in the critical care medicine environment.

As in the previous edition of this work, the fifth edition of the *Manual* is intended to parallel our major textbook *Irwin and Rippe's Intensive Care Medicine*. This latter, hardcover book is now in its sixth edition and continues to be a leading source of intensive care knowledge both in the United States and throughout the world.

The fifth edition of the Manual continues the user-friendly, outline format that we began to employ in the last edition to try to give busy house officers more direct and immediate access to the information that they need to manage complicated and time-sensitive issues of the practice of critical care medicine. As in previous editions, we have challenged the authors to emphasize salient concepts and focus on key, clinically relevant points. Annotated references are provided at the close of each chapter to guide the interested reader through key articles in the relevant literature.

The Manual of Intensive Care Medicine opens with an extensive section on Procedures and Techniques. The next seven sections are divided according to organ systems. In each chapter within these sections, discussions of key conditions that present in the intensive care or coronary care unit environments are presented together with targeted discussions focusing on treatment.

We are delighted to welcome new Section Editors in this portion of the book in the following areas: Dr. Akshay Desai in Cardiovascular Problems and Coronary Care, Dr. Pan-Yen Fan in Renal Problems, Dr. Daniel Libraty in Infectious Disease Problems, Dr. Domenic Nompleggi in Gastrointestinal and Hepatobiliary Problems, and Dr. Patrick Fogarty in Hematologic Problems.

Section IX presents a review of key considerations in "Pharmacology, Overdoses and Poisonings" recognizing that these remain important areas in intensive care. In this section we are delighted to welcome a new Section Editor, Dr. Luke Yip.

As in the previous edition, there are extensive sections on surgical issues in critical care such as shock and trauma. The *Manual* closes with sections on Neurology, Transplantation, Rheumatology and Immunology, Psychiatry, and Moral, Ethical, Legal and Public Policy Issues in Intensive Care—all of which are crucial to a comprehensive view of adult intensive care medicine.

We wish to acknowledge that many of the chapter authors for the current *Manual* have also made major contributors to our larger format textbook, *Irwin and Rippe's Intensive Care Medicine*. Although the *Manual of Intensive Care Medicine* has been edited and revised with the expert guidance of many section editors, many of the chapters were developed based on the expert knowledge of the original textbook contributors, reorganized and rewritten in a style necessary for the scope of this portable text.

We also wish to once again acknowledge and thank a number of individuals without whose able assistance the fifth edition of this *Manual* would not have been possible. First and foremost, Dr. Rippe's Editorial Director, Elizabeth Grady who continues to do a superb job in organizing and expediting all aspects of the manuscript preparation for this book and many others. Without Beth's superb editorial skills, projects such as this would not be possible. Karen Barrell, Dr. Irwin's Administrative Assistant also has provided important assistance in managing his complex clinical and academic endeavors. Carol Moreau, Executive Assistant to Dr. Rippe, expertly juggles the diverse aspects of his clinical, research and travel calendar to carve out time for projects of this magnitude. Debra Adamonis office assistant to Beth Grady and Carol Moreau, provides wonderful daily logistical support.

A special word of thanks to the editorial team at Lippincott, Williams and Wilkins who support all of our medical editing projects and have supported the process every step of the way. We wish to particularly thank our editor, Frances Destefano, for multiple helpful suggestions and support throughout the process of writing this book. Nicole Dernoski also provided expert logistical support throughout the process.

Special thanks are due to the Section Editors of the *Manual*—each of whom contributed long hours and the outstanding expertise necessary to assure that the *Manual* would continue to contain up to date, user-friendly and practical information.

Finally, we wish to thank our families: Diane Irwin; Rachel, Andrew, Truman and Bailey Koh; Sara, John, Benjamin, Jacob, and Isaac DiIorio; Jamie, Andrew, Emmett and Asher McIntosh; and Rebecca and Adam Slater; Stephanie, Hart, Jaelin, Devon and Jamie Rippe who continue to love and support us in all of our efforts, both personal and academic and make it all worth while.

James M. Rippe, MD
Richard S. Irwin, MD

Procedures and Techniques

I

AIRWAY MANAGEMENT AND ENDOTRACHEAL INTUBATION

1

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I. GENERAL PRINCIPLES

A. A major responsibility of the anesthesiologist or critical care physician is the maintenance of adequate ventilation and pulmonary gas exchange in critically ill patients. Airway management in intensive care patients differs significantly from routine surgical procedures in the operating room.

B. Critical care physicians should be familiar with the equipment and the techniques to maintain and secure the airway.

II. ANATOMY. The airway is divided into the upper airway that begins functionally at the nares or mouth and extends to the glottis and lower airway, which includes the trachea, the bronchi, and the subdivisions of the bronchi.

A. Nose

The nose has a number of functions: respiratory, olfaction, humidification, filtration, and phonation.

B. Larynx

1. The laryngeal skeleton consists of the hyoid bone and the thyroid, cricoid, epiglottic, arytenoid, corniculate, and cuneiform cartilages.

2. The cricoid cartilage is the only structure that completely encircles the airway. Two nerves that are branches of the vagus innervate the larynx.

a. The motor innervation to the cricothyroid muscle is supplied by the external branch of superior laryngeal nerve. The internal branch of superior laryngeal nerve supplies the sensory innervation above the vocal cords.
b. The recurrent laryngeal nerve supplies all other motor innervation to the laryngeal musculature and also provides sensory innervation to the larynx below the vocal cords.

C. Trachea

1. The adult trachea begins at the cricoid cartilage. It is 10 to 20 cm long and 12 mm in diameter.
2. It divides into right and left main bronchi at the level of fourth and fifth thoracic vertebrae. In the adult, the right main bronchus is wider and shorter and takes off at a less acute angle than the left, thereby making right main bronchus intubation more likely.

III. EVALUATION OF THE AIRWAY

A. The ability to rapidly evaluate the patient's airway before endotracheal intubation is very important. A difficult airway in some patients will remain undetected despite the most careful preoperative airway examination.

B. If possible, the airway should be evaluated while the patient is sitting upright. Several clinical criteria can be assessed.

1. Mouth opening (interincisor gap should be >4 cm)
2. Mallampati classification (Fig. 1-1)
3. Head and neck movement

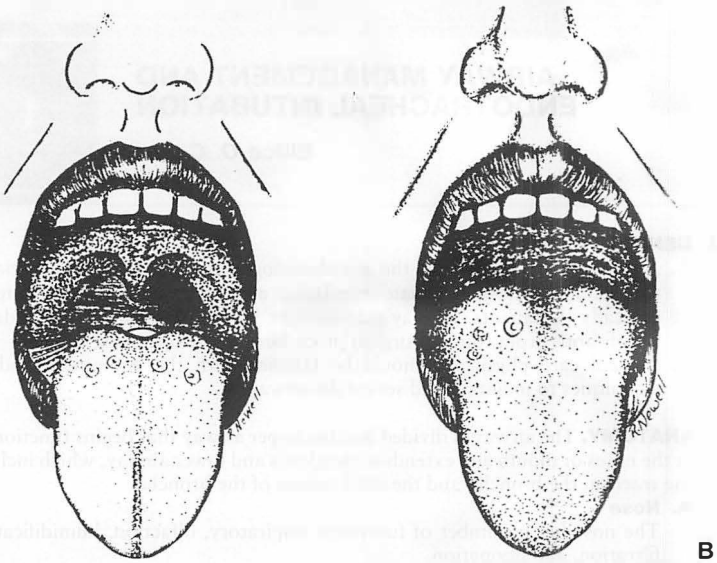

Figure 1-1. Mallampati classification: class I airway, faucial pillars, soft palate, and uvula can be visualized **(A)**; class II airway, faucial pillars, and soft palate can be visualized but the uvula is masked by the base of the tongue; and class III airway, only the soft palate can be visualized. The patient **(B)** has a class III airway, which is one of the predictors of difficult orotracheal intubation. (From Mallampati SR, Gatt SP, Gugino LD, et al. A clinical sign to predict difficult tracheal intubation: a prospective study. *Can Anaesth Soc J* 1985;32:420, with permission.)

4. Ability to prognath (i.e., to bring the lower incisors in front of the upper incisors)
5. Thyromental distance (should be >6.5 cm)
6. Body weight
7. Previous history of difficult intubation
   a. The single most reliable predictor of a difficult airway is a history of difficult airway.

C. The presence of cervical collars, halo devices, trauma to the mandible or neck, morbid obesity, burns, and obstructive sleep apnea may signal a difficult airway.

D. History of snoring, facial hair, edentulous patients, patients older than 56 years, and body mass index >26 are preoperative clinical predictors for difficult mask ventilation.

IV. AIRWAY EQUIPMENT

A. An oxygen source, face masks of different sizes, a bag-valve ventilation device, tonsillar suction, and suction source with canister and tubing.

B. Oral and nasopharyngeal airways (Fig. 1-2).

C. Laryngoscope blades and handle. Two basic types of laryngoscope blades are available: the curved blade (Macintosh) and the straight blade (Miller). The Miller blade is more useful in patients who have a cephalad and anterior laryngeal inlet (Fig. 1-3).

D. Various sizes of endotracheal tubes with stylets. The selection of proper tube diameter is very important. In adults, endotracheal tubes with internal diameter of 7.0 to 8.0 mm are commonly used for women, whereas for men it is 8.0 to 9.0 mm.

E. A device to detect end-tidal carbon dioxide: colorimetric detector or capnograph.

F. The required size of the endotracheal tubes used in children may be based on this formula: Endotracheal tube size (mm) = (16 + age [yr])/4.

G. Laryngeal mask airways (LMAs) can be used to provide a temporary airway until a more definite airway can be achieved. The LMA is contraindicated

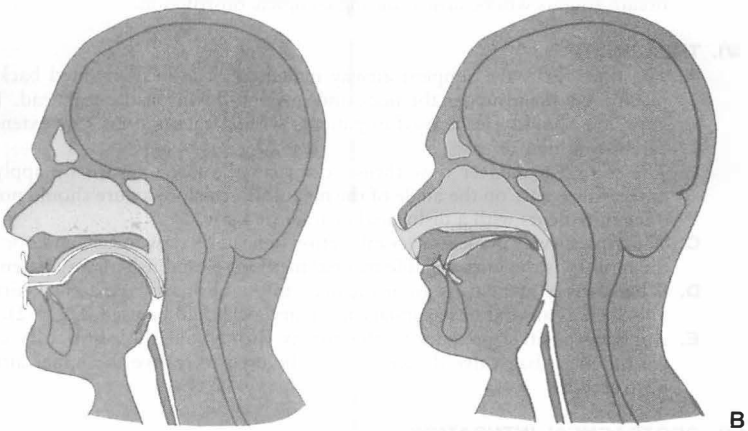

Figure 1-2. A: The proper position of the oropharyngeal airway. **B:** The proper position of the nasopharyngeal airway. (Reprinted with permission from Dorsch JA, Dorsch SE. *Understanding anesthesia equipment*. Baltimore: Williams & Wilkins, 1984.)

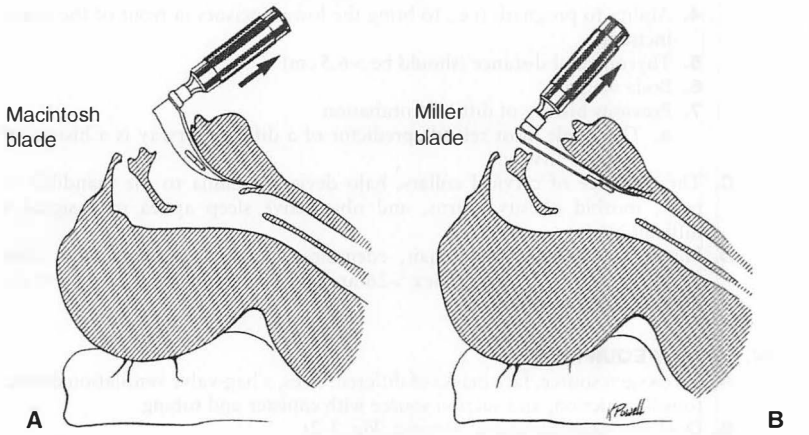

Figure 1-3. The two basic types of laryngoscope blades — Macintosh **(A)** and Miller **(B)**. The Macintosh blade is curved. The blade tip is placed in the vallecula, and the handle of the laryngoscope pulled forward at a 45-degree angle. This maneuver allows visualization of the epiglottis. The Miller blade is straight. The tip is placed posterior to the epiglottis, thereby pinning the epiglottis between the base of the tongue and the straight laryngoscope blade. The motion on the laryngoscope handle is the same as that used with the Macintosh.

in patients at risk of aspiration due to the presence of a full stomach (Fig. 1-4).

V. AIRWAY OBSTRUCTION

A. The hallmark of upper airway obstruction is diminished or absent airflow in the presence of continued respiratory effort.

B. Airway obstruction can be complete or partial. Partial obstruction will be accompanied by snoring during expiration or with stridor during inspiration. Breath sounds will be absent during complete obstruction.

VI. TREATMENT

A. The head tilt is the simplest airway maneuver. The head is tilted back by placing one hand under the neck and pushing down on the forehead. This approach should not be used in patients with a fractured neck or extensive cerebrovascular disease.

B. The second maneuver (jaw thrust) displaces the jaw forward by applying anterior pressure on the angle of the mandible. This procedure should not be done in patients with a dislocated or fractured jaw.

C. The triple airway maneuver (combination of head tilt, jaw thrust, and opening the mouth) is the most reliable manual method to establish airway patency.

D. When airway maneuvers are inadequate to establish airway patency, airway aids such as an oral or nasopharyngeal airway should be used (Fig. 1-2).

E. Applying positive pressure to the airway throughout the respiratory cycle via the mask-bag-valve device can also be used to relieve the upper airway obstruction.

VII. OROTRACHEAL INTUBATION

A. Endotracheal intubation achieves four main goals:

1. Airway protection

2. Provides upper airway patency

Figure 1-4. Correct position of the laryngeal mask airway. (From Maltby JR, Loken RG, Watson NC, et al. The laryngeal mask airway: clinical appraisal in 250 patients. *Can J Anaesth* 1990;37:509, with permission.)

3. Pulmonary hygiene
4. Allows mechanical positive pressure ventilation

B. Traditional teaching suggests that the optimal position is the "sniffing" position: the head should be resting on a pad, which flexes the neck on the chest with concomitant extension of the head on the neck. However, recent studies suggest that the sniffing position may not be any better than simple head extension in facilitating orotracheal intubation.

C. The laryngoscope handle is held in the left hand while the patient's mouth is opened as wide as possible. The laryngoscope blade is inserted into the right side of the mouth, the tongue is swept to the left, and the blade is advanced forward toward the base of the tongue.

D. The curved blade is advanced into the vallecula and upward force at a 45-degree angle is used to raise the epiglottis. The straight blade is advanced and the tip of the blade is positioned beneath the epiglottis and upward force is applied in the same manner as with the curved blade. Do not rotate the blade back onto the teeth.

E. Once the glottic opening is visualized, the endotracheal tube is advanced through the vocal cords until the cuff just disappears. The cuff is inflated to a pressure of 22 to 32 cm H_2O. If a cuff pressure gauge is unavailable, the tube is inflated until moderate tension is felt in the pilot balloon to the cuff.

F. Determine that the tube is in the trachea. Signs of tracheal intubation consist of presence of CO_2 in the exhaled breath, breath sounds over the chest, lack of breath sounds over the stomach, lack of gastric distention, and respiratory gas moisture in the endotracheal tube.

G. Insertion of the tube to 23 cm at the incisors in males and 21 cm in females generally provides optimal endotracheal tube position.

H. In the unconscious patient who is considered to have a full stomach, laryngoscopy with the application of cricoid pressure should be considered (Sellick maneuver). Cricoid pressure should be applied by using the thumb and forefinger together to push downward on the cricoid cartilage. This maneuver may prevent passive regurgitation of stomach contents into the trachea during intubation. A recent study casts doubt on the utility of cricoid pressure to prevent passive regurgitation.

VIII. NASOTRACHEAL INTUBATION

A. The nasal approach generally provides the easier route for intubation.

B. Topical vasoconstrictors such as phenylephrine or cocaine (4%) should be applied to the nares to minimize nasal bleeding.

C. A well-lubricated, warmed tube with the cuff fully deflated should be inserted through either prepared nostril. Once the tube is beyond the nasopharynx, both blind and direct laryngoscopic techniques can be used to accomplish nasotracheal intubations.

D. Nasotracheal intubation is contraindicated in basilar skull fractures, coagulopathies, and intranasal abnormalities.

IX. FLEXIBLE ENDOSCOPY AND ALTERNATIVE TECHNIQUES OF AIRWAY MANAGEMENT

A. Flexible endoscopy is useful in suspected spine injury, known or anticipated difficult airway, morbid obesity, and in patients with high risk of aspiration.

B. It may be used in both awake and anesthetized patients through oral or nasal route.

C. It may be useful in critically ill patients to evaluate the endotracheal tube patency and position and to change endotracheal tubes in patients with difficult airways.

D. Flexible endoscopy can be used with other intubation or alternative airway management techniques to overcome many difficult airways.

E. The LMA or its variants and new generation supraglottic ventilatory devices (laryngeal tube, Cobra PLA) are other alternative devices to manage the patient with a difficult airway. Recently, four new rigid videolaryngoscopes (GlideScope, Airtraq, McGrath, and Airway Scope) that provide a non–line-of-sight view of the glottis have also become available.

F. Needle cricothyrotomy and percutaneous dilatational tracheostomy can be done for emergent airway access (see Chapter 11).

X. COMPLICATIONS OF ENDOTRACHEAL INTUBATION

A. During intubation

1. Laryngospasm
2. Laceration
3. Bruising of lips or tongue
4. Damage to teeth
5. Aspiration
6. Endobronchial or esophageal intubation
7. Perforation of oropharynx, trachea, or esophagus
8. Epistaxis

B. Postextubation

1. Laryngospasm, sore throat, hoarseness, stridor, glottic or subglottic edema, post-extubation granuloma
2. Long-term intubation may result in tracheal stenosis, tracheomalacia, and tracheal mucosal ulceration

XI. EXTUBATION

- **A.** Should be done in the patient who is fully awake and can protect his airway.
- **B.** Oropharyngeal secretions should be suctioned, head of the bed should be elevated, and endotracheal tube should be removed after a cuff leak test.
- **C.** In patients with a known difficult airway, extubation using a flexible bronchoscope or airway exchange catheter should be considered.
- **D.** Supplemental oxygen should be provided and patient should be observed in a monitoring setting.
- **E.** Emergency airway equipment should be available to manage postextubation problems.

XII. NONINVASIVE VENTILATION

- **A.** Noninvasive positive pressure ventilation (NPPV) can be delivered nasally or by facemask (see Chapter 53).
- **B.** Have two major modes of supplying support: bilevel positive airway pressure (BIPAP) or continuous positive airway pressure (CPAP).
- **C.** NPPV has improved treatment in select patients with acute respiratory failure, lowered rates of endotracheal intubations, airway complications, and improved survival.
- **D.** In patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) with hypercarbic respiratory failure, NPPV reduces respiratory rate, dyspnea scores, and mortality rate and decreases hospital discharge times.

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CENTRAL VENOUS CATHETER

Alan Orquiola, Theofilos P. Matheos, and Stephen O. Heard

2

I. GENERAL PRINCIPLES

A. Catheter types

1. Single lumen
2. Multilumen (double, triple, or quad)
3. Introducer
4. Double-lumen dialysis catheters

B. Site selection

1. Major sites
   a. Internal jugular vein (IJV)
   b. Subclavian vein (SCV)
   c. External jugular vein (EJV)
   d. Femoral vein
   e. Antecubital vein (peripherally inserted central catheters)
2. Depends on skill of operator: greater risk of pneumothorax with subclavian approach
3. Risk of infection: femoral > internal jugular > subclavian
4. Avoid sites involving infection, burns or other dermatologic processes

C. Methods to reduce risk of catheter infection

1. Education program with safety checklist
2. Empowering nursing to stop procedure if sterile technique is violated
3. Dedicated catheter cart stocked with all necessary supplies
4. Use chlorhexidine preparatory solution
5. Use subclavian site
6. Use maximum barrier precautions: cap, mask, sterile gloves and gown, sterile drape that entirely covers patient
7. Remove catheters when no longer needed
8. Avoid guide wire exchanges as possible
9. Use antimicrobial impregnated catheters if infection rates remain high despite institution of infection control measures
10. Avoid use of femoral site and move catheter from femoral site to another as soon as possible

D. Use of ultrasonographic guidance

1. Certain patient characteristics that carry higher risk of complications when using the anatomic approach
   a. Anatomy: morbid obesity; local scarring; radiation therapy; short, thick neck; transplant patients; edema
   b. Comorbidities: coagulopathy; bullous emphysema; maximal ventilator support
2. Allows better visualization of the anatomy, exact vessel location, and avoidance of preexisting thrombus
3. Decreases failure rate, multiple attempts at cannulation, mechanical rates and infection rates
4. Disadvantages: steep learning curve

II. INDICATIONS

- **A.** Monitoring of fluid status
- **B.** Administration of irritant medications or vasoactive substances
- **C.** Total parenteral nutrition
- **D.** Hemodialysis
- **E.** Placement of a temporary transvenous pacing wire
- **F.** Procurement of venous access when peripheral vein cannulation is not possible
- **G.** Aspiration of air in surgical procedures considered high risk for venous air embolism (e.g., posterior fossa craniotomy with the patient in the sitting position)
- **H.** Venous access during cardiopulmonary resuscitation

III. PROCEDURE

- **A.** Universal protocol with a time-out must be followed
- **B. Antecubital approach** (Fig. 2-1A)
  1. Patient's arm is at the side.
  2. Basilic vein may be found with aid of ultrasonography.
  3. The antecubital fossa is prepared and draped with strict aseptic technique.

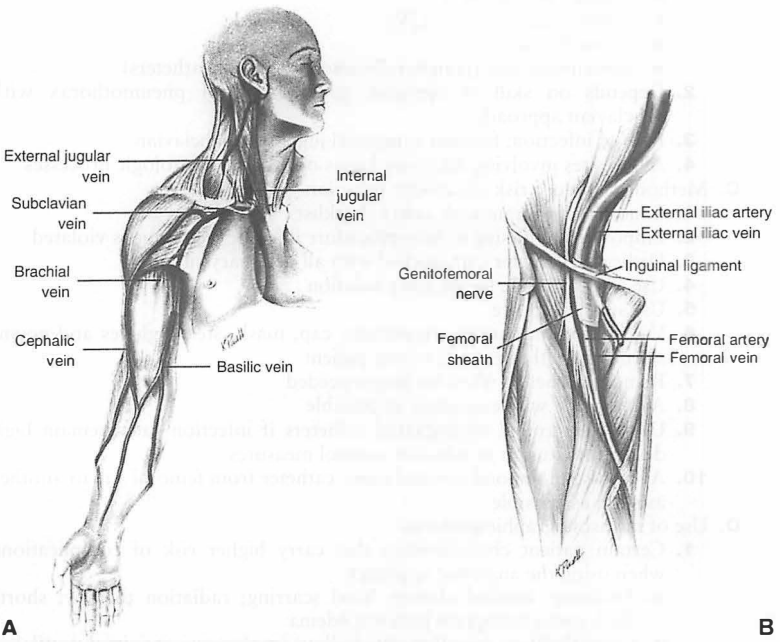


Figure 2-1. A: Venous anatomy of the upper extremity. The basilic vein is found in the medial part of the antecubital fossa and joins the brachial vein in the upper arm to form the axillary vein. The external jugular vein (EJV) is formed by the union of the posterior auricular and retromandibular veins, anterior and caudal to the ear; courses obliquely across the anterior surface of the sternocleidomastoid muscle (SCM); pierces the deep fascia posterior to the SCM and joins the subclavian vein at a sharp acute angle behind the medial third of the clavicle. **B:** Anatomy of the femoral vein. The femoral vein is a direct continuation of the popliteal vein and becomes the external iliac vein at the inguinal ligament. At the ligament, it lies in the femoral sheath medial to the femoral artery and nerve.

4. A tourniquet is placed proximally to distend the vein.
5. Basilic vein is entered proximal to crease at a 45-degree angle with the needle bevel pointing upward and cephalad.
6. When free backflow of blood is confirmed, the tourniquet is released, a guide wire is inserted through the needle, and the needle is removed.
7. A vessel dilator is threaded over the guide wire if necessary.
8. The dilator is removed and the catheter is advanced over the guide wire.
9. The length of insertion is estimated by measuring the distance from the venipuncture site to the manubriosternal junction.
10. The guide wire is removed and the catheter is sutured into place.
11. The first-pass success rate is 70% with the basilic vein approach.

C. IJV approach

1. Approaches to IJV cannulation are the anterior, central, and posterior (Fig. 2-2).
2. Central
   a. The patient is placed in a 15-degree Trendelenburg position and the head is turned to the contralateral side.
   b. Using maximum barrier precautions, after infiltration of local anesthetic, the operator punctures the skin with a 22-gauge "finder" needle with an attached syringe at the apex of the triangle formed

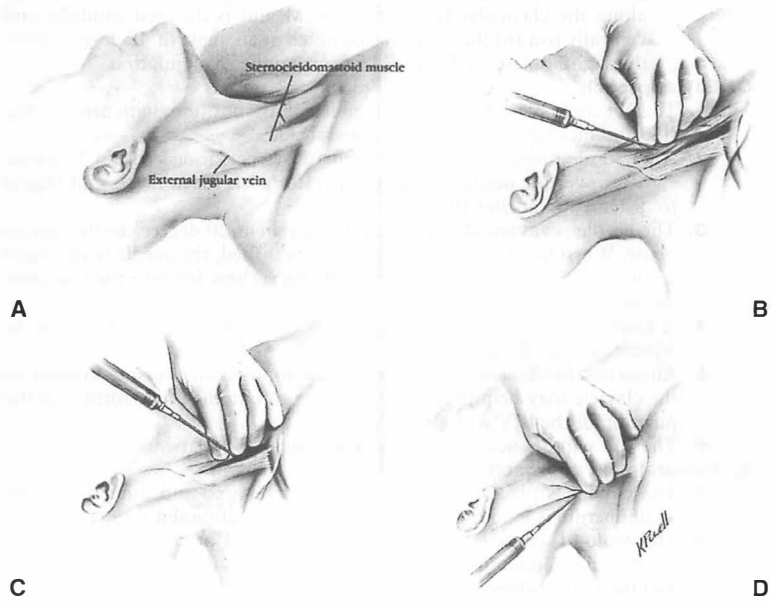


Figure 2-2. **A:** Surface anatomy. The internal jugular vein emerges from the base of the skull and enters the carotid sheath dorsally with the internal carotid artery, courses posterolaterally to the artery beneath the sternocleidomastoid muscle (SCM), lies medial to the anterior portion of the SCM in its upper part and beneath the triangle formed by the two heads of the muscle in the lower part, and enters the superior vena cava near the medial border of the anterior scalene muscle and beneath the sternal border of the clavicle. **B:** Anterior approach. **C:** Central approach. **D:** Posterior approach. To provide greater clarity of the anatomic landmarks, the sterile drape has been omitted from the figure.

by the two muscle bellies of the sternocleidomastoid muscle (SCM) and the clavicle. The internal carotid artery pulsation is usually felt 1 to 2 cm medial to this point.

c. The finder needle is directed at a 45-degree angle toward the ipsilateral nipple while the operator applies constant aspiration on the syringe. After successful venipuncture with the finder needle, the large-bore needle is introduced in the identical plane.

d. After cannulation, the guide wire is then inserted through the large needle. Depth of insertion is limited to 15 to 20 cm to avoid arrhythmias.

e. A scalpel is used to make a larger skin incision (if needed). The bevel of the scalpel is against the guide wire and the blade is facing away from the vessel. A dilator is advanced over the guide wire to dilate the tract and then removed. Care must be taken to hold the guide wire in place during dilator insertion to reduce the risk of vessel perforation. The central venous catheter (CVC) is then threaded over the guide wire.

3. Anterior approach (Fig. 2-2). Initial needle insertion is 0.5 to 1 cm lateral to the carotid artery pulsation at the midpoint of the sternal head of the SCM.

4. Posterior approach

a. The EJV is the key landmark.

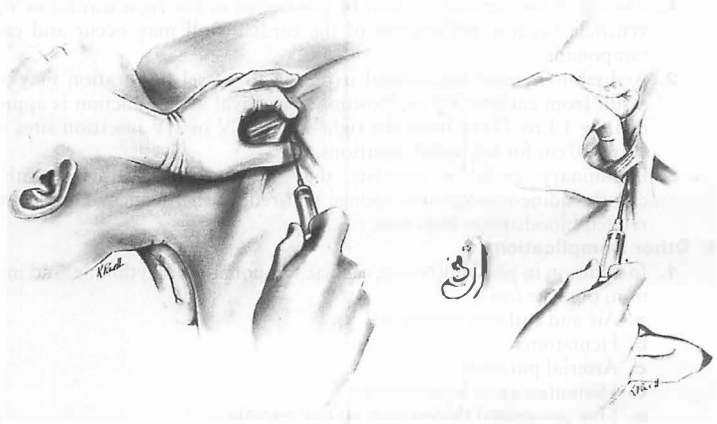
b. The needle is inserted 1 cm dorsal to the point where the EJV crosses the posterior border of the SCM or 5 cm cephalad from the clavicle along the clavicular head of the SCM and is directed caudally and ventrally toward the suprasternal notch at an angle of 45 degrees from the sagittal plane and with a 15-degree upward angulation.

D. EJV approach (Fig. 2-1A)

1. The patient is placed in a slight Trendelenburg position, with arms by the side and face turned to the contralateral side.
2. After sterile preparation, the venipuncture is performed with a 16-gauge catheter over the needle, using the operator's left index finger and thumb to distend and anchor the vein.
3. The needle is advanced in the axis of the vein at 20 degrees to the frontal plane. When free backflow of blood is established, the needle is advanced a few millimeters further, and the catheter is threaded into the vein over the needle.
4. A guide wire can be introduced through this catheter, and a CVC can be advanced over the guide wire.
5. Abduction of the ipsilateral arm and anteroposterior pressure exerted on the clavicle may help the guide wire to negotiate the angle formed at the junction of the EJV with the SCV.
6. The EJV can be successfully cannulated in 80% of patients.

E. Femoral vein approach (Fig. 2-1B)

1. The patient is placed supine, the groin is prepared and draped, and the venipuncture is made 1 to 1.5 cm medial to the femoral arterial pulsation.
2. The femoral arterial pulsation is usually found at the junction of the medial and middle third of a line joining the anterior superior iliac spine and the pubic tubercle.
3. An 18-gauge thin-walled needle attached to a syringe is inserted at a 45-degree angle pointing cephalad and 2 to 3 cm inferior to the inguinal ligament to minimize the risk of a retroperitoneal hematoma in the event of an arterial puncture.
4. Once venous blood return is established, the syringe is depressed to skin level and free aspiration of blood is reconfirmed.
5. A guide wire and subsequently a dilator are advanced, and the catheter is finally threaded over the guide wire after the dilator has been removed.



A B

Figure 2-3. **A:** Patient positioning for subclavian cannulation. The subclavian vein (SCV) is a direct continuation of the axillary vein, beginning at the lateral border of the first rib and extending 3 to 4 cm along the undersurface of the clavicle to join the ipsilateral internal jugular vein behind the sternoclavicular articulation to become the brachiocephalic vein. The SCV is bordered by muscles anteriorly, the subclavian artery and brachial plexus posteriorly, and the first rib inferiorly. **B:** Cannulation technique for the supraclavicular approach. To provide greater clarity of the anatomic landmarks, the sterile drape has been omitted from the figure.

F. SCV approach (Fig. 2-3)

1. The patient is placed in a 15- to 30-degree Trendelenburg position, with a small bedroll between the scapulae.
2. The patient's head is turned to the contralateral side, and arms are by the side.
3. Infraclavicular approach
   - **a.** Skin puncture is made with an 18-gauge thin-wall needle attached to a syringe, 2 to 3 cm caudal to the midpoint of the clavicle and directed toward the suprasternal notch until it abuts the clavicle.
   - **b.** The needle is "walked" down the clavicle until the inferior edge is cleared.
   - **c.** As the needle is advanced, it is kept as close to the inferior edge of the clavicle as possible to avoid puncturing the dome of the pleura.
   - **d.** When blood return is established, the needle bevel (initially facing upward) is turned 90 degrees toward the heart, the syringe is removed, the guide wire is inserted, the needle is removed, and a dilator is advanced over the guide wire and removed.
   - **e.** The CVC is advanced over the guide wire to the appropriate depth.
4. Supraclavicular approach
   - **a.** The skin puncture is just superior to the clavicle and is lateral to the insertion of the clavicular head of the SCM.
   - **b.** The needle is advanced toward the contralateral nipple, just under the clavicle, and it should enter the jugular subclavian at a depth of 1 to 4 cm.
   - **c.** A 90% to 95% success rate can be achieved with this approach.

IV. POSTPROCEDURE CONSIDERATIONS

A. A chest radiograph is required to confirm proper position of the catheter and to ensure absence of a pneumothorax.

1. The tip of the catheter cannot be positioned in the right atrium or right ventricle because perforation of the cardiac wall may occur and cause tamponade.
2. Arrhythmias from mechanical irritation or vessel perforation may also result from catheter tip malposition. The caval atrial junction is approximately 13 to 17 cm from the right-sided SCV or IJV insertion sites and 15 to 20 cm for left-sided insertions.
3. Preliminary evidence suggests that dressing the catheter with a chlorhexidine-impregnated sponge will reduce the incidence of catheter-related bloodstream infection.

B. Other Complications

1. In addition to pneumothorax, cardiac tamponade, arrhythmias, and infection, observe for:
   - **a.** Air and catheter embolism
   - **b.** Hematoma
   - **c.** Arterial puncture
   - **d.** Hemothorax or hydrothorax
   - **e.** Line-associated thrombosis and/or embolism

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ARTERIAL LINE PLACEMENT AND CARE

Khaldoun Faris

3

I. GENERAL PRINCIPLES

A. Cannulation sites

1. Radial artery
2. Dorsalis pedis artery
3. Brachial artery
4. Femoral artery
5. Axillary artery

B. Anatomy

1. The radial artery is one of two final branches of the brachial artery. It lies just lateral to the flexor carpi radialis at the wrist (Fig. 3-1). The anastomoses between radial and ulnar arteries provide excellent collateral flow to the hand. A competent superficial or deep arch must be present to ensure adequate collateral flow.
2. The dorsalis pedis artery runs from the level of the ankle to the great toe. It lies superficially and just lateral to the tendon of the extensor hallucis longus.
3. The brachial artery lies in the antecubital fossa, medial to the tendon of the biceps, and in close proximity to the median nerve.
4. The common femoral artery courses under the inguinal ligament near the junction of the ligament's medial and middle thirds (Fig. 3-2).
5. The axillary artery begins at the lateral border of the first rib and ends at the inferior margin of the teres major muscle. The artery is mostly superficial and covered only by skin and fasciae.

C. Site selection

1. The ideal artery should have extensive collateral circulation that will maintain the viability of distal tissues if thrombosis occurs.
2. The site should be comfortable for the patient, accessible for nursing care, and close to the monitoring equipment.
3. Sites involved by infection or disruption in the epidermal barrier should be avoided.
4. Larger arteries and catheters provide more accurate (central aortic) pressure measurements. Distal artery recordings yield higher systolic values than central artery recordings, but the mean pressures are similar.

II. INDICATIONS

A. Hemodynamic monitoring
1. Beat-to-beat changes
2. Waveform inspection
3. The effect of arrhythmia on perfusion
4. Continuous cardiac output (CO) monitoring using arterial pulse contour analysis
5. Assessment of systolic pressure variation (SPV) or pulse pressure variation (PPV) to predict fluid responsiveness

B. Frequent arterial blood gas sampling (more than two measurements per day)

C. Arterial administration of drugs such as thrombolytics

D. Intra-aortic balloon pump use

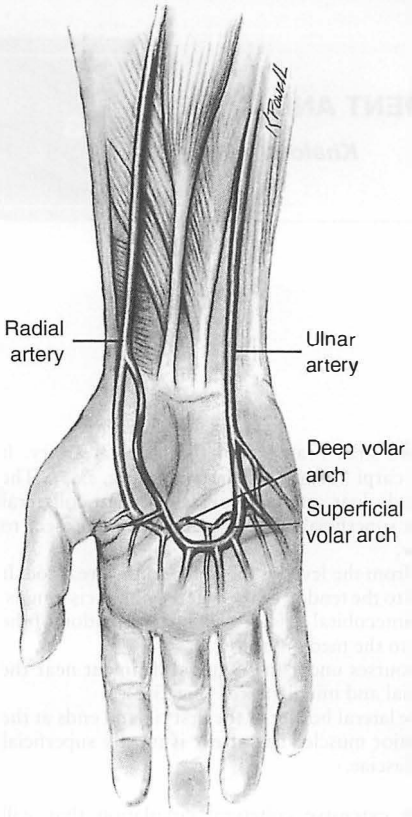

Figure 3-1. Anatomy of the radial artery. Note the collateral circulation to the ulnar artery through the deep volar arterial arch and dorsal arch.

III. PROCEDURE

A. Equipment

1. The equipment necessary to display and measure arterial waveform includes:
   - **a.** An appropriate intravascular catheter
   - **b.** Fluid-filled noncompliant tubing with stopcocks
   - **c.** A transducer
   - **d.** A constant flushing device
   - **e.** Electronic monitoring equipment
2. Using this equipment, intravascular pressure changes are transmitted through the hydraulic (fluid-filled) elements to the transducer, which converts mechanical displacement into a proportional electrical signal. The signal is amplified, processed, and displayed as a waveform by the monitor.
3. Sources of error
   - **a.** Improper zeroing of the system and zero drift are the most important sources of error.
   - **b.** Calibration of the system is usually not necessary because of standardization of the disposable transducer.
   - **c.** If the zero referencing and calibration are correct, a fast-flush test will assess the system's dynamic response.

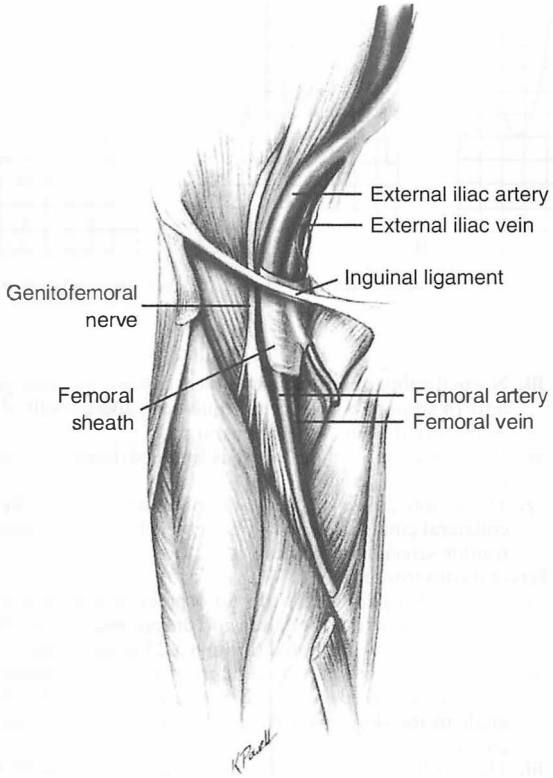

Figure 3-2. Anatomy of the femoral artery and adjacent structures. The artery is cannulated below the inguinal ligament.

d. An optimum fast-flush test results in undershoot followed by small overshoot, then settles to the patient's waveform (Fig. 3-3).

e. Overdamped tracings are usually caused by air bubbles, kinks, clot formation, compliant tubing, loose connections, a deflated pressure bag, or anatomic factors. All these problems are usually correctable.

f. Underdamped tracings are caused by long tubing or an increased inotropic or chronotropic state.

B. Technique

1. A time-out and the universal protocol must be followed. Foaming in and out, skin disinfection, and draping should be carried out as described in Chapter 2.

2. Radial artery cannulation

a. Modified Allen test

i. The modified Allen test is sometimes used to assess the degree of collateral flow.

ii. To perform this test, the examiner compresses both radial and ulnar arteries and asks the patient to clench and unclench the fist repeatedly until pallor of the palm is produced. One artery is then released, and the time to blushing of the palm is noted. The procedure is repeated with the other artery.

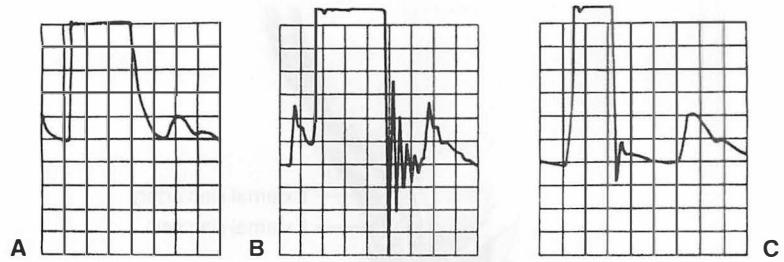

Figure 3-3. Fast-flush test. **A:** Overdamped system. **B:** Underdamped system. **C:** Optimal damping.

iii. Normal palmar blushing is complete before 7 seconds (positive test), 8 to 14 seconds is considered equivocal, and a result of 15 or more seconds is abnormal (negative test).

iv. Hyperextension of the hand is avoided because it may cause a false-negative result.

v. The modified Allen test does not necessarily predict the presence of collateral circulation, and some centers have abandoned its use as a routine screening procedure.

b. Percutaneous insertion

i. The hand is placed in 30 to 60 degrees of dorsiflexion. The volar aspect of the wrist is prepared and draped using the sterile technique and lidocaine is infiltrated through a 25-gauge needle.

ii. A 20-gauge, Teflon 1.5- to 2-in. catheter-over-needle apparatus is used for the puncture. Entry is made at a 30- to 60-degree angle to the skin, approximately 3 cm proximal to the distal wrist crease.

iii. The needle and cannula are advanced until arterial blood return is noted in the hub (Fig. 3-4). A small amount of further advancement is necessary for the cannula to enter the artery as well.

iv. With this accomplished, needle and cannula are brought flat to the skin and the cannula is advanced to its hub with a firm, steady rotary action.

v. Correct positioning is confirmed by pulsatile blood return on removal of the needle.

vi. The cannula is then secured firmly and attached to the transducer tubing. Aseptic ointment is applied and the site is bandaged.

vii. Video instruction for the insertion of a radial arterial line is available at the website for *New England Journal of Medicine* www.nejm.org.

c. Special catheter

i. Catheters with self-contained guidewires to facilitate passage of cannula into the artery are available.

ii. Percutaneous puncture is made in the same manner, but when blood return is noted in the catheter hub, the guidewire is passed through the needle into the artery to serve as a stent for subsequent catheter advancement.

iii. The guidewire and needle are then removed and placement is confirmed by pulsatile blood return.

3. Dorsalis pedis artery cannulation

a. The patient's foot is placed in plantar flexion and is prepared in the usual manner.

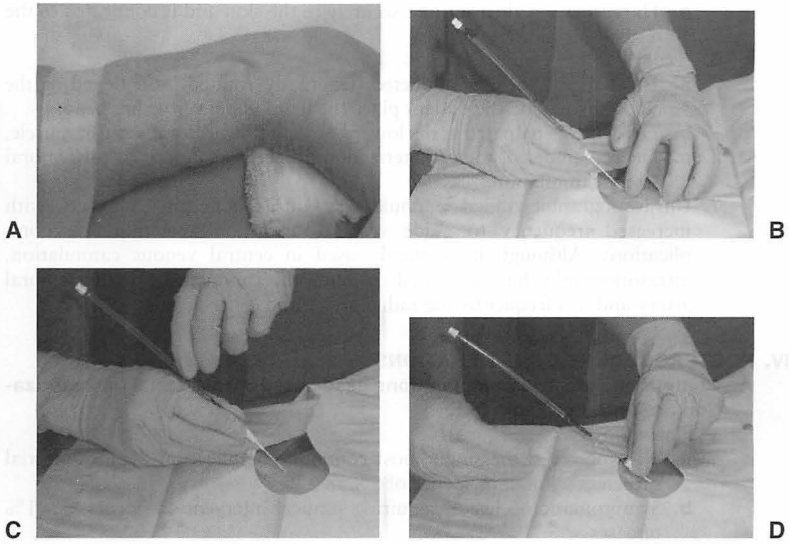

Figure 3-4. Cannulation of the radial artery. **A:** A towel is placed behind the wrist, and the hand is immobilized with tape. **B:** The radial artery is fixated with a 20-gauge catheter-needle-guidewire apparatus. **C:** The apparatus is withdrawn until pulsatile blood return is noted and then the guidewire is advanced. **D:** The catheter is advanced over the guidewire into the artery.

   b. Vessel entry is obtained approximately halfway up the dorsum of the foot.
   c. Advancement is the same as with cannulation of the radial artery.
   d. Systolic pressure readings are usually 5 to 20 mm Hg higher with dorsalis pedis catheters than with radial artery catheters, but mean pressure values are generally unchanged.

4. Brachial artery cannulation
   a. Brachial artery cannulation is infrequently performed because of concern regarding the lack of effective collateral circulation.
   b. The median nerve lies in close proximity to the brachial artery in the antecubital fossa and may be punctured in 1% to 2% of cases.
   c. Cannulation of the brachial artery can be performed with a 2-in. catheter over-the-needle apparatus as described for radial artery catheterization.
5. Femoral artery cannulation
   a. The artery is cannulated using the Seldinger technique and any one of several available prepackaged kits.
   b. The patient lies supine with the leg extended and slightly abducted.
   c. Skin puncture should be made a few centimeters caudal to the inguinal ligament to minimize the risk of retroperitoneal hematoma or bowel perforation.
   d. The thin-walled needle is directed, bevel up, cephalad at a 45-degree angle. When arterial blood return is confirmed, the needle and syringe are brought down against the skin to facilitate guidewire passage.
   e. The guidewire is inserted, the needle is withdrawn, and a stab incision is made with a scalpel at the skin puncture site.
   f. The catheter is threaded over the guidewire to its hub, and the guidewire is withdrawn.

g. The catheter is then sutured securely to the skin and is connected to the transducer tubing.

6. Axillary artery cannulation
   a. The patient's arm is abducted, externally rotated, and flexed at the elbow by having the patient place the hand under his or her head.
   b. The artery is palpated at the lower border of the pectoralis major muscle.
   c. The remainder of the catheterization proceeds as described for femoral artery cannulation.
7. Ultrasonographic-guided cannulation: Ultrasonography is used with increased frequency to guide vessel cannulation and minimize complications. Although it is mainly used in central venous cannulation, ultrasonography has been used to guide the cannulation of the femoral artery and less frequently the radial artery and other arteries

IV. POSTPROCEDURE CONSIDERATIONS

A. Complications. The complications associated with arterial catheterization are listed in Table 3-1.

1. Thrombosis
   a. Thrombosis is the single most common complication of intra-arterial catheters with an incidence of 5% to 25%.
   b. Symptomatic occlusion requiring surgical intervention occurs in <1% of cases.
   c. Most patients eventually recanalize, generally by 3 weeks after removal of the catheter.

TABLE 3-1 Complications Associated with Arterial Cannulation

Site	Complications
All sites	Pain and swelling
	Thrombosis
	Asymptomatic
	Symptomatic
	Embolization
	Hematoma
	Hemorrhage
	Limb ischemia
	Catheter-related infection
	Local
	Systemic
	Diagnostic blood loss
	Pseudoaneurysm
	Heparin-associated thrombocytopenia
Radial artery	Cerebral embolization
	Peripheral neuropathy
Femoral artery	Retroperitoneal hemorrhage
	Bowel perforation
	Arteriovenous fistula
Axillary artery	Cerebral embolization
	Brachial plexopathy
Brachial artery	Median nerve damage
	Cerebral embolization

   d. If evidence of ischemia persists after catheter removal, thrombolytic therapy, radiologic or surgical embolectomy, and cervical sympathetic blockade are treatment options.
2. Cerebral embolization
   a. Factors that increase the risk for retrograde passage of air into the cerebral circulation are patient size and position (air travels up in a sitting patient), injection site, and flush rate.
   b. The risk is minimized by clearing all air from tubing before flushing, opening the flush valve for no more than 2 to 3 seconds, and avoiding overaggressive manual flushing of the line.
3. Diagnostic blood loss (DBL)
   a. In patients with frequent arterial blood gas determinations, DBL can be substantial and result in a transfusion requirement.
   b. DBL can be minimized in several ways, including tubing systems that use a reservoir for blood sampling, continuous intra-arterial blood gas monitoring, point of care microchemistry analysis, and the use of pediatric collection tubes.
4. Infection
   a. Infectious sequelae are the most important clinical complications associated with arterial cannulation.
   b. Operators must wash their hands and wear sterile gloves during insertion of radial artery catheters, and triple barrier precautions are appropriate for large artery cannulations.
   c. Nursing personnel should follow strict guidelines when drawing blood samples or manipulating tubing.
   d. Daily inspection of the site is mandatory, and the catheter should be removed promptly if signs of infection are noted.
   e. It is no longer necessary to change arterial catheters routinely because studies of catheters remaining in place a week or longer have not demonstrated a higher rate of clinically important infection.

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4 PULMONARY ARTERY CATHETERS

Khaldoun Faris

I. GENERAL PRINCIPLES

A. Objectives

1. Assess left ventricular (LV) or right ventricular (RV) function.
2. Monitor hemodynamic status.
3. Guide treatment with pharmacologic and nonpharmacologic agents.
4. Provide prognostic information.

B. Types

1. Standard pulmonary artery catheter (PAC)
2. Pacing PAC
3. Continuous cardiac output PAC
4. Continuous mixed venous O_2 PAC
5. RV ejection fraction PAC

II. INDICATIONS

A. Cardiovascular disease

1. Myocardial infarction, associated with cardiogenic shock, mechanical complications, or right heart failure
2. Severe or progressive congestive heart failure
3. Primary pulmonary hypertension for diagnosis and to guide vasodilator therapy
4. Shock

B. Perioperative period

1. Cardiac surgery
2. Aortic and peripheral vascular surgery
3. Major abdominal and thoracic surgery

C. Critical illness

1. Major trauma
2. Severe sepsis and septic shock
3. Acute renal failure
4. Major burns
5. Acute respiratory distress syndrome (ARDS) with multiple-organ dysfunction
6. Severe head injury with refractory intracranial hypertension
7. Cerebral vasospasm
8. Severe preeclampsia/eclampsia

III. PROCEDURE

A. Equipment

1. The standard catheter length is 110 cm, and the most commonly used external diameter is 5 or 7 Fr.
2. A balloon is present 1 to 2 mm from the tip; when it is inflated with air or filtered CO_2, it guides the catheter from the greater intrathoracic veins through the right heart chambers into the pulmonary artery PA.
3. The standard PAC used in the intensive care unit (ICU) is a quadruple-lumen catheter, which has a lumen containing electrical leads for a thermistor

positioned at the catheter surface, 4 cm proximal to its tip. The thermistor measures PA blood temperature and allows thermodilution cardiac output measurements.

4. A five-lumen catheter allows passage of a specially designed 2.4-Fr bipolar pacing electrode probe through the additional lumen for intracardiac pacing.
5. Continuous mixed venous oxygen saturation measurement is clinically available using a fiberoptic five-lumen PAC.
6. Continuous cardiac output can be measured by catheters equipped with a filament located in the RV portion of the catheter and a rapid response thermistor at the distal end. Pulse-heating currents are applied to the filament randomly and temperature changes are detected by the thermistor.
7. Catheters equipped with fast-response (95 ms) thermistors allow determination of right ventricle ejection fraction (RVEF) and RV systolic time intervals.

B. Technique

1. Standard PAC insertion procedure
   - **a.** A time out is performed to ensure "correct patient and side" and informed consent has been obtained if appropriate.
   - **b.** Central venous access using the appropriate size introducer sheath must first be obtained using sterile technique including maximum barrier precautions (see Chapter 2).
   - **c.** Continuous monitoring of the electrocardiogram (ECG) and pressure waveforms of the catheter is required, as well as equipment and supplies for cardiopulmonary resuscitation.
   - **d.** Pass the catheter through the introducer sheath into the vein and advance it, using the marks on the catheter shaft indicating 10-cm distances from the tip, until the tip is in the right atrium.
   - **e.** This maneuver requires advancement of approximately 35 to 40 cm from the left antecubital fossa, 10 to 15 cm from the internal jugular vein, 10 cm from the subclavian vein, and 35 to 40 cm from the femoral vein.
   - **f.** A right atrial waveform on the monitor with appropriate fluctuations accompanying respiratory changes or cough confirms proper intrathoracic location (Fig. 4-1).
   - **g.** With the catheter tip in the right atrium, inflate the balloon with the recommended amount of air or carbon dioxide.
     - **i.** Inflation of the balloon should be associated with a slight feeling of resistance—if it is not, suspect balloon rupture and do not attempt further inflation or advancement of the catheter until balloon integrity has been properly reevaluated.
     - **ii.** If significant resistance to balloon inflation is encountered, suspect malposition of the catheter in a small vessel; withdraw the catheter and readvance it to a new position.
     - **iii.** Do not use liquids to inflate the balloon because they may be irretrievable and could prevent balloon deflation.
   - **h.** With the balloon inflated, advance the catheter until an RV pressure tracing is seen. Continue advancing the catheter until the diastolic pressure tracing rises above that observed in the RV center, thereby indicating PA placement. Raising the head of the bed and tilting the patient to the right will facilitate passage of the catheter through the RV and reduce the risk of arrhythmias.
   - **i.** Advancement beyond the PA position results in a fall on the pressure tracing from the levels of systolic pressure noted in the RV and PA. When this is noted, record the pulmonary artery occlusion pressure (PAOP) and deflate the balloon.

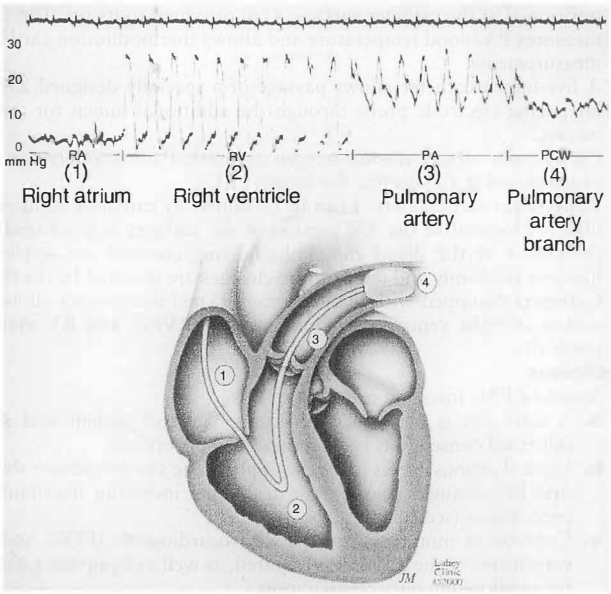

Figure 4-1. Pressure tracing recordings with corresponding locations as the pulmonary artery catheter is passed into the occlusion position. PCW, pulmonary capillary wedge. (Reprinted with permission from O'Donnell JM, Nacul FE. Surgical intensive care medicine. Kluwer Academic Publishers, 2001:47.)

j. Phasic PA pressure should reappear on the pressure tracing when the balloon is deflated. If it does not, pull back the catheter with the deflated balloon until the PA tracing appears.
  i. Carefully record the balloon inflation volume needed to change the PA pressure tracing to the PAOP tracing.
  ii. If the inflation volume is significantly lower than the manufacturer's recommended volume, or if subsequent PAOP determinations require decreasing balloon inflation volumes as compared with an initial appropriate volume, the catheter tip has migrated too far peripherally and should be pulled back immediately.

k. Most introducers have a valve that can be tightened to secure the catheter in the correct PA position. To avoid catheter kinkage, the valve should not be tightened too much.

l. Order a chest radiograph to confirm the catheter's position; the catheter tip should appear no more than 3 to 5 cm from the midline.

2. Pacing PAC insertion procedure

a. A pacing catheter has an additional lumen, 19 cm from the catheter tip (the RV port), which allows passage of a specially designed 2.4-Fr pacemaker wire (probe).

b. The catheter is inserted as described for a standard PAC.

c. Connect the RV port to a pressure transducer to verify the location of the orifice in the RV. Ideally, the RV orifice is positioned 1 to 2 cm distal to the tricuspid valve.
  i. To achieve this after initial placement, pull the catheter back until a right atrial pressure tracing is recorded from the RV port.

ii. Advance the catheter (with balloon inflated) until an RV pressure tracing is first obtained. At this point, the opening of the RV port is at the level of the tricuspid valve; simply advancing the catheter an additional 1 to 2 cm will place the opening in the desired position.
iii. A special package enables sterile introduction of the pacemaker probe. Attach the tip of the pacemaker probe introducer package to the hub of the RV port.
iv. Advance the 2.4-Fr pacing probe gently through the pacing lumen. Passage of the probe is facilitated by keeping the extravascular portion of the PAC as straight as possible and by keeping the probe on its packaging spool during insertion.
v. Allow the spool to spin slowly as the probe is advanced. When the marker on the probe reaches the 0 marking on the external part of the RV lumen, the tip of the probe is at the lumen opening.
vi. Connect the distal electrode of the probe to the V lead of an ECG and advance it until ST-segment elevation occurs, thereby indicating contact with the endocardium.
vii. Connect the probe to a pacemaker generator and check the thresholds.
viii. Obtain a chest radiograph to ensure proper probe placement at the RV apex.

IV. POSTPROCEDURE CONSIDERATIONS

A. Pressure and waveform interpretation

1. Normal resting right atrial pressure is 0 to 6 mm Hg.
2. The normal resting RV pressure is 17 to 30/0 to 6 mm Hg.
3. The RV systolic pressure should equal the PA systolic pressure (except in cases of pulmonic stenosis or RV outflow tract obstruction).
4. The RV pressure should equal the mean right atrial pressure during diastole when the tricuspid valve is open.
5. Normal resting PA pressure is 15 to 30/5 to 13 mm Hg with a normal mean pressure of 10 to 18 mm Hg.
6. The normal resting PAOP is 2 to 12 mm Hg and averages 2 to 7 mm Hg below the mean PA pressure.
7. Balloon occlusion may be confirmed by measuring an oxygen saturation of 95% or more from blood withdrawn from the distal lumen.
8. PAOP should be measured at end expiration because pleural pressure returns to baseline at the end of passive deflation.

B. Cardiac output measurement

1. Most PACs are equipped with a thermistor 4 cm from the tip that allows calculation of cardiac output using the thermodilution principle.
2. In practice, a known amount of cold or room temperature solution (typically 10 mL of normal saline in adults and 5 mL of normal saline in children) is injected into the right atrium through the catheter's proximal port.
3. The thermistor allows recording of the baseline PA blood temperature and subsequent temperature change.
4. Cardiac output is inversely proportional to the integral of the time versus temperature curve.
5. Thermodilution cardiac output is inaccurate in low-output states, tricuspid regurgitation, and atrial or ventricular septal defects.

C. Complications

1. Balloon rupture
2. Knotting
3. Pulmonary infarction (peripheral migration of the catheter with persistent undetected wedging of the catheter)

4. PA perforation
   a. Incidence is approximately 0.1% to 0.2%, although some postmortem series suggest that the true incidence of PA perforation is higher.
   b. Risk factors include pulmonary hypertension, mitral valve disease, advanced age, hypothermia, and anticoagulant therapy.
   c. Technical factors related to PA hemorrhage are distal placement or migration of the catheter, excessive catheter manipulation, use of stiffer catheter designs, and multiple overzealous or prolonged balloon inflations.
   d. PA perforation typically presents with hemoptysis.
   e. Emergency management for significant bleeding includes:
      i. Immediate wedge arteriography, intubation of the unaffected lung, and consideration of emergent embolization of the bleeding artery or emergency lobectomy or pneumonectomy.
      ii. PAC balloon tamponade resulted in rapid control of bleeding in one case report.
      iii. Application of positive end-expiratory pressure (PEEP) to intubated patients may also produce tamponade of hemorrhage caused by a PAC.
5. Thromboembolic complications
6. Rhythm disturbances
   a. Atrial and ventricular arrhythmias occur commonly during insertion of PACs.
   b. Patients with pre-existing left bundle branch block are at risk of developing complete heart block during catheter insertion.
7. Intracardiac damage
8. Catheter-related bloodstream infection and bacterial endocarditis

D. Clinical use of PACs

1. In unstable situations, PACs allow for direct and indirect measurement of several determinants of cardiac performance thereby supplying additional data to aid in clinical decision making (Table 4-1). However, a number of recent well-conducted clinical studies have shown either no benefit or increased morbidity and mortality associated with its use. Consequently, the use of PACs has decreased significantly in recent years.
2. A randomized trial conducted by the Canadian Critical Care Clinical Trials Group to compare goal-directed therapy guided by a PAC with standard care without the use of a PAC in elderly, high-risk surgical patients showed no improvement in mortality.
3. A multicenter randomized controlled trial conducted in France demonstrated that the use of PACs in the management of shock or ARDS, or both, albeit safe, does not improve mortality or morbidity.
4. A multicenter randomized controlled study conducted in the United Kingdom showed no clear evidence of benefit or harm by managing critically ill patients with a PAC.
5. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial concluded that adding the PAC to careful clinical assessment did not affect overall mortality or hospitalization in patients with severe symptomatic and recurrent heart failure.
6. The ARDS clinical trials network compared PAC-guided therapy in acute lung injury to central venous catheter (CVC)-guided therapy. The PAC-guided therapy did not improve survival of organ function but was associated with more complications.

TABLE 4-1 **Hemodynamic Parameters in Commonly Encountered Clinical Situations (Idealized)**

	RA	RV	PA	PAWP	AO	CI	SVR	PVR
Normal	0–6	25/0–6	25/6–12	6–12	130/80	≥2.5	1,500	≤250
Hypovolemic shock	0–2	15–20/0–2	15–20/2–6	2–6	≤90/60	<2.0	>1,500	≤250
Cardiogenic shock	8	50/8	50/35	35	≤90/60	<2.0	>1,500	≤250
Septic shock	—	—	—	—	—	—	—	—
Early	0–2	20–25/0–2	20–25/0–6	0–6	≤90/60	≥2.5	<1,500	<250
Late[a]	0–4	25/4–10	25/4–10	4–10	≤90/60	<2.0	>1,500	>250
Acute massive pulmonary embolism	8–12	50/12	50/12–15	≤12	≤90/60	<2.0	>1,500	>450
Cardiac tamponade	12–18	25/12–18	25/12–18	12–18	≤90/60	<2.0	>1,500	≤250
AMI without LVF	0–6	25/0–6	25/12–18	≤18	140/90	≤2.5	1,500	≤250
AMI with LVF	0–6	30–40/0–6	30–40/18–25	>18	140/90	>2.0	>1,500	>250
Biventricular failure secondary to LVF	>6	50–60/>6	50–60/25	18–25	120/80	~2.0	>1,500	>250
RVF secondary to RVI	12–20	30/12–20	30/12	<12	≤90/60	<2.0	>1,500	>250
Cor pulmonale	>6	80/>6	80/35	<12	120/80	~2.0	>1,500	>400
Idiopathic pulmonary hypertension	0–6	80–100/0–6	80–100/40	<12	100/60	<2.0	>1,500	>500
Acute VSR[b]	6	60/6–8	60/35	30	≤90/60	<2.0	>1,500	>250

RA, right atrium; RV, right ventricle; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; AO, aortic; CI, cardiac index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; AMI, acute myocardial infarction; LVF, left ventricular failure; RVF, right ventricular failure; RVI, right ventricular infarction; VSR, ventricular septal rupture.

[a] Hemodymanic profile seen in approximately one third of patients in late septic shock.

[b] Confirmed by appropriate RA–PA oxygen saturation step-up.

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CARDIOVERSION AND DEFIBRILLATION

Paulo J. Oliveira and Naomi F. Botkin

5

I. GENERAL PRINCIPLES

A. Basic concepts

1. Electric countershock
   - a. Involves delivering a quantity of electrical energy to depolarize the myocardium leading to termination of a tachyarrhythmia.
   - b. Definitions
     - i. **Cardioversion** delivers the shock at a specific point in the electromechanical cycle, which is *synchronized* to coincide with the QRS complex of the electrocardiogram (ECG).
       - (a) There is a significant risk of inducing ventricular fibrillation (Vfib) should the countershock fall on the "vulnerable" period of late ventricular systole marked by the T wave on the ECG.
       - (b) Under most circumstances, emergency and elective treatment of various tachyarrhythmias requires *synchronized* cardioversion.
     - ii. **Defibrillation** delivers electrical energy in a nonsynchronized manner to terminate Vfib and pulseless ventricular tachycardia (VT).
       - (a) Because Vfib/pulseless VT is immediately life threatening and there is no well-defined QRS complex, a random electrical countershock is delivered during the cardiac cycle.
       - (b) By definition, defibrillation is *unsynchronized*.

B. Physiology of arrhythmia and countershock

1. Reentry
   - a. Electric countershock is capable of terminating arrhythmias that involve a reentrant circuit (defined as electrical activation over a closed pathway of conduction tissue).
   - b. Cardioversion and defibrillation disrupt the process of reentry by simultaneously depolarizing a vast majority or threshold quantity of excitable tissue.
   - c. Examples of reentrant arrhythmias which can be terminated:
     - i. Atrial fibrillation (Afib)
     - ii. Atrial flutter
     - iii. Atrioventricular (AV) nodal reentrant tachycardia
     - iv. Most VT and Vfib
2. Increased automaticity
   - a. Arrhythmias due to increased impulse formation, in contrast, uniformly do not respond to electric countershock therapy.
   - b. Examples of unresponsive, arrhythmias involving triggered activity:
     - i. Sinus tachycardia
     - ii. Focal atrial tachycardia
     - iii. Some types of VT

C. Mechanism of action

1. Effective countershock silences the vast majority of myocardium through depolarization.
2. The remaining mass is insufficient to perpetuate the arrhythmia.

3. Multiple factors are involved in success of countershock therapy including energy level, type of shock waveform, tissue impedance, and myocardial refractory state.
4. Subthreshold shocks may extinguish fibrillatory wavefronts, but often new wavefronts will reinitiate leading to perpetuation of the fibrillation.

II. INDICATIONS

A. Urgent
   1. Hemodynamic instability due to tachyarrhythmia
   2. Acute respiratory distress, congestive heart failure, and angina due to tachyarrhythmia
   3. In acute care setting, must be careful not to mistake sinus tachycardia, which is common in hypotensive patients, for a shockable rhythm

B. Elective
   1. Tachyarrhythmias that occur in the absence of the acute symptoms and signs described earlier
   2. Risks and benefits must be carefully weighed

III. PRECAUTIONS

A. Extreme caution in the setting of digitalis toxicity and electrolyte imbalance—increased risk of VT and Vfib

B. Severe conduction disease (i.e., sick sinus syndrome)—risk of developing significant bradyarrhythmia after cardioversion

C. Risk of thromboembolism in patients with Afib for an indeterminate or prolonged period of time

IV. PROCEDURE

A. Technical considerations

1. Waveform types
   a. Monophasic
      i. Unipolar and delivers current in one direction through the heart
      ii. Standard in older model defibrillators
      iii. Requires higher energy levels to terminate arrhythmia
   b. Biphasic
      i. Bipolar nature allows for delivery of current in two directions through the myocardium with reversal of polarity during the return phase
      ii. Standard on most current and newly manufactured defibrillators
      iii. Allows fewer shocks to be given and a lower total energy with equal, and perhaps superior, efficacy
2. Electrodes
   a. Hand-held paddles
      i. Larger paddle size will decrease transthoracic resistance, increasing energy delivered to myocardium.
      ii. Increased pressure applied to chest with paddles will also decrease impedance and potentially improve efficacy of countershock.
      iii. Adequate layer of conductive gel must be applied—ultrasonographic gel is nonconductive.
   b. Self-adhesive pads
      i. Have become more common due to convenience and ease of use
      ii. Advantages: equally effective, no gel required, decrease contact with bed and patient during delivery of shock, minimizing risk to staff
      iii. If defibrillator has pacing capabilities, can allow for temporary external pacing

c. Anatomic placement
   i. Minimize impedance by avoiding breast tissue and clipping excessive body hair
   ii. Optimal placement—controversial
      (a) Anterior–lateral: Anterior pad/paddle on right infraclavicular chest and lateral pad/paddle located lateral to the left chest in a longitudinal orientation
      (b) Anterior–posterior: Anterior pad/paddle placed as before and posterior pad/paddle to the left of the spine at the level of the lower scapula
   iii. Biphasic waveform devices make positioning choice less of an issue

B. Patient preparation

1. Patients with urgent indications due to tachyarrhythmia, such as unconsciousness or hemodynamic instability, should have countershock urgently performed.
2. In the elective setting, the guidelines given below should be followed:
   a. Ensure NPO (*nil per os*) status for 6 to 8 hours to decrease risk of aspiration.
   b. Obtain informed consent.
   c. Follow universal protocol.
   d. Maintain constant heart rhythm monitoring and 12-lead ECG before and after countershock.
   e. Ensure adequate sedation with medications having a rapid onset of action and a short half-life, that is, a benzodiazepine, such as midazolam, and/or a narcotic agent, such as fentanyl.
   f. Continue further monitoring including frequent assessment of blood pressure and pulse oximetry—supplemental oxygen usually provided through nasal cannula.

C. Cardioversion procedure/using defibrillator

1. If QRS amplitude is low, optimize detection by changing leads—essential if *synchronized* cardioversion to be performed
2. Select "synchronization" function if cardioversion to be performed
3. Select initial energy appropriate for specific device and arrhythmia present on monitor
   a. Vfib, pulseless VT: monophasic, 360 J; biphasic, 120 to 200 J
   b. VT with pulse: monophasic, 100 J; biphasic, unknown
   c. Afib: monophasic, 100 to 200 J; biphasic, 100 to 120 J
   d. Atrial flutter: monophasic, 50 to 100 J; biphasic, unknown
4. Charge capacitor, clear the area, and then deliver shock
5. Be aware that many devices automatically default back to "unsynchronized" mode after shock is delivered
6. If no change in rhythm, escalate energy as appropriate and consider consulting a cardiologist or electrophysiology specialist.

D. Management of specific arrhythmias

1. Vfib and pulseless VT
   a. Important changes in the advanced cardiac life support (ACLS) algorithm for Vfib/pulsless VT in the 2005 guidelines published by the American Heart Association.
   b. No longer recommending delivery of three "stacked" shocks.
   c. Vasopressors (epinephrine or vasopressin) may be given before or after second shock and antiarrhythmic agents (lidocaine or amiodarone) may be considered before or after third shock.
   d. Emphasis is placed on timely delivery of adequate, uninterrupted cardiopulmonary resuscitation (CPR) between shocks.

e. CPR delivered in this manner (5 cycles of 30 compressions and 2 breaths per cycle or 2 minutes total) has been associated with improved success of defibrillation and potentially improved neurologic outcome.

2. Afib
   a. General overview
      i. Most common indication for cardioversion in general population.
      ii. Cardioversion in AFib should be performed in the hemodynamically unstable patient or under elective circumstances to attempt reversion to normal sinus rhythm.
      iii. Elective cardioversion for stable AFib may become less common.
      iv. Published data (Atrial Fibrillation Follow-up Investigation of Rhythm Management [AFFIRM] trial) has demonstrated that overall outcome may be more dependent on rate control and anticoagulation than on rhythm normalization.
   b. Anticoagulation
      i. Afib/flutter is associated with development of thrombus in left atrial appendage or cavity during or after cardioversion.
      ii. Risk of pericardioversion thromboembolism is 5.3% in patients not anticoagulated versus 0.8% in those who are anticoagulated.
      iii. Afib of 24- to 48-hour duration is unlikely to be associated with thromboembolism.
      iv. Two options in patients with Afib of longer or indeterminate duration:
         (a) Transesophageal echocardiogram (TEE)
            (1) If no thrombus is noted in left atrial appendage, cardioversion may be safely performed.
            (2) Anticoagulation with warfarin (goal international normalized ratio [INR] 2 to 3) should be provided for 4 weeks after cardioversion.
            (3) Time required for return of organized mechanical activity after cardioversion.
         (b) Defer cardioversion until the patient has been anticoagulated at therapeutic range for 3 to 4 weeks
            (1) Must, again, anticoagulate for a minimum of 4 weeks after cardioversion

V. POSTPROCEDURE CONSIDERATIONS

A. Complications

1. Thermal burns to the chest—risk may be decreased with biphasic waveform devices (lower total energy required).
2. Risk of thromboembolic events, particularly when cardioverting AFib or atrial flutter.
3. Countershocks can induce tachyarrhythmias and bradyarrhythmias.
4. Defibrillation in asystole should always be avoided because excessive vagal response may suppress intrinsic nodal activity.
   a. Always consider the possibility that Vfib with small-amplitude waves ("fine Vfib") may mimic asystole.
   b. Check more than one lead before assuming a diagnosis of asystole.
5. Depolarizing the myocardium may inhibit the recovery of ventricular escape beat and thereby lead to worsening intrinsic pacemaker failure in individuals with baseline conduction abnormalities.
6. Clinically significant myocardial damage from cardioversion or defibrillation is unlikely. Minimize risk further by delivering shocks no less than 1 minute apart.

7. Applying countershocks to patients with digoxin toxicity may be proarrhythmogenic. Check digoxin level and correct electrolytes before procedure to minimize this risk.

B. Special circumstances

1. Patients with implanted pacemakers and defibrillators
   - **a.** May undergo external cardioversion and defibrillation safely.
   - **b.** External energy delivery may alter programming of internal device.
   - **c.** Energy may also be conducted down an internal lead causing local myocardial injury or changing the devices functional thresholds.
   - **d.** Never place pads/paddles directly over the internal device.
   - **e.** Perform interrogation of device immediately after electric countershock delivery.
2. Cardioversion and defibrillation in pregnancy
   - **a.** Procedure has been performed in all trimesters without obvious fetal effects or induction of premature labor.
   - **b.** Consider fetal heart rhythm monitoring during cardioversion.
3. Accidental hypothermia
   - **a.** Ventricular arrhythmias and asystole may be refractory to conventional therapy until the patient has been rewarmed.
   - **b.** Cardiac arrest in this situation should be managed with an initial attempt at defibrillation and use of appropriate pharmacologic therapy.
   - **c.** If unsuccessful, aggressive rewarming should continue and further attempts at defibrillation held until the core temperature reaches 30°C to 32°C.
   - **d.** Optimal antiarrhythmic agent has not been determined.

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PERICARDIOCENTESIS

Dinesh Chandok and Dennis A. Tighe

6

I. GENERAL PRINCIPLES

A. Pericardiocentesis is an important and potentially life-saving procedure whereby a needle is inserted into the space between the visceral and parietal pericardium for the purpose of either sampling or draining pericardial fluid.

B. Diagnostic versus therapeutic pericardiocentesis

1. Diagnostic pericardiocentesis is performed to obtain small amounts of pericardial fluid for culture, cytologic study, or other fluid analyses.
2. Therapeutic pericardiocentesis is intended to drain fluid from the pericardial space to relieve pressure that limits diastolic filling.
3. Diagnostic and therapeutic pericardiocenteses are best performed electively, under controlled circumstances, with echocardiographic or fluoroscopic support.
4. In contrast, in the management of a patient with severe hemodynamic compromise, pericardiocentesis should be performed on an emergency basis.

C. Pericardial anatomy. Normally, only 15 to 50 mL of clear fluid is present in the pericardial space, with a composition similar to that of plasma ultrafiltrate.

1. Visceral pericardium is composed of a single layer of mesothelial cells covering the myocardium and is loosely adherent to the underlying muscle by a network of blood vessels, lymphatics, and connective tissue.
2. Parietal pericardium is composed of a thick layer of fibrous connective tissue surrounding another mesothelial monolayer. This fibrous capsule is relatively nondistensible.

D. Diseases affecting the pericardium

1. Several disease states may lead to inflammation of the pericardium and subsequent fluid accumulation including infections, malignancies, certain rheumatologic disorders, uremia, myocardial infarction, and myocardial rupture.
2. The composition of the fluid may become exudative, purulent, or frank blood, depending on the underlying cause.

E. Cardiac tamponade. Abrupt accumulation of fluid of 250 mL or less may lead to the clinical signs and symptoms of tamponade with equalization of pressures in all four cardiac chambers due to the relative noncompliance of the parietal pericardium. However with slowly developing effusions, the parietal pericardium is able to stretch and significantly larger amounts of fluid (sometimes >2 L) may accumulate without hemodynamic compromise. Three other clinical conditions promote hemodyanamic compromise, even in the absence of large pericardial effusion: intrasvascular volume depletion, impaired ventricular systolic function, and ventricular hypertrophy with decreased elasticity of the myocardium (diastolic dysfunction).

II. PROCEDURE

A. General considerations

1. In the patient with tamponade physiology, the treatment is drainage of the pericardial fluid. While awaiting performance of pericardiocentesis,

some authors recommend medical treatment with volume infusion and, if needed, use of inotropic agents and vasoactive drugs. Medical treatment should be viewed as only a temporizing measure. It should be cautioned that aggressive fluid resuscitation may actually worsen the hemodynamic picture by intensifying the ventricular interactions and likely proves beneficial only to those patients who are hypovolemic. Administration of diuretics is contraindicated. Mechanical ventilation should be avoided as it may further depress cardiac output.

2. If time allows, a coagulation profile should be checked and corrected.
3. The authors recommend performing right heart catheterization whenever possible to measure pressures before and after pericardiocentesis.

B. Material preparation

1. *Site preparation*: 2% chlorhexidine gluconate and 70% isopropyl alcohol combination solution or equivalent (10% providone-iodine solution is used only when there is a sensitivity to the chlorhexidine), large sterile drape, sterile gowns and gloves, masks and caps; 1% lidocaine (without epinephrine), atropine, and code cart to bedside
2. *Procedure*: a pericardiocentesis kit or an 18-gauge, 8-cm thin-walled needle with blunt tip; number 11 blade; multiple syringes (20 to 60 mL); electrocardiograph (ECG); hemostat; sterile alligator clip; specimen collection tubes; and pericardial drain if indicated
3. *Post procedure*: sterile gauze, dressings, and sutures

C. Patient preparation

1. The universal protocol should be followed and maximum barrier precautions should be utilized.
2. The patient should be placed in a comfortable supine position with the head of the bed elevated to approximately 45 degrees or more.
3. The fully upright position may be necessary for extremely dyspneic patients. This position allows free-flowing effusions to collect inferiorly and anteriorly where they are most accessible through a subxiphoid approach.

D. Pericardiocentesis procedure

1. Previously, pericardiocentesis was performed blindly or guided by ECG needle-tip monitoring. At present, pericardiocentesis should be performed under imaging guidance. The primary imaging modality used currently is bedside echocardiography to determine the location of the fluid, the presence of loculations, and the most accessible entry site into the pericardial space.
2. In general, the distance between the skin and the parietal pericardium is approximately 6.0 to 7.5 cm. The distance may be greater in obese patients or those with a protuberant abdomen.
3. The clinician should attach the needle to a 10-mL syringe, approximately half-filled with 1% lidocaine. This technique permits delivery of anesthesia to the subcutaneous tissues and pericardium during needle entry while allowing sufficient space in the syringe for withdrawal of pericardial fluid.

E. Needle entry site selection

1. Inspect and palpate to locate the xiphoid process and the left costal margin.
2. The needle entry site should be 0.5 cm lateral to the left border of the xiphoid process and 1.0 cm inferior to the costal margin.
3. The pericardial space may be entered at various points along the anterior thorax as guided by echocardiography, generally choosing the shortest distance between the skin and the fluid in the pericardial space. The subxiphoid approach is preferred in an emergency situation.

F. Site preparation

1. Strict sterile technique should be followed at all times. A wide area of the skin in the xiphoid region is prepared with a 2% chlorhexidine gluconate in 70% isopropyl alcohol combination solution (or equivalent) and the area is draped with a large fenestrated sterile drape.

2. The skin is anesthetized with 1% lidocaine without epinephrine.
3. A small skin incision is made at the entry site with a scalpel to facilitate the insertion of the blunt needle through the skin; the pericardiocentesis needle does not have a beveled edge to minimize the risk of myocardial puncture.

G. Needle insertion

1. When passing through the skin, the angle of entry should be 45 degrees. Direct the needle superiorly, aiming toward the patient's left shoulder.
2. Draw back on the plunger of the syringe while advancing the needle and before injecting the anesthetic agent.
3. The posterior edge of the bony thorax is usually only 1.0 to 2.5 cm below the skin, but this distance may be greater in obese patients. If the bony thorax is contacted during needle entry, reposition the needle so that it may be advanced under the costal margin.
4. Once the needle tip has passed beyond the posterior border of the bony thorax, the angle between the needle and the skin should be reduced to approximately 15 degrees. This angle of entry should be maintained while the needle is directed toward the left shoulder.

H. Needle advancement

1. Move the needle only in a straight trajectory from front to back. Moving the needle side to side may injure epicardial blood vessels and lymphatics.
2. Aspirate while advancing the needle. Pause to inject the subcutaneous tissues with lidocaine at periodic intervals.
3. A "give" will be felt on entry into the pericardial space and as fluid is aspirated (usually 6 to 7.5 cm from the skin).
4. A vasovagal response can occur when the pericardium is breached. Intravenous atropine or saline infusion may be required to reverse bradycardia and hypotension.
5. Observe the surface ECG monitor while advancing. The occurrence of frequent premature ventricular contractions may indicate myocardial contact. In this situation, the needle should be withdrawn slightly and repositioned.

I. Fluid evacuation. A large-volume pericardial effusion may be evacuated by attaching a 50-mL syringe to the pericardiocentesis needle with repeated aspirations. In general, we do not recommend this technique because manipulation of the needle during repeated attempts may cause trauma to the myocardium or frank rupture. The recommended approach is placement of a pericardial drain. To accomplish this, a multilumenal pigtail-type catheter is introduced over a guidewire, as in the Seldinger technique, into the pericardial space and connected to a drainage bag.

J. Tamponade. If the procedure was performed to relieve tamponade, the patient's hemodynamic status should improve promptly. Such improvement may be observed after the evacuation of as little as 50 to 100 mL of fluid. Clinical signs that indicate relief of tamponade include an increase in systemic blood pressure and cardiac output with a concomitant fall in right atrial pressure and resolution of pulsus paradoxus.

III. POSTPROCEDURE CONSIDERATIONS

A. Monitoring. After pericardiocentesis, close monitoring is required to gauge the rate of pericardial effusion reaccumulation and the potential return of tamponade.

B. Chest radiograph. All patients should have an end-expiratory chest radiograph immediately following the procedure to detect the presence of a pneumothorax.

C. A transthoracic echocardiogram should be obtained within several hours of the pericardiocentesis to confirm adequacy of pericardial drainage and at periodic intervals thereafter as indicated clinically.

D. **Potential complications.** Cardiac puncture with or without hemopericardium or myocardial infarction; pneumothorax; ventricular arrhythmias; bradycardia; injury to adjacent abdominal organs; cardiac arrest; coronary artery laceration; infection; fistula formation; pulmonary edema.

E. **Complications are most likely when the effusion is small (<250 mL), located posteriorly, loculated, or if the maximum anterior pericardial space is <10 mm as determined by echocardiography.**

F. **An unguided attempt at pericardiocentesis,** as performed under emergency conditions, is also associated with higher complication rates.

G. **Pericardial fluid samples should be sent to appropriate laboratories for analysis.**

H. **Diagnostic studies may include** white blood cell count with differential; hematocrit; glucose, total protein, lactate dehydrogenase; Gram stain and culture for bacteria, fungi, and acid-fast bacilli; cytology; amylase; cholesterol; antinuclear antibody and rheumatoid factor; adenosine deaminase, total complement; C3; and rarely in selected cases specific viral or parasite studies.

I. **Pericardial drain removal.** The pericardial drain should be removed when the total output from it is <50 mL/day.

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THE INTRA-AORTIC BALLOON AND COUNTERPULSATION

7

Robert C. Steppacher and Bruce S. Cutler

I. GENERAL PRINCIPLES

A. The intra-aortic balloon pump (IABP) is designed to assist an ischemic ventricle through improvement in coronary artery perfusion and reduction in systemic afterload by counterpulsation.

B. Counterpulsation increases myocardial oxygen supply by diastolic augmentation of coronary perfusion, and decreases myocardial oxygen requirements through afterload reduction.

II. INDICATIONS

A. Cardiogenic shock. The intra-aortic balloon (IAB) was developed with the hope of reversing cardiogenic shock after myocardial infarction. Counterpulsation should be initiated as soon as it is determined that the shock state is not responsive to intravascular volume manipulation and drug therapy. The ideal candidate for IAB placement should have a reversible anatomic or functional derangement responsible for the shock state.

B. Reversible mechanical defects. Counterpulsation is effective in the initial stabilization of patients with mechanical intracardiac defects complicating myocardial infarction, such as acute mitral regurgitation and ventricular septal perforation, while preparations for definitive treatment are under way.

C. Unstable angina. Counterpulsation is indicated for ongoing myocardial ischemia in the face of maximal medical therapy.

D. Weaning from cardiopulmonary bypass.

E. Preoperative use. In high-risk patients such as those with critical stenosis of coronary arteries or severely depressed left ventricular function.

F. Bridge to transplantation. Provide mechanical support for patients in congestive heart failure who are awaiting cardiac transplantation.

G. Other indications. Control unstable angina before and during coronary angioplasty and atherectomy. Counterpulsation may be lifesaving after a failed angioplasty, to support the myocardium until emergency aortocoronary revascularization can be performed. The IAB has also been used during interhospital transfers of unstable patients, for treatment of heart failure after myocardial trauma, and for perioperative support for high-risk noncardiac surgery.

III. CONTRAINDICATIONS

A. Absolute contraindications

1. Aortic valvular insufficiency
2. Aortic dissection
3. Severe aortoiliac disease
4. Thoracic aortic aneurysm

B. Relative contraindications

1. Gastrointestinal bleeding
2. Thrombocytopenia
3. Other bleeding diathesis

4. Abdominal aortic aneurysm
5. Presence of a vascular graft

C. Contraindications to sheathless insertion

1. Morbid obesity
2. Scarring at puncture site

IV. PROCEDURE

A. Equipment

1. IABs are available in various sizes, with different balloon volumes and catheter diameters (Table 7-1). The catheter itself has two concentric lumina. The central lumen is used to pass a guidewire during insertion and to monitor central aortic pressure. The outer lumen is the passageway for gas exchange and is connected to a console that controls balloon operation as well as having a monitoring function. Helium is used as the driving gas.
2. Required equipment
   a. A manufacturer-supplied sterile insertion kit
   b. Portable fluoroscope or transesophageal echocardiography (TEE)
   c. Chlorhexidine prep solution, sterile drapes, gown, gloves, cap, and mask
   d. 1% Lidocaine with syringe and fine gauge, 1.5-in. needle
   e. Sterile gauze pads
   f. No. 11 scalpel
   g. Dilute heparin solution (10,000 units in 500 mL of 0.9% saline)
   h. Fixation device, either suture or Stat-Lock©
   i. Heparin 10,000 units drawn into 10-mL syringe
   j. Pressure monitoring line

B. Technique

1. Universal precautions should be followed.
2. After careful assessment of the patient, the side with the best circulation is chosen for IAB insertion. The procedure should be performed with the patient supine on a bed or table that permits the use of fluoroscopy. Both inguinal areas are prepared and draped in a sterile manner. Maximum barrier precautions are used. The instructions for preparing the IAB should be followed closely as the technique varies with the manufacturer.
3. Lidocaine (1%) is instilled subcutaneously and subdermally over the femoral artery pulse. The puncture site should be in the common femoral artery, 1 cm below the inguinal ligament, directly over the femoral pulsation (Fig. 7-1).

TABLE 7-1 Commercially Available Intra-Aortic Balloon (IAB) Sizes

Manufacturer	Trade name	Sheath size (Fr)	Guidewire (in.)	Balloon volumes (mL)
Datascope	Sensation	7	0.018	34, 40
Datascope	Linear	7.5	0.025	25, 34, 40
Datascope	Fidelity	8	0.025	25, 34, 40
Datascope	True Sheathless	9.5	0.030	34, 40
Datascope	Percor Stat-DL©	10.5	0.030	50
Arrow	FiberOptix™	7.5 or 8	0.025	30, 40
Arrow	UltraFlex™	7.5	0.025	30, 40
Arrow	Ultra 8®	8	0.025	30, 40
Arrow	NarrowFlex®	8	0.030	30, 40
Abiomed	iPulse™	8	0.025	40

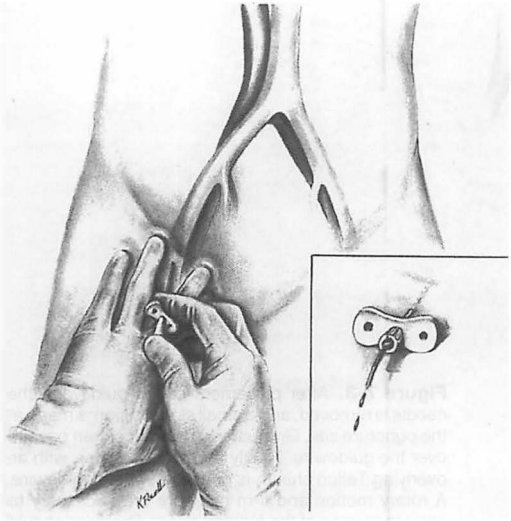

Figure 7-1. The arterial access needle is inserted at a 45-degree angle into the common femoral artery at the level of the inguinal ligament. Inset: Pulsatile jet of blood indicates that the needle is properly located in the center of the arterial lumen.

4. After cannulation of the artery, a J-guidewire is advanced under fluoroscopy until the tip is in the thoracic aorta (Fig. 7-2). At this point, the patient should be intravenously anticoagulated with 80 units/kg of heparin.
5. A small incision is made at the puncture site to allow passage of graduated dilators. After the largest dilator with an overlying Teflon sheath has been

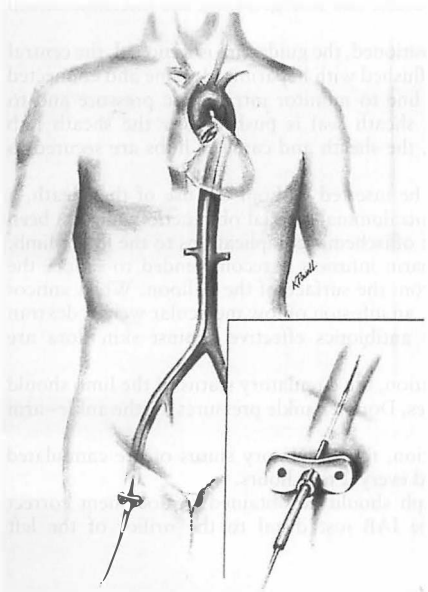

Figure 7-2. When the arterial access needle is properly placed in the artery (inset) the guidewire is advanced under fluoroscopic control until the tip is in the thoracic aorta.

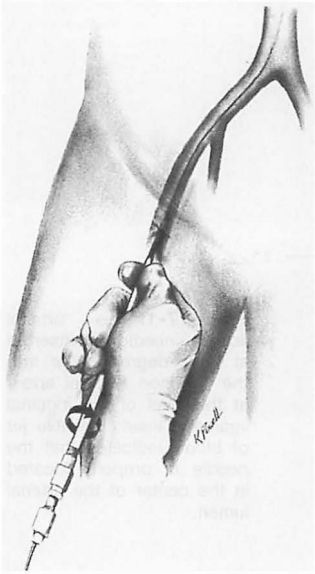

Figure 7-3. After placement of the guidewire, the needle is removed, and a small skin incision is made at the puncture site. Graduated dilators are then passed over the guidewire. Finally the largest dilator, with an overlying Teflon sheath is passed over the guidewire. A rotary motion and firm pressure are necessary to enter the lumen of the femoral artery. Pressure should be maintained over the insertion site during catheter exchanges to prevent hematoma formation.

passed over the guidewire, the dilator is removed, leaving the guidewire in place. A one-way valve prevents black bleeding (Fig. 7-3).

6. The IAB is advanced over the guidewire, through the sheath, so that its radiopaque tip is positioned 2 cm distal to the ostium of the left subclavian artery (Fig. 7-4).
7. The balloon catheter must be inserted to the level of the double line to be sure that the entire membrane has emerged from the insertion sheath (Fig. 7-4).
8. When the IAB is properly positioned, the guidewire is removed, the central lumen is aspirated and then flushed with heparinized saline and connected to the pressure monitoring line to monitor intra-aortic pressure and to time counterpulsation. The sheath seal is pushed over the sheath hub to control bleeding. Finally, the sheath and catheter hubs are secured to the skin.
9. Alternatively, the IAB may be inserted without the use of the sheath, a technique that reduces the intraluminal arterial obstruction and has been reported to decrease the risk of ischemic complications to the lower limb.
10. Anticoagulation with a heparin infusion is recommended to reduce the risk of thromboembolism from the surface of the balloon. When anticoagulation is contraindicated, an infusion of low molecular weight dextran may be used. Prophylactic antibiotics effective against skin flora are recommended.
11. As soon as the IAB is in position, the circulatory status of the limb should be checked by assessing pulses, Doppler ankle pressures, or the ankle–arm index.
12. While the device is in position, the circulatory status of the cannulated extremity must be monitored every 2 to 4 hours.
13. A portable supine radiograph should be obtained to document correct placement of the tip of the IAB just distal to the orifice of the left subclavian artery.

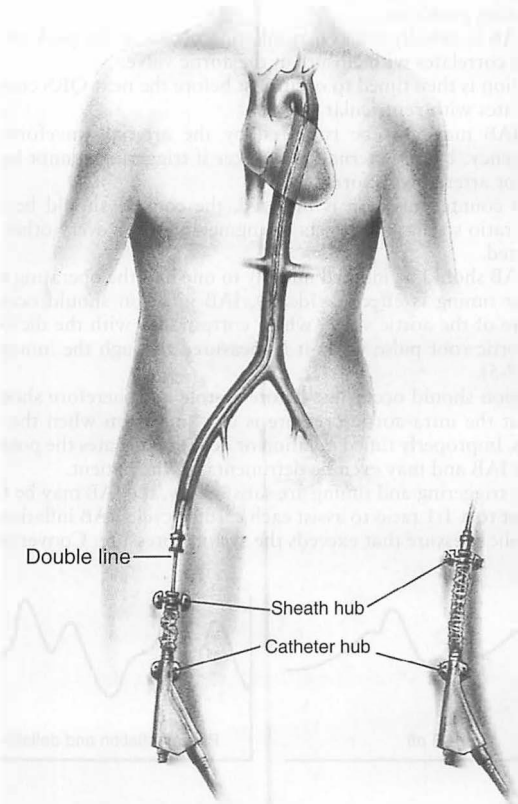

Figure 7-4. The tip of the intra-aortic balloon is positioned 2 cm distal to the orifice of the left subclavian artery. The balloon must be inserted to the level of the double line on the balloon catheter to be sure that the entire membrane has emerged from the sheath. Inset: The sheath seal is pushed over the sheath hub to control bleeding. The sheath and catheter hubs are sutured in place.

V. POSTPROCEDURE CONSIDERATIONS

A. Assess for acute limb ischemia

1. Acute limb ischemia may occur any time after initiation of counterpulsation, but is most likely to occur immediately after IAB placement. Initial management is conservative if the ischemia is mild, but severe ischemia requires prompt treatment, which may involve removal and replacement of the IAB at another site or even a vascular bypass procedure in IAB-dependent patients.

B. Assess triggering and timing of the IABP

1. Proper timing of the inflation–deflation cycle of the balloon is crucial to the optimal functioning of the IABP.
2. The R wave of the patient's electrocardiogram (ECG) is the most common means of triggering balloon deflation. It is therefore important to select

the lead with the most pronounced R wave to minimize the likelihood of triggering problems.

3. The IAB is initially set so that inflation occurs at the peak of the T wave, which correlates with closure of the aortic valve.
4. Deflation is then timed to occur just before the next QRS complex, which correlates with ventricular systole.
5. The IAB may also be triggered by the arterial waveform, or, in an emergency, by an external pacemaker if triggering cannot be effected by ECG or arterial waveform.
6. When counterpulsation is initiated, the console should be set to a 1:2 assist ratio so that the effects of augmentation on every other beat can be analyzed.
7. The IAB should be inflated initially to one half the operating volume until proper timing is effected. Ideally, IAB inflation should occur just after closure of the aortic valve, which corresponds with the dicrotic notch of the aortic root pulse when it is measured through the lumen of the IAB (Fig. 7-5).
8. Deflation should occur just before systole and therefore should be timed so that the intra-aortic pressure is at a minimum when the aortic valve opens. Improperly timed inflation or deflation negates the potential benefit of the IAB and may even be detrimental to the patient.
9. When triggering and timing are satisfactory, the IAB may be fully inflated and set to a 1:1 ratio to assist each cardiac cycle. IAB inflation results in a diastolic pressure that exceeds the systolic pressure. Conversely, deflation

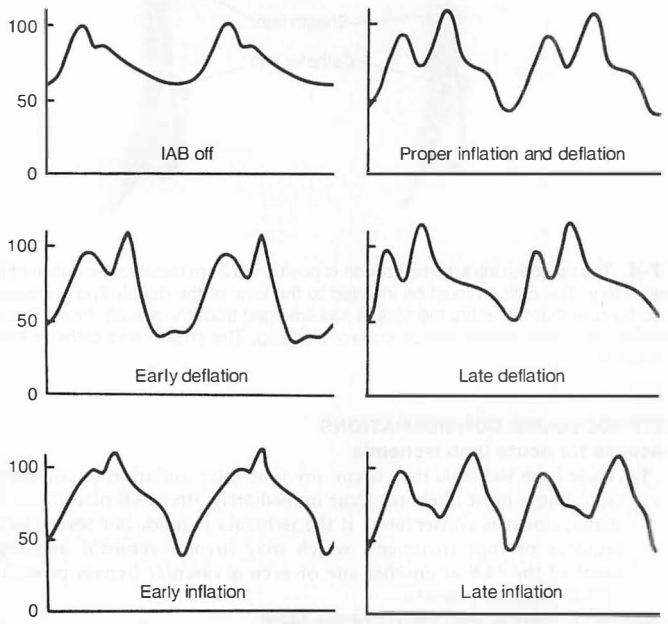

Figure 7-5. Arterial waveforms demonstrating proper and improper timing of the IAB pump. Adjustments for timing of inflation and deflation during the cardiac cycle, may be made on the pump console.

of the balloon reduces end-diastolic pressure by 15 to 20 mm Hg and systolic pressure by 5 to 10 mm Hg.

10. Timing should be rechecked every 1 to 2 hours or when there is a change in triggering mode or in the patient's clinical status.
11. Some of the functions monitored by the IAB console include the volume and pressure in the IAB, the presence of gas leaks, the loss of ECG or arterial trigger signal, and improper deflation of the IAB.

C. Weaning from counterpulsation

1. Cessation of counterpulsation involves two steps: weaning and IAB removal.
2. The patient may be weaned by progressively reducing the assist ratio or IAB volume. Usually, a period of 1 to 2 hours is required to establish stability at each new assist level. When the patient has been weaned to 1:3 and has been stable, the IAB may be removed.
3. The heparin infusion should be stopped 2 hours before IAB removal.
4. The operator should not attempt to withdraw the balloon into the sheath. Instead, the IAB and sheath are removed as a unit, and prolonged pressure (30 to 40 minutes) is applied to the arteriotomy site, which is typically 2 to 3 cm proximal to the puncture site. The use of sandbags is not recommended. Rarely, surgical management is required to control ongoing bleeding from the insertion site.
5. If any resistance is felt during removal, surgical consultation is advised.

D. Complications of counterpulsation

1. The overall complication rate for percutaneous IAB is approximately 5%.
2. Complications during insertion:
   a. The most common complication related to insertion is failure of the IAB to pass the ileofemoral system because of atherosclerotic occlusive disease. The reported failure rate is 5% to 7%.
   b. Other, more serious complications of IABP insertion include aortic dissection and arterial perforation, with a reported incidence of 1% to 2%.
   c. Arterial perforation is an acute emergency requiring urgent surgical treatment
3. Complications during IAB therapy:
   a. Limb ischemia is the most common complication of counterpulsation and is sufficiently severe to require removal of the IAB in 6% of patients. Several large reviews report that the most important risk factors for limb ischemia are female gender, insulin-dependent diabetes, age older than 75 years, and significant peripheral vascular occlusive disease.
   b. Infection, thrombocytopenia, and embolization of platelet aggregates or atherosclerotic debris have been reported.
   c. Rupture of the IAB occurs in 2% of patients and may cause gas embolization. Blood in the connecting tubing is the hallmark of rupture. Its presence requires immediate cessation of counterpulsation, placement of the patient in Trendelenburg position, and prompt removal of the IAB.
   d. IAB rupture may trap a thrombus within the balloon lumen, preventing percutaneous removal.
4. Complications during or after removal:
   a. Arterial perfusion of the limb should be checked after hemostasis at the puncture site and IAB removal by palpation of pedal pulses and measurement of the ankle–brachial index.
   b. The puncture site should be examined for hematoma, false aneurysm formation, and arteriovenous fistula for several hours.

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CHEST TUBE INSERTION AND CARE

Gustavo G. Angaramo

8

I. GENERAL PRINCIPLES. Chest tube insertion (tube thoracostomy) involves the placement of a sterile tube into the pleural space to evacuate air or fluid into a closed collection system to restore negative intrathoracic pressure, promote lung expansion, and prevent lethal levels of pressure from developing in the thorax.

II. ANATOMY AND PHYSIOLOGY OF THE PLEURAL SPACE

A. The pleural space is a closed, serous sac surrounded by two separate layers of mesothelial cells, the parietal and visceral pleura. Normally there is a negative intrapleural pressure of −2 to −5 cm of water.

B. The pleural layers are in close apposition and under normal physiologic conditions allow free expansion of the lung in a lubricated environment.

III. INDICATIONS

A. Pneumothorax

1. Accumulation of air in the pleural space is the most common indication for chest tube placement.

2. Diagnosis is often confirmed by chest radiography.

3. The risk of a recurrent ipsilateral spontaneous pneumothorax is as high as 50% and the risk of a third episode is 60% to 80%.

B. Hemothorax

1. Accumulation of blood in the pleural space can be classified as spontaneous, iatrogenic, or traumatic.

C. Empyema

1. Empyemas are pyogenic infections of the pleural space that may result from:

a. Necrotizing pneumonia

b. Septic pulmonary emboli

c. Spread of intra-abdominal infections

d. Inadequate drainage of a traumatic hemothorax

D. Pleural effusion

1. Treatment of transudative pleural effusions is aimed at controlling the underlying cause (congestive heart failure, nephrotic syndrome, and cirrhosis). Tube thoracostomy is uncommonly indicated.

2. Exudative effusions, however, often require tube drainage depending on whether the fluid is free or loculated.

IV. CONTRAINDICATIONS

A. There are no absolute contraindications to chest tube insertion.

B. There are many *relative* contraindications:

1. Anticoagulation

2. Prior ipsilateral thoracic surgery due to potential adhesions between the lung and the chest wall

3. Extensive bullous lung disease

V. PROCEDURE

A. Preparation

1. Follow universal protocol.
2. Sterile technique including maximum barrier precautions is mandatory whether the procedure is performed in the operating room, the intensive care unit, or the emergency room.
3. Obtain a detailed informed consent.
4. Careful titration of parenteral opioids or benzodiazepines (if necessary) and injection of a local anesthetic to provide a relatively painless procedure.
5. Standard large-bore drainage tubes are made of either Silastic or rubber:
   a. Rubber tubes elicit more pleural inflammation, have fewer drainage holes, and are not easily identified on chest radiograph.
   b. Silastic chest tubes are either right angled or straight, have multiple holes, and contain a radiopaque stripe with a gap to mark the most proximal drainage holes.
   c. Sizes are available from 6 to 40 Fr, with size selection dependent on the patient population and the type of collection being drained.

B. Technique

1. To properly insert a chest tube, the following steps are suggested:
   a. Examine the x-ray carefully.
   b. Gather all the necessary equipment:
      i. A scalpel
      ii. Two Kelly clamps
      iii. A suture
      iv. Local anesthesia (10 mL of 1% lidocaine)
      v. Needles (25-gauge for the skin and a 22-gauge for deeper layers)
      vi. Syringes (10 mL), dressings, tape, and a filled drainage apparatus (Pleur-Evac)
   c. **Prepare the patient**
      i. Follow the universal protocol. Position the patient with the operative side up, in the lateral decubitus position.
      ii. Mark the fourth or fifth intercostal space in the anterior axillary line by landmarks (chest tubes are occasionally inserted in the second intercostal space for pneumothoraces only!) (Fig. 8-1).
   d. **Prepare and drape the surgical site**
      i. The area is prepared under sterile conditions with 10% povidone-iodine solution.
      ii. The area is draped to include the ipsilateral nipple as a landmark.
   e. **Anesthetize the area**
      i. Include the skin over the incision site, periosteum above and below ribs, and the pleura.
      ii. Use 10 mL of 1% lidocaine, but have a syringe full in reserve if the patient needs supplementary medication during the procedure.
      iii. Tunnel the chest tube slightly to avoid air leak on removal. Therefore, the actual entry point into the pleura will not be directly under the skin incision.
   f. **Make a skin incision**
      i. This should be no larger than the index finger (2 cm) because this is the actual "instrument" that will insert into the chest.
   g. **Make the subcutaneous tunnel**
      i. This should be done with ***spreading*** motions, only using a Kelly clamp.
      ii. *Do not cut any tissue.* This will greatly decrease bleeding and will make a tract that will collapse on tube removal and seal off.

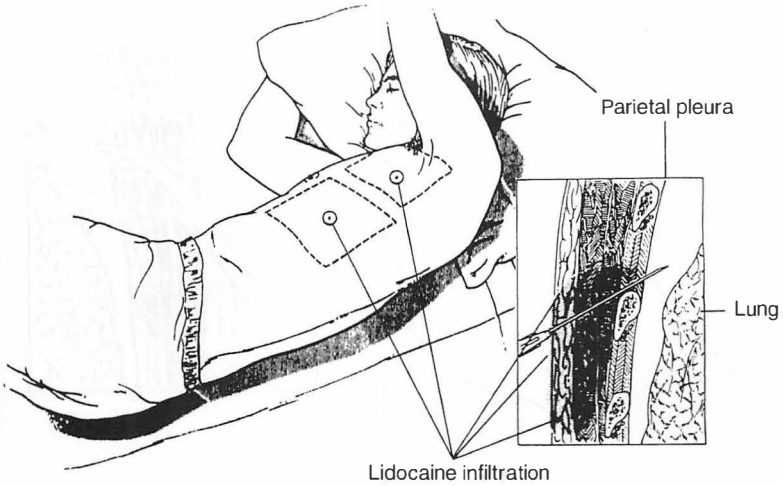

Figure 8-1. Proper patient positioning for chest tube insertion. (From Lancey RA. Chest tube insertion and care. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2008, with permission.)

iii. Spread along the interspace, going posteriorly for approximately 2 to 3 cm. This will place the tube in the posterior–superior direction, which will drain air and fluid well.

h. Enter the pleural space

i. Using the tips of a Kelly clamp closed, holding the body of the clamp with two hands, preventing uncontrolled entry and possible damage to underlying structures.

ii. Once entered, spread the pleura with the tips of the clamp and do not insert the clamp into the chest (Fig. 8-2A).

i. Digitally explore the pleural space

i. A finger is inserted into the pleural space to explore the anatomy and confirm proper location and lack of pleural symphysis (Fig. 8-2B).

ii. If the space is not free, ***do not insert the tube***. Suture the skin hole closed. The lung will not collapse if the lung and pleura are adherent to the chest wall!

j. Insert the tube

i. The easiest way to do this is to have the tip of the tube clamped in the Kelly clamp.

ii. Push the Kelly clamp and the tip of the chest tube into the pleural space, release the clamp, and continue inserting the tube.

iii. Direct the tube posteriorly and superiorly (Fig. 8-3A and 8-3B).

iv. The location of the tube should be confirmed by observing flow of air (seen as condensation within the tube) or fluid from the tube.

v. Suture the tube to the skin to avoid slippage. *Be sure that all the holes are into the chest.*

vi. The suture is left long around the tube.

vii. To seal the tunnel, the suture is tied when the tube is pulled out (Fig. 8-4).

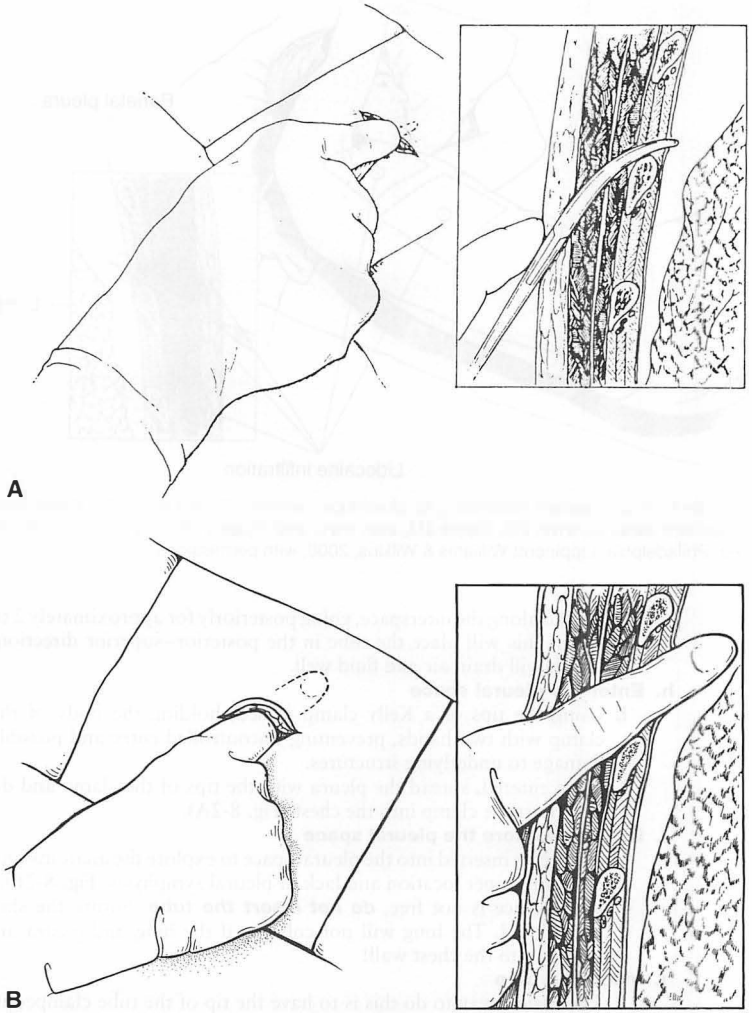

Figure 8-2. **A:** Enter the pleural space. **B:** Digitally explore the pleural space. (From Laney RA. Chest tube insertion and care. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2008, with permission.)

k. Connect to the Pleur-Evac

i. *Do not evacuate more than 1,000 mL of fluid at a time.*

ii. In a case of a massive hemothorax or effusion, allow the lung to re-expand for approximately 15 to 30 minutes before taking off another 1,000 mL maximum.

iii. Re-expansion pulmonary edema (*ex vacuo*) is a real and dangerous phenomenon.

l. Order a chest radiograph.

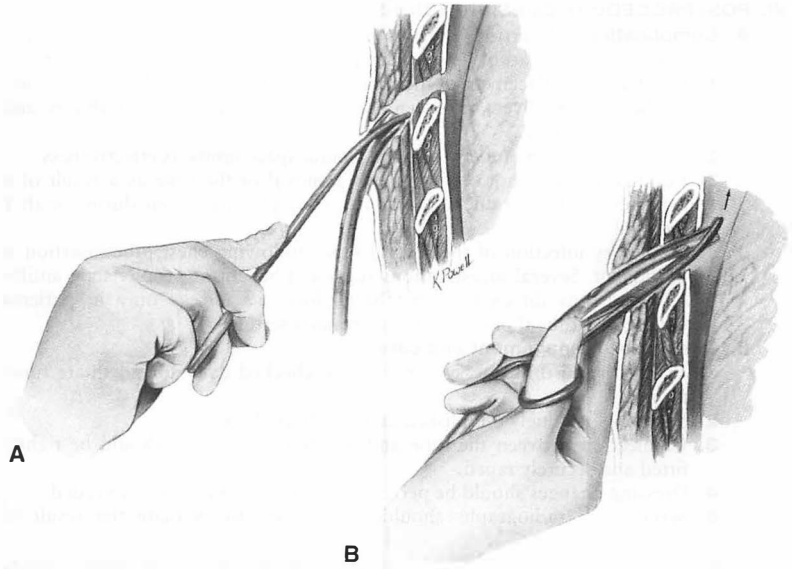

Figure 8-3. **A:** The end of the chest tube is grasped with a Kelly clamp and guided through the chest incision. **B:** The chest tube is oriented toward the apex. (From Lancey RA. Chest tube insertion and care. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2008, with permission.)

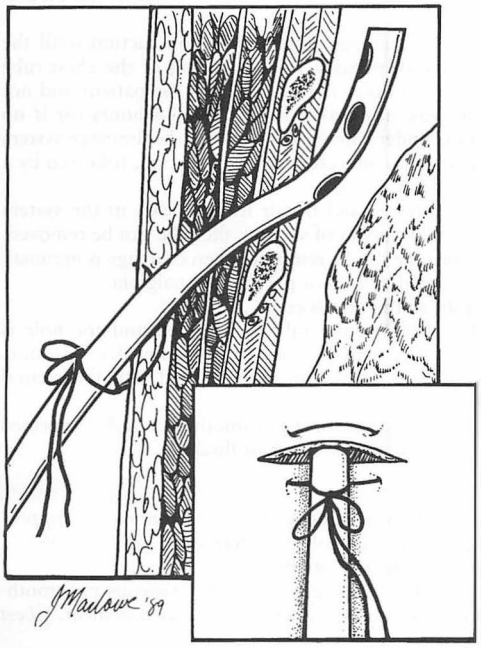

Figure 8-4. The tube is securely sutured to the skin with a 1-0 or 2-0 silk suture. The suture is left long, wrapped around the tube. To seal the tunnel, the suture is tied when the tube is pulled out. (From Lancey RA. Chest tube insertion and care. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2008, with permission.)

VI. POSTPROCEDURE CONSIDERATIONS

A. Complications. Insertion alone is usually accompanied by a 1% to 2% incidence of complications, even when performed by experienced personnel:

1. Unintentional placement of the tube through the intercostals vessels or into the lung, heart, liver, or spleen can result in considerable morbidity and possible mortality.
2. Malposition of the tube within the pleural space limits its effectiveness.
3. Residual pneumothorax may follow removal of the tube as a result of a persistent air leak or due to entry of air through the tube site during or after removal.
4. Secondary infection of the pleural space following chest tube insertion is infrequent. Several investigations suggested benefit of prophylactic antibiotic regimens directed against *Staphylococcus aureus* only in patients undergoing tube thoracostomy in a trauma setting.

B. Chest tube management and care

1. The tube and drainage system must be checked daily for adequate functioning.
2. Suction is routinely established at 15 to 20 cm H_2O.
3. Connection between the tube and the drainage system should be tightly fitted and securely taped.
4. Dressing changes should be performed every 2 to 3 days or as needed.
5. Serial chest radiographs should be obtained to evaluate the result of drainage.
6. Chest tubes can be pulled back but not *readvanced* into the pleural space, and if a tube is to be replaced, it should always be at a different site rather than the same hole.

C. Chest tube removal

1. Indications for removal of chest tubes include:
   a. Resolution of the pneumothorax or fluid accumulation in the pleural space, or both.
   b. For a pneumothorax, the drainage system is left on suction until the air leak stops. If an air leak persists, brief clamping of the chest tube can be performed to confirm that the leak is from the patient and not the system. When the leak has ceased for >24 to 48 hours (or if no fluctuation is seen in the underwater seal chamber), the drainage system is placed on water seal by disconnecting the wall suction, followed by a chest film several hours later.
   c. If no pneumothorax is present and no air leak appears in the system with coughing and reestablishment of suction, the tube can be removed.
   d. For fluid collections, the tube can be removed when drainage is minimal.
2. Tube removal is often preceded by oral or parenteral analgesia.
3. The suture holding the tube to the skin is cut.
4. As the patient takes deep breaths, the tube is removed and the hole is simultaneously covered with petrolatum gauze dressing at peak inspiration, at which point only positive pressure can be generated into the pleural space.
5. A chest x-ray is performed to check for a pneumothorax and is repeated 24 hours later to rule out accumulation of air or fluid.

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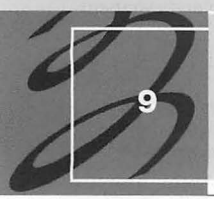

9 BRONCHOSCOPY

Oren P. Schaefer and Richard S. Irwin

I. GENERAL PRINCIPLES

A. Definition. The endoscopic examination of the bronchial tree.

B. Can be performed with either flexible or rigid bronchoscope.

C. Compared with rigid bronchoscopy, flexible bronchoscopy (FB) is more comfortable and safer for the patient, allows visualization of the entire tracheobronchial tree, and does not require general anesthesia or an operating room.

II. DIAGNOSTIC INDICATIONS

A. Hemoptysis

1. To localize the bleeding site and diagnose its cause.
2. With active bleeding, the site and origin are disclosed in approximately 90%. The yield is 50% after bleeding stops.

B. Atelectasis. To rule out endobronchial obstruction by malignancy or foreign body; mucus plugging, however, is most common. Often, mucus plugging extends peripherally beyond visualization of the bronchoscope.

C. Diffuse parenchymal disease

1. Transbronchial lung biopsy and bronchoalveolar lavage (BAL) can offer information about parenchymal processes.
2. BAL is an aid in diagnosing opportunistic infections in the immunocompromised host.
3. Lung biopsy with fluoroscopy can improve localization and minimize pneumothorax.

D. Acute inhalation injury

1. To identify the anatomic level and severity of injury after smoke inhalation.
2. Upper airway obstruction may develop within 24 hours of inhalation injury.
3. Acute respiratory failure is more likely with mucosal change at segmental or lower levels.

E. Blunt chest trauma. To rule out airway fracture after blunt trauma, suggested by hemoptysis, lobar atelectasis, pneumomediastinum, or pneumothorax.

F. Assessment of intubation damage. To assess laryngeal or tracheal damage from endotracheal tubes.

G. Cultures

1. To identify organisms that colonize the respiratory tract when a patient is unable to expectorate sputum.
2. Protected specimen brush with quantitative culture improves accuracy of routine bronchoscopic culture.
3. Aspirates obtained from the bronchoscope in an unintubated patient are no more predictive than cultures obtained by expectorated sputum. Both are associated with high false-positive and false-negative rates.

H. Diagnosis of ventilator-associated pneumonia (VAP)

1. To provide a specimen for culture.
2. Purulent secretions surging from distal bronchi during exhalation may be predictive of VAP.
3. Recent data suggests BAL with quantitative culture, may be no more predictive than endotracheal aspirate with nonquantitative culture.

III. THERAPEUTIC INDICATIONS

- **A.** Excessive secretions/atelectasis
  - **1.** Lobar atelectasis not responding to chest physical therapy, incentive spirometry, and cough.
  - **2.** Instillation of *N*-acetylcysteine (NAC), surfactant, and recombinant DNase have been utilized to help liquefy inspissated mucus. No clinical trials clearly support their routine use.
- **B.** Foreign bodies
  - **1.** Rigid bronchoscopy is the procedure of choice to remove aspirated foreign bodies.
  - **2.** Devices are available to help remove foreign bodies with the flexible scope.
- **C.** Endotracheal intubation. The bronchoscope, used as an obturator, with an endotracheal tube passed over it, can help place the endotracheal tube transnasally or orally in patients with difficult airways.
- **D.** Hemoptysis
  - **1.** Endobronchial tamponade can stabilize the patient to allow for more definitive therapy.
    - **a.** Tamponade can be achieved with an inflated balloon-tipped catheter wedged in the lobar orifice.
  - **2.** Massive hemoptysis can be controlled with iced saline lavage.
- **E.** Central airway obstructing lesions. Consider laser photoresection or stenting of obstructing lesions of the larynx, trachea, and major bronchi.
- **F.** Closure of bronchopleural fistula
  - **1.** To visualize a proximal or localize a more distal bronchopleural fistula.
  - **2.** Materials injected through the bronchoscope may seal the fistula.
- **G.** Percutaneous bedside tracheostomy. When routinely used, bronchoscopic visualization during the procedure significantly decreases the complications associated with this procedure.

IV. COMPLICATIONS

- **A.** When performed by a trained specialist, routine FB is extremely safe.
- **B.** Mortality should not exceed 0.1%.
- **C.** Death results from excessive premedication or topical anesthesia, respiratory arrest from hemorrhage, laryngospasm, or bronchospasm, and cardiac arrest from acute myocardial infarction.
- **D.** Overall complication rate is <8.0%.
- **E.** Nonfatal complications: fever, pneumonia, vasovagal reactions, laryngospasm and bronchospasm, hypotension, cardiac arrhythmia, pneumothorax, anesthesia-related problems, and aphonia.

V. CONTRAINDICATIONS

- **A.** Poorly experienced physician
- **B.** Uncooperative patient
- **C.** Unable to maintain adequate oxygen tension
- **D.** Coagulopathy in patients from whom biopsy specimens (brush or forceps) will be taken
- **E.** Unstable cardiac patients
- **F.** Untreated, symptomatic asthmatic patients (FB has been rarely used to relieve mucoid obstruction in intubated patients with status asthmaticus)
- **G.** Severe, chronic obstructive pulmonary disease with associated hypercapnea (premedication, sedation, and supplemental oxygen must be used with caution)
- **H.** *Elevated* intracranial pressure (anesthetize using a combination of medications for cerebral protection, paralysis to prevent cough, and monitor to ensure adequate cerebral perfusion pressure)

VI. PROCEDURAL CONSIDERATIONS

A. Preprocedural

1. Presence of underlying disease such as asthma, cardiovascular disease, uremia, and bleeding diathesis should be assessed.
2. Presence of drug allergies or medication that interferes with coagulation should be assessed.
3. Has the patient had a chest radiograph, electrocardiogram, and assessment of oxygenation?
4. Has the patient fasted before the procedure?
5. Has informed consent for the procedure and moderate sedation been obtained?
6. Has premedication been ordered?
7. Does the patient have intravenous access?
8. Always perform a time-out and follow the universal protocol to verify the correct patient procedure.

B. Procedural

1. Local anesthesia is achieved by nebulized lidocaine and topical lidocaine jelly.
   a. Lidocaine is absorbed through mucous membranes, and significant, even toxic, blood levels can be reached after topical administration.
   b. Levels in the low therapeutic range are achieved if a total of <200 mg is used.
   c. Sudden change in mental status, hallucinations, seizures, increased sedation, or hypotension should suggest lidocaine toxicity.
   d. Methemoglobinemia has also been described with use of topical ester anesthetics. Use methylene blue to treat this complication.
2. Unintubated patients: transnasal or transoral passage of the bronchoscope
3. Intubated patients
   a. The bronchoscope is passed through a swivel adapter with a rubber diaphragm that prevents loss of the delivered tidal volume. Use a bite block to prevent damage to the bronchoscope.
   b. Consider the following before and during bronchoscopy
      i. Endotracheal tube 8 mm or greater internal diameter allows for delivery of adequate tidal volume and safe passage of adult size bronchoscope. The risk of damage to the bronchoscope increases with smaller tubes.
      ii. Positive end-expiratory pressure (PEEP) of 20 cm H_2O may develop with bronchoscopy, with the risk of barotrauma.
      iii. PEEP already being delivered should be discontinued.
      iv. Inspired oxygen concentration must be increased to 100%.
      v. Expired volumes should be constantly measured; tidal volume usually has to be increased by 40% to 50%.
      vi. Suctioning will decrease delivered tidal volume and should be minimized.
4. During bronchoscopy, continuous oxygen therapy, oximetry, electrocardiography, and blood pressure monitoring are necessary.

C. Postprocedural

1. Obtain a chest radiograph to rule out pneumothorax
   a. After transbronchial biopsy in the nonintubated patient
   b. After routine bronchoscopy in the intubated, mechanically ventilated patient
      i. Return the ventilated patient to preprocedure ventilator settings.
      ii. In unintubated patients, supplemental oxygen is continued for 4 hours.
      iii. Monitor frequent vital signs until the patient is stable for at least 2 hours.
      iv. Patients must not eat or drink until local anesthesia has worn off (approximately 1 to 2 hours).

v. Fever after the procedure is common due to release of cytokines; fever associated with shaking chills and lasting >24 hours raises concern for postbronchoscopy pneumonia.

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10 THORACENTESIS

Mark M. Wilson and Richard S. Irwin

I. GENERAL PRINCIPLES

A. Thoracentesis is the introduction of a needle, cannula, or trocar into the pleural space to remove accumulated fluid or air.

B. History (cough, dyspnea, or pleuritic chest pain) and examination (dullness to percussion, decreased breath sounds, and decreased tactile fremitus) suggest that an effusion is present.

C. Chest radiograph (CXR) or ultrasonographic examination is essential to confirm the clinical suspicion.

D. Analysis of pleural fluid yields clinically useful information in >90% of cases.

E. Thoracentesis may be performed for diagnostic (generally 50 to 100 mL) or therapeutic (evacuation of air or >100 mL fluid) reasons.

F. The most common causes of pleural effusions are congestive heart failure, parapneumonic, malignancy, and postoperative sympathetic effusions.

II. INDICATIONS AND CONTRAINDICATIONS

A. Consider thoracentesis for pleural effusions in patients with pleurisy, who are febrile or are suspect for infection, whose clinical presentation is atypical for congestive heart failure, or whose course does not progress as anticipated.

B. Relative contraindications include those settings in which a complication from the procedure may prove catastrophic (i.e., known underlying bullous disease, the presence of positive end-expiratory pressure, a patient with only one functional lung).

C. Absolute contraindications include an uncooperative patient, the inability to identify the top of the rib at the planned puncture site clearly, operator inexperience with the procedure, and coagulopathy that cannot be corrected.

D. For pleural fluid, present in only small quantity (less than half a hemidiaphragm obscured on an upright posterior-anterior [PA] CXR) or when the fluid is not freely flowing (i.e., loculated), directed guidance with dynamic (real-time) ultrasonography or computed tomography is necessary to minimize the risk for serious complications.

III. PROCEDURE

A. Technique for diagnostic (needle only or catheter-over-needle) removal of freely flowing fluid

1. Obtain a lateral decubitus CXR to confirm a free-flowing pleural effusion.
2. Obtain informed written consent for the procedure.
3. Follow your institution-specific policy to ensure and document that you have the "right patient, right procedure, right site."
4. With the patient sitting, arms at side, mark the inferior tip of the scapula on the side to be tapped. This approximates the eighth intercostal space, the lowest level that may be safely punctured unless previous sonography determined that a lower interspace can safely be entered.
5. Position the patient sitting at the edge of the bed, leaning forward over a pillow-draped bedside table, with arms crossed in front to elevate and spread the scapulae. An assistant should stand in front of the table to prevent any unexpected movements.

6. Percuss the patient's posterior chest for the highest point of the effusion. The interspace below this should be entered in the posterior axillary line. Mark the superior aspect of the rib with your fingernail (the inferior border of each rib contains an intercostal artery and should be avoided).
7. Using sterile technique, cleanse and drape the area surrounding the puncture site.
8. Anesthetize the superficial skin with 2% lidocaine using a 25-gauge needle. Use an 18- to 22-gauge needle to anesthetize the deeper soft tissues, aiming for the top of the rib. Always aspirate as the needle is advanced and before instilling lidocaine to ensure that the needle is not in a vessel or the pleural space. Fluid enters the syringe on reaching the pleural space. The patient may experience discomfort as the needle penetrates the well-innervated parietal pleura. Be careful not to instill anesthetic into the pleural space; it is bactericidal for most organisms, including *Mycobacterium tuberculosis*. Estimate the required depth of insertion and remove the needle.
9. Insert the catheter-over-needle apparatus (or 20-gauge, 1.5-in. needle attached to a three-way stopcock and 50-mL syringe) along the anesthetic tract, always aspirating through the syringe as the needle is slowly advanced. Once pleural fluid returns using the needle-only technique, stabilize the needle by attaching a clamp to the needle where it exits the skin to prevent further advancement of the needle into the pleural space. Once pleural fluid is obtained using the catheter-over-needle technique, direct the apparatus downward to ensure that the catheter descends to the most dependent area of the pleural space. Advance the catheter forward in a single smooth motion as the inner needle is simultaneously withdrawn.
10. Fill a heparinized blood gas syringe with pleural fluid from the side port of the three-way stopcock, express all air from the sample, cap it, and place in a bag containing iced slush for immediate transport to the laboratory.
11. Fill the 50-mL syringe and transfer its contents into appropriate collection tubes and containers. Always maintain a closed system during the procedure to prevent room air from entering the pleural space. For most diagnostic studies, 30 to 50 mL is ample fluid collection.
12. When the thoracentesis is complete, remove the needle (or catheter) from the patient's chest. Apply pressure to the wound for several minutes, and apply a sterile bandage.
13. Obtain a postprocedure upright end-expiratory CXR if a pneumothorax is suspected. Immediately after the procedure, draw venous blood for total protein and lactate dehydrogenase (LDH) determinations. These studies are necessary to interpret pleural fluid values.

B. Technique for therapeutic removal of freely flowing fluid

1. Follow steps 1 to 8 as described previously.
2. Removal of >100 mL of pleural fluid involves placement of a catheter into the pleural space. Commercial kits are widely available, each with specific instructions for performing this procedure. Operators should be thoroughly familiar with the recommended procedure and should receive appropriate supervision from an experienced operator before performing therapeutic thoracentesis on their own.

C. Technique for removal of freely moving pneumothorax

1. Follow the same general protocol described earlier for catheter-over-needle removal of freely flowing fluid but instead, position the patient supine with the head of the bed elevated 30 to 45 degrees.
2. Prepare the anterior second or third intercostal space in the midclavicular line (to avoid the more medial internal mammary artery).
3. Have the bevel of the catheter-over-needle apparatus facing upward and direct the needle superiorly so that the catheter can be guided to the superior aspect of the hemithorax.

4. Air may be actively withdrawn by syringe or pushed out when intrapleural pressure is supra-atmospheric (e.g., during a cough), as long as the catheter is intermittently open to the atmosphere. Air can leave but not reenter the pleural space if a one-way valve system (Heimlich valve) is attached or if the catheter is put to underwater seal.
5. If a tension pneumothorax is known or suspected and a chest tube is not readily available, quickly insert a 14-gauge angiocatheter according to the foregoing technique. If a tension pneumothorax is present, air will escape under pressure. When the situation has been stabilized, replace the catheter with a sterile chest tube.

IV. POSTPROCEDURE CONSIDERATIONS

A. The overall complication rate from thoracentesis is as low as 5% when performed by experienced intensivists but may be as high as 50% to 78% when performed by those less experienced.

B. Major, possibly life-threatening, complications may occur in up to 15% to 19% and include pneumothorax, hemorrhage, hypotension, re-expansion pulmonary edema, venous or cerebral air embolism (rare), and sheared catheter fragments left in the pleural space (rare).

C. The risk of pneumothorax varies depending on baseline patient characteristics (e.g., presence or absence of chronic obstructive pulmonary disease), operator experience, and the method used to perform the procedure.

D. Minor complications also depend on the method used and occur in 16% to 63%, including dry tap, anxiety, dyspnea, cough, pain, and subcutaneous hematoma or seroma.

V. INTERPRETATION OF PLEURAL FLUID ANALYSIS

A. A transudate is biochemically defined by meeting *all* the following (Light's) criteria: pleural fluid-to-serum ratio for total protein <0.5, pleural fluid-to-serum ratio for LDH <0.6, and an absolute pleural fluid LDH less than two thirds the upper limits of normal of the serum LDH. Alternative diagnostic criteria also exist with similar accuracy, sensitivity, and specificity values compared with Light's criteria. If a transudate is present, then generally no further tests on pleural fluid are generally indicated.

B. An exudate is present when any of the criteria for transudate are not met. Further evaluation is usually warranted.

1. A pleural fluid pH <7.20 narrows the differential diagnosis to systemic acidemia, empyema or parapneumonic effusion, malignancy, rheumatoid or lupus effusion, extrapulmonary tuberculosis, ruptured esophagus, or urinothorax. These effusions may potentially require consideration for chest tube drainage.
2. Pleural fluid glucose levels <50% of the serum level may be found with empyema, malignancy, rheumatoid or lupus effusion, extrapulmonary tuberculosis, or ruptured esophagus.
3. Although not diagnostic, pleural fluid white blood cell counts exceeding 50,000/mm^3 strongly suggest bacterial pneumonia or empyema but may also be seen in effusions associated with rheumatoid arthritis. Pleural fluid lymphocytosis is nonspecific, but when present in >80% of cells suggests tuberculosis or malignancy.
4. Grossly bloody effusions contain >100,000 cells/mm^3 and are most commonly seen in trauma, malignancy, or pulmonary infarction. Hemothorax is defined by a pleural fluid hematocrit of 30% or greater of the serum hematocrit.
5. Chylous pleural effusions are defined by triglyceride levels >110 mg/dL and may be seen with trauma involving the thoracic duct, malignancy (especially lymphoma), and in patients with advanced liver disease.

6. If initial cytologic results are negative for malignancy and a strong clinical suspicion exists, additional pleural fluid samples can increase the chance of a positive result. The addition of a pleural biopsy increases the yield to a modest amount over cytology on two separate specimens. Cytologic examination may also definitively diagnose rheumatoid pleuritis.

Suggested Reading

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11 TRACHEOSTOMY

Mark L. Shapiro

I. GENERAL PRINCIPLES

- **A.** Invasive procedure usually performed by surgeons in most centers
  - **1.** Pulmonologists have been approved in some centers
- **B.** Patients who warrant tracheostomy have a mortality rate of 2% to 5%
  - **1.** Secondary to comorbid disease states
- **C.** Can be performed in almost any setting safely
  - **1.** Emergency department
  - **2.** Intensive care unit
  - **3.** Operating room
- **D.** Variety of techniques
  - **1.** Open
  - **2.** Semiopen
  - **3.** Percutaneous

II. ANATOMY OF THE TRACHEA

- **A.** Distal continuation of the larynx
- **B.** Much shorter in pediatric population than adults
- **C.** Thyroid cartilage
  - **1.** Easily palpable
  - **2.** Most superior cartilage
- **D.** Cricothyroid membrane
  - **1.** Exists between thyroid cartilage and cricoid cartilage
  - **2.** Access for emergent cricothyrotomy
  - **3.** Palpable indentation between the two cartilages
  - **4.** Do not perform emergent cricothyrotomy in children younger than 9 years old
    - **a.** Emergent tracheotomy is procedure of choice
- **E.** Cricoid cartilage is the only continuous ring of the trachea
- **F.** Occupies neck and thorax
- **G.** Immediately anterior to the esophagus
- **H.** Divides into right and left mainstem bronchi and subsequently into lobar bronchi
  - **1.** Principal bronchi originate behind the aorta, to the right and just below the arch
  - **2.** Carina (bifurcation) at the level of seventh thoracic vertebra
- **I.** The tracheotomy is covered in detail later in this chapter. Accepted sites are the second or third tracheal ring

III. INDICATIONS

- **A.** Airway obstruction
  - **1.** Thyroid tumors
  - **2.** Pharyngeal abscess
  - **3.** Granulation tissue from prolonged intubation/irritation

4. Severe inflammation
   a. Asthma
   b. Trauma
   c. Anaphylaxis

B. Prolonged mechanical ventilation
1. Head injuries
2. Severe chronic obstructive pulmonary disease (COPD)
3. Quadriplegia
4. High spine injuries
5. Improves pulmonary toilet, but does not necessarily decrease incidence of pneumonia

C. Prophylaxis
1. Facial reconstruction
2. Esophageal reconstruction

D. Comfort
1. Decreases work of breathing
2. Decreases risk of sinus infection (nasotracheally intubated)
3. Shortens duration of mechanical ventilation

E. Contraindications
1. Recent surgical procedures
   a. Contamination of wound
      i. Anterior cervical spine surgery
      ii. Median sternotomy

IV. PROCEDURE

A. Considerations
1. In elective tracheotomies, ensure that the patient is not coagulopathic
   a. Liver disease
   b. Therapeutic anticoagulation

B. Obese patient needs
1. Extra long cannula—very important
2. May need a headlight
3. Liberal incision

C. Patients on moderate amounts of positive end-expiratory pressure (PEEP)
1. Caution on patients' responsiveness to PEEP
2. If PEEP is >10 cm H_2O, consider delaying the procedure
   a. Derecruitment of alveoli may occur
      i. Hypoxemia
      ii. Acute lung injury
   b. Subcutaneous emphysema and pneumomediastinum should not prevent one from proceeding with tracheostomy and may assist with treating an injury to the trachea if identified more cephalad

D. Closed head injured with increased intracranial pressure (ICP)
1. Inappropriate for tracheostomy while ICP is elevated or uncontrolled
2. Percutaneous tracheostomy may increase ICP when facilitated with bronchoscopy
3. Elevated $Paco_2$ during bronchoscopy

E. Thyroid disease
1. Enlarged thyroid can be a source of uncontrolled bleeding and poor visualization

F. High-riding innominate artery
1. Rare, but noteworthy in those with enlarged necks and source of threatening bleeding

G. Open
- **1.** Follow universal protocol
- **2.** General anesthesia
- **3.** Inspect the surgery technician's table for needed equipment
- **4.** Test cuff
- **5.** Ensure that 6.5 mm internal diameter endotracheal tube (ET) is available. Very useful in emergency situations if a tracheostomy cannula is not immediately available
- **6.** Make sure that anesthesiologist has released the ET tube holder and all tape is ready for removal on request
  - **a.** If cervical spine injury, do not extend or flex neck, but maintain neutral attitude
  - **b.** Do not overextend neck because second and third tracheal rings may be displaced too far superiorly
  - **c.** Prepare neck with 2% chlorhexidine gluconate in 70% isopropyl alcohol combination solution (or equivalent). Ten percent povidone-iodine should only be used if the patient is sensitive to chlorhexidine
- **7.** Infiltrate area of anticipated incision with 1% lidocaine with epinephrine
- **8.** Longitudinal or transverse incision is acceptable
  - **a.** Longitudinal to avoid anterior jugular veins and facilitate speed of procedure
  - **b.** Transverse for cosmetic purposes
  - **c.** Make incision below cricoid ring and above third tracheal ring
- **9.** Combination of blunt dissection and electrocautery through midline raphae and then down to pretracheal fascia
  - **a.** Thyroid often obstructs view
    - **i.** Very vascular
    - **ii.** Cautious electrocautery or suture ligation and divide, or use cricoid hook to elevate gland out of the way by inserting into membrane just inferior to cricoid cartilage
- **10.** Continuous assessment and palpation to maintain midline integrity
- **11.** Identify trachea, cricoid cartilage, and third tracheal ring
- **12.** Extirpate partial anterior portion of third tracheal ring
- **13.** Tracheal dilators to dilate tracheostomy
- **14.** Anesthesiologist to retract ET under surgeon's request
- **15.** Place tracheostomy catheter into surgical wound gently, following curve of cannula and anatomy of trachea
  - **a.** Attach breathing circuit to tracheostomy cannula.
  - **b.** Inflate balloon.
  - **c.** Observe for end-tidal carbon dioxide on monitor.
  - **d.** Suture in place with four-point fixation and trachea ties.

H. Percutaneous technique
- **1.** Follow universal protocol.
- **2.** Prepare neck as described earlier.
- **3.** Respiratory therapist presence to maintain minute volume and ventilation during procedure.
- **4.** Use flexible bronchoscope to visualize tracheal tree.
- **5.** Retract ET tube slowly.
- **6.** Transilluminate second or third tracheal ring.
- **7.** Anesthetize area with 1% lidocaine with epinephrine.
- **8.** Pull bronchoscope into lumen of ET tube to protect scope from percutaneous catheter placement.
- **9.** Insert percutaneous needle into lumen of trachea, perpendicular to skin under direct visualization through bronchoscope to avoid perforating the posterior aspect of the trachea and entering esophagus.
- **10.** Place guidewire through needle into trachea, then remove needle.

11. Over the guidewire, pass dilator(s)—kits vary—until able to pass trachea cannula easily.
12. Suture into place.

I. Semiopen
1. Variation of the two above techniques
2. Higher risk of tracheoesophageal fistula
3. Ultrasonography may be advantageous

V. POSTPROCEDURE CONSIDERATIONS

A. Postprocedure chest radiography (CXR)
1. Even though not shown to be cost effective, often the standard of care
2. CXR for those who are symptomatic only
3. Look for bronchial plugging and pneumothorax

B. Tracheal stenosis
1. Older literature suggests that stenosis occurs more frequently with open procedures.
2. Occurred more frequently in the past with ET tubes with high-pressure/low-volume cuffs. Modern cuffs are high volume/low pressure.
3. Newer literature is controversial.
   a. Appears to be equivocal; follow-up and practitioner's experience appear to be most important.
   b. When tracheal stenosis does occur, it appears to occur higher and earlier when compared to open tracheotomies.

C. Tracheoinnominate artery fistula
1. Rare event and rapidly fatal, even when recognized early.
2. Prototypical patient is female; long, gracile neck; and slender.
3. Etiology is often placement of tracheostomy below the third tracheal ring.
   a. Can be due to percutaneous needle placement into innominate artery directly through trachea
   b. Caution with overextension of neck because it retracts thoracic airway cephalad

D. Cost
1. Multiple studies describe cost savings when comparing percutaneous method to open technique as:
   a. The procedure is performed in the intensive care unit, not in the operating room
   b. A single kit is used
   c. No complications occur with the procedure

E. Efficiency
1. In many cases, can be done faster than a conventional open tracheostomy
2. Does not occupy an operating room; therefore, allows other larger cases to resume/commence
   a. Obviates turnover time issues
   b. Operating rooms finish earlier leading to improved anesthesia and surgeon satisfaction

Suggested Reading

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GASTROINTESTINAL ENDOSCOPY

Savant Mehta

12

I. GENERAL PRINCIPLES. This chapter reviews the indications, contraindications, techniques, and complications of gastrointestinal (GI) endoscopy in critically ill patients.

A. Charged-coupled device chip technology and video monitors have replaced fiber optic bundles on newer instruments, although fiber optic and rigid endoscopes are still in use.

B. Wheels and buttons on the handle of the flexible instrument control tip deflection, suction, and air and water insufflation.

II. INDICATIONS. Although cardiopulmonary complications of GI endoscopy are infrequent, the procedure should be performed only when the tangible benefits clearly outweigh the risks. GI endoscopy in patients with clinically insignificant bleeding or minimally troublesome GI complaints should be postponed until the medical–surgical illnesses improve. All endoscopists performing diagnostic GI procedures should be competent in endoscopic therapy.

A. Upper GI endoscopy

1. Upper GI bleeding. Patients with evidence of hemodynamic instability, continuing need for transfusions, or suspected variceal bleeding should undergo urgent upper endoscopy with plans for appropriate endoscopic therapy

2. Caustic ingestion

3. Foreign body ingestion

4. Percutaneous endoscopic gastrostomy (PEG) placement

B. Endoscopic retrograde cholangiopancreatography (ERCP)

1. This technique is used only occasionally in the intensive care unit (ICU)

2. Indications

a. Cholangitis unresponsive to medical therapy

b. Acute gallstone pancreatitis complicated by cholangitis or jaundice

c. Severe gall stone pancreatitis within the first 24 hours

C. Lower GI endoscopy

1. Acute lower GI bleeding, however, this procedure is technically difficult. Colonoscopy appears to have the highest yield in diagnosing and sometimes treating lower GI bleeding. It is safe when appropriate resuscitation has been performed. Technetium-labeled erythrocyte scanning and angiography are other methods commonly used for localizing a bleeding site.

2. Endoscopic colonic decompression has been advised in critically ill patients with acute adynamic ileus when the diameter of the right colon exceeds 12 cm. Other studies suggest that the colonic dilation may not progress to life-threatening complications and decompression is unnecessary. Decompression by colonoscopy should not be first-line therapy for pseudo-obstruction. Nasogastric and rectal tubes placement, discontinuation of offending medications (opioids and phenothiazines), treatment of underlying illness, and frequent repositioning (every 2 hours) of debilitated patients in the ICU often allows resolution of pseudo-obstruction. In patients who

have not had a response to conservative therapy, treatment with neostigmine (2 mg) should be tried.

D. Enteroscopy

1. Suspected small bowel bleeding with evidence of continued bleeding with no obvious source seen on endoscopy or colonoscopy.

III. CONTRAINDICATIONS

A. GI perforation. Endoscopy (with the associated need for air insufflation) should be avoided in patients with known or suspected GI perforation and in those known to be at high risk of perforation.

B. Hemodynamic instability is a relative contraindication for endoscopy, but the benefit of therapeutic endoscopy may outweigh the risks in critically ill patients.

C. Coagulopathy. The risk of a bleeding complication of endoscopic sphincterotomy is higher in patients with gross coagulopathy and ERCP may be delayed while the coagulopathy is corrected.

D. Aspiration. Endotracheal intubation and heavy sedation or general anesthesia may be necessary to facilitate the procedure. Patients with acute upper GI bleeding who are confused or stuporous should have their airway protected with an endotracheal tube before endoscopy is performed.

IV. COMPLICATIONS

A. Bleeding. Most bleeding is minimal and self-limited, but repeat endoscopy and surgery may be necessary to control recurrent bleeding. Angiography can assist in localizing the bleeding source in postendoscopy bleeding.

B. Perforation. Perforation of the bowel may result, and antibiotics and intravenous fluids should be given; surgery may be required. If duodenal perforation is encountered after endoscopic sphincterotomy, early medical therapy and stabilization of the patient may preclude the need for surgery.

C. Cardiopulmonary complications. Aspiration of stomach contents and blood in acute upper GI bleeding can be minimized by protecting the airway with endotracheal intubation in patients with severe bleeding or an altered mental state.

D. Infections. Infectious complications can be minimized by appropriate use of prophylactic antibiotics in high-risk patients (with prosthetic mechanical valves or grafts) or high-risk procedures (before PEG placement, dilation, sclerotherapy, ERCP).

E. Others. Sedative medications have their own complications, usually as a consequence of medication-induced hypoxemia (2 to 5/1,000 cases). Other complications can occur, including apnea, hypotension, and, rarely, death (0.3 to 0.5/1,000 cases).

V. TECHNIQUES

A. Upper GI endoscopy

1. Fluid resuscitation and optimal treatment of hypoxemia should precede all endoscopic examinations.
2. Endotracheal intubation should be considered in obtunded patients with severe bleeding or in those undergoing removal of foreign bodies. Nasogastric or orogastric lavage with a large-bore tube (>40 Fr) should be performed to evacuate blood and clots from the stomach before endoscopy is performed in a patient with acute GI bleeding.
3. Upper GI bleeding is the most common indication for upper endoscopy in the ICU. Patients with continued or recurrent upper GI bleeding should have urgent upper endoscopy as early as possible, certainly within 6 to 8 hours of presentation. In patients with massive hemorrhage, endoscopy may be performed in the operating room in anticipation of surgical therapy.

4. The team consists of an experienced endoscopist, a specially trained endoscopy assistant, and a nurse skilled in monitoring patients undergoing endoscopy. A topical anesthetic is applied to the patient's pharynx to reduce the gag reflex. Intravenous anxiolytics and/or opioids are used (see Chapter 20).
5. Proper patient monitoring is needed, with frequent (every 5 minutes) blood pressure and pulse measurements and continuous measurement of oxygen saturation by pulse oximetry.
6. Endoscopy is performed with a "therapeutic" instrument, equipped with a large operating channel to allow suctioning of blood, and hemostatic therapy. The endoscope is passed, and the upper GI tract is rapidly surveyed to locate the site of bleeding and facilitate surgical therapy if endoscopic therapy fails. If an active bleeding site is found, hemostatic therapy may be attempted immediately.
7. In patients with significant recent bleeding and endoscopic evidence of recent hemorrhage (a visible vessel or adherent clot on an ulcer), hemostatic therapy to prevent recurrent bleeding should be strongly considered.
8. Actively bleeding lesions in the upper GI tract can be treated by injection therapy, mechanical clipping devices, band ligation, argon plasma coagulation, heater probe therapy, or monopolar and bipolar electrocoagulation.
   a. Injection therapy is simple and inexpensive, requiring only a needle catheter and various liquid media to effect hemostasis, including absolute ethanol, sclerosants (sodium morrhuate), glue or vasoconstrictors (epinephrine). Injection therapy may be less effective in briskly bleeding ulcers or in bleeding esophageal varices. Injection therapy using epinephrine, absolute alcohol, or sclerosants (sodium morruhate, ethanolamine) allows treatment of lesions even when seen tangentially. Injection therapy generally begins on the periphery of the lesion, with injections in all four quadrants. Variceal sclerotherapy involves a direct or paravariceal injection of 1 to 4 mL of sclerosant.
   b. A newer method of banding esophageal varices is superior to sclerotherapy in terms of overall complications, recurrent bleeding, and mortality. Banding of varices is performed with an endoscopic adaptor that allows placement of small rubber bands directly onto a varix.
   c. Heater probes generate heat using electrical current delivered to the tip of the catheter, whereas bipolar electrocautery delivers electrical current directly to the tissue and causes coagulation necrosis. Because hemostatic therapy with the heater probe or bicap equipment requires an *en face* view, lesions seen tangentially may be difficult to treat with these methods.

B. Lower GI endoscopy

1. This procedure can be extremely difficult to perform in critically ill patients with colonic hemorrhage.
2. Instruments available for the examination of the lower GI tract include the following:
   a. Anoscope, which is useful mainly to evaluate for hemorrhoids or fissures
   b. Sigmoidoscope
   c. Colonoscope
3. Colonoscopy
   a. Colonoscopes are generally 140 to 180 cm long and are necessary to reach colonic lesions situated proximal to the splenic flexure.
   b. Patient preparation for colonoscopy usually consists of a gallon of nonabsorbable polyethylene glycol given by mouth over 4 to 6 hours or by nasogastric tube, 12 hours before examination. Magnesium citrate may be used over 24 to 48 hours in patients who have been taking clear liquids.

c. Abdominal pressure that is applied by an assistant during colonoscopy may assist in advancing the colonoscope.

C. Enteroscopy

1. Instruments available for examining the small bowel include the following:
   a. Push enteroscope—typically 200 to 240 cm in length; can be introduced orally, similar to a regular endoscope up to the mid-jejunum
   b. Single or double balloon enteroscope—a novel type of endoscope that can be introduced through mouth to examine the entire small bowel
   c. Video capsule enteroscope—a small camera swallowed or placed endoscopically and allowed to pass spontaneously through the entire small bowel while transmitting pictures to a recorder outside the body

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DIAGNOSTIC PERITONEAL LAVAGE AND PARACENTESIS

13

Mark L. Shapiro

I. GENERAL PRINCIPLES

- **A.** Introduction
  - **1.** Diagnostic peritoneal lavage (DPL)
  - **2.** Diagnostic peritoneal aspirate (DPA)
- **B.** Initial step of the DPL, that is, without lavage
- **C.** Done in hypotensive patients, specifically aspirating for blood
- **D.** DPA sensitivity and specificity reported as 89% and 100% versus focused assessment with sonography in trauma (FAST) examination 50% and 95%, respectively, in one study
- **E.** DPL often performed emergently in the traumatically injured
- **F.** Ease of conduct
- **G.** Expedites patient disposition
- **H.** Versatile: blunt and penetrating trauma
- **I.** Rapid
- **J.** Relatively simple

II. ACCURACY

- **A.** Can detect as little as 20 mL of blood
- **B.** Sensitivity approximates 85% to 98% in the DPA
  - **1.** Dependent on deftness of surgeon and magnitude of intraperitoneal injuries
  - **2.** Cannot diagnose contained retroperitoneal structures
- **C.** Specificity approximates 93% to 97% in the DPA
- **D.** Blunt trauma
  - **1.** Positive DPL
    - **a.** Ten milliliters gross blood on initial aspiration
    - **b.** Red blood cell (RBC) $>100{,}000/mm^3$ in lavage fluid
    - **c.** White blood cell (WBC) $>500/mm^3$
    - **d.** Amylase higher than 175 U/dL
    - **e.** Presence of food, particulate matter, stool, bile
    - **f.** Cannot read the print on the side of the liter bag of crystalloid because of turbidity of fluid return
  - **2.** Negative DPL
    - **a.** Often considered negative when the above criteria are not present.
    - **b.** Multiple reasons for equivocal findings (i.e., 50,000 to 99,000 RBCs, 400 WBCs, etc.); leave catheter in and repeat in 2 to 3 hours if patient remains stable.
    - **c.** Surgical dogma (under recent scrutiny) states that if the print on the side of a liter bag of crystalloid is legible, it is reasonably safe to say the DPL is negative ($<100{,}000$ RBC/mm^3).
- **E.** Penetrating trauma
  - **1.** Positive DPL
    - **a.** Same criteria as blunt, with the exception of RBC count
      - **i.** RBC count of 10,000 is commonly accepted as positive.
      - **ii.** Some institutions desire 1,000 as positive.
      - **iii.** Sensitivity ranges from 67% to 100%.

iv. Accuracy ranges from 97% to 98%.
v. Nontherapeutic laparotomy rate is 10% to 15%.
2. Negative DPL: not satisfying the above criteria

III. INDICATIONS

A. Clinical judgment supersedes overall.
B. Note: The surgeon must decide whether to perform the DPL because he or she is the one who will operate or not operate and follow up on these patients. Without surgical presence, the patient must be transferred to a trauma center.
C. Most commonly accepted indication: hypotension and unstable patient.
1. Hemorrhagic shock
2. Intoxication
a. Ethanol
b. Illicit drugs
3. Associated head injury
D. Other acceptable criteria include:
1. Multitrauma patients who will undergo general anesthesia
2. Penetrating injuries suspected of invading multiple body cavities (e.g., transdiaphragmatic)
3. Computed tomography (CT) scanner is unavailable

IV. CONTRAINDICATIONS

A. Absolute
1. Predetermined exploratory laparotomy (e.g., penetrating abdominal wound with evisceration)
B. Relative
1. Multiple previous abdominal operations
2. Grossly distended abdomen
a. Tympanitic
b. Gravid uterus
3. Abdominal wall hematomas (high false-positive rate)

V. OTHER MODALITIES

A. CT scan
B. FAST
1. Reliability range for the FAST examination
a. 90% to 98% accurate
b. 88% to 98% sensitive
c. 93% to 97% specific
C. Local wound exploration
D. Celiotomy

VI. PROCEDURE

A. Control the situation and environment.
B. Think clearly.
C. Decompress hollow viscus.
1. Nasogastric/orogastric decompression
a. Salem sump
b. Often distended by aggressive bag-valve-mask ventilation, anxiety with aerophagia, esophageal intubation, or oral contrast
2. Urinary bladder decompression: Foley catheter
D. Decide to incise above or below the umbilicus.
1. Above the umbilicus for those patients with:
a. Pelvic fractures
i. Large retroperitoneal bleeding
ii. Stay above arcuate line

   b. Gravid uterus
      i. Perforate the uterus
      ii. Increases morbidity and mortality of fetus and mother
   2. Below the umbilicus for most others:
      a. Unless a previous surgery obviates this choice
      b. Ease of placing the catheter into proper anatomic space
E. Follow universal protocol and use of maximum barrier precautions is preferred.
F. Infiltrate with 1% lidocaine with epinephrine for length of incision (2 cm).
   1. Epinephrine to decrease skin bleeding, which may obstruct view or confound results
G. Choose open, semiopen, blind technique:
   1. On the basis of experience mostly.
   2. All can be performed rapidly.
   3. Blind technique has marginally, but significantly more complications.
   4. Most often performed is the semiopen technique.
   5. Semiopen technique:
      a. Incision is made through the skin to expose the fascia.
      b. Two penetrating towel clips placed in closed position, placed into surgical wound facing each other.
      c. Clamps are opened at the same time in the surgical wound.
      d. Clamps are closed while pressing downward grasping the fascia.
      e. Clamps and fascia are raised anteriorly through the surgical wound.
      f. Anterior fascia is incised.
      g. Peritoneal dialysis catheter is placed at 45 to 60 degrees to the vertical, aimed toward the pelvis.
      h. Two distinct "pops" should be appreciated as catheter enters peritoneum.
      i. Fenestrated catheter is advanced through Seldinger technique into place.
      j. One liter (or 25 mL/kg) of crystalloid is infused into peritoneal cavity (can use pressure bag) through two-way intravenous tubing.
      k. Once in, bag is placed on floor to dependent drainage.
      l. At least 200 to 300 mL should be collected into the bag before 70 mL is sent for laboratory analysis and quantification.
      m. Catheter may be removed and skin stapled shut or keep the site sterile and repeat if necessary in 3 hours

VII. GENERAL PRINCIPLES OF PARACENTESIS

A. Parecentesis is performed as an adjunctive study for a variety of medical and sometimes surgical conditions.
B. Patients should have documentation of ascites by history, physical examination, or radiographically before the paracentesis (trauma DPL excepted).

VIII. INDICATIONS

A. Therapeutic
   1. Removal of ascitic fluid to alleviate cardiovascular or pulmonary embarrassment
   2. Resuscitation with albumin is recommended for fluid replacement in this particular patient population, specifically those with cirrhotic ascites
B. Diagnostic
   1. Etiology of ascites
      a. DPL in trauma
      b. Transudative
         i. Cirrhosis
         ii. Hepatitis due to alcohol

iii. Portal vein thrombosis
iv. Fulminant hepatic failure
v. Congestive heart failure
vi. Nephrotic syndrome

c. Exudative
i. Peritonitis
ii. Carcinomatosis
iii. Ischemic bowel/bowel obstruction
iv. Pancreaticobiliary inflammation

IX. CONTRAINDICATIONS

A. Gravid uterus
B. Gross distension of hollow viscus
C. Organomegaly
D. Multiple prior abdominal surgeries
E. Localized infection at percutaneous site

X. PROCEDURE

A. Follow universal protocol.
B. For added accuracy and decreased risk of complications, use ultrasonography.
C. Prepare skin with alcohol–chlorhexidine solution (e.g., Dura-Prep).
D. Select site.
1. Midline approximately 3 cm from umbilicus
2. Lateral to rectus muscles in the lower quadrant
E. Anesthetize with 1% lidocaine with epinephrine and make a skin wheel.
F. Retract skin gently (creates a Z-track) to attenuate risk of leaking ascitic fluid at completion of procedure.
G. Under sterile conditions, percutaneously insert paracentesis catheter through Seldinger technique into peritoneal cavity.
H. If paracentesis kit is unavailable or constant drainage is not indicated, an 18- to 22-gauge needle may be used.
I. This can be connected to a negative pressure specimen bottle.
J. Approximately 50 mL is all that is needed for most diagnostic studies.
K. Place sterile dressing over procedure site.

TABLE 13-1 Common Laboratory Studies with Findings in the Diagnostic Paracentesis

	Gram stain	$Albumin_{S/A}$[a]	Glucose	Specific gravity	Cytology	Total protein
Spontaneous bacterial peritonitis	+/–	1.1	>50	>1.016 if purulent	–	<1.0
Cirrhosis	–	>1.1	–	<1.016	–	<2.5
Congestive heart failure	–	>1.1	–	Variable <1.016	–	>2.5
Neoplastic process	–	<1.1 >1.1 with Hepatic metastases	Normal to low	Variable >1.016	+	>2.5 Can be <3.0 if liver replaced with metastases
Nephrosis	–	<1.1	–	<1.016	–	<2.5

[a]Serum albumin/ascites albumin gradient.

XI. DIAGNOSTIC STUDIES (Table 13-1)

- **A.** Gram stain, acid-fast bacilli (AFB) smear, culture, and sensitivity
- **B.** Cytology
- **C.** Cell count, lactate dehydrogenase (LDH), total protein, glucose, amylase, and triglyceride
- **D.** Specific gravity
- **E.** Albumin for determination of serum albumin/ascites albumin gradient

XII. COMPLICATIONS

- **A.** Bleeding
- **B.** Infection
- **C.** Perforation of bowel, bladder, stomach, or vessel
- **D.** Exacerbation of encephalopathy, renal failure, electrolyte disturbance, and hypotension

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GASTROESOPHAGEAL BALLOON TAMPONADE FOR ACUTE VARICEAL HEMORRHAGE

14

Marie T. Pavini

I. GENERAL PRINCIPLES

A. Definitions

1. Esophageal variceal hemorrhage: an acute, severe, dramatic complication of the patient with portal hypertension that carries a high mortality and significant incidence of recurrence.

2. Gastroesophageal balloon tamponade: a multilumenal tube with esophageal and gastric inflatable cuffs that can be inflated to compress esophageal varices and gastric cardia submucosal veins.

II. ALTERNATIVE PROCEDURES AND THERAPEUTICS

A. Sclerotherapy is a first-line therapy offering a lower incidence and severity of complications and greater success in controlling bleeding.

B. Band ligation is also a first-line therapy carrying a more desirable complication and success profile.

C. Combined vasoactive pharmacologic therapy and balloon tamponade can control hemorrhage in 90% of cases.

D. Octreotide or combination vasopressin and nitroglycerin diminishes portal vein pressure while emergency endoscopy is performed to confirm the diagnosis.

E. Percutaneous transhepatic embolization is recommended in poor-risk patients who do not stop bleeding despite other measures.

F. Esophageal devascularization with gastroesophageal stapling can be performed for patients without cirrhosis as well as for low-risk patients with cirrhosis.

G. Transjugular intrahepatic portosystemic shunt (TIPS) is used as a bridge to transplant.

H. Esophageal transection is an extreme measure used to control bleeding.

I. Removable self-expanding metal esophageal stents placed without radiographic assistance are being studied.

III. INDICATIONS

A. Therapeutic

1. Gastroesophageal balloon tamponade is indicated in patients with esophageal variceal hemorrhage in whom neither sclerotherapy nor band ligation is technically possible, readily available, or has failed.

B. Diagnostic

1. With use of the infragastric balloon suction port, it is possible to differentiate bleeding from esophageal and gastric varices.

IV. CONTRAINDICATIONS

A. Balloon tamponade is contraindicated in patients with recent esophageal surgery or esophageal stricture.

B. Some authors do not recommend balloon tamponade when a hiatal hernia is present, although there are reports of successful hemorrhage control in such patients (Fig. 14-1).

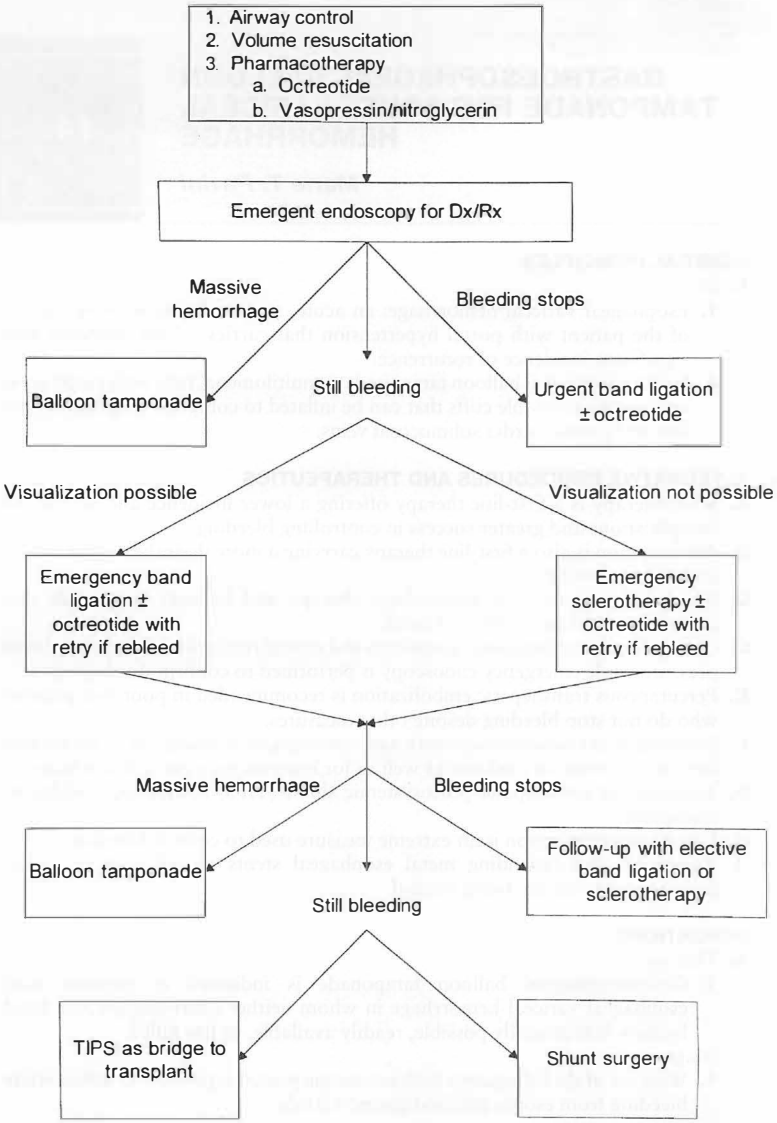

Figure 14-1. Management of esophageal variceal hemorrhage. Dx, diagnosis; Rx, therapy; TIPS, transjugular intrahepatic portosystemic shunt. (From Pavini MT, Puyana JC. Management of acute esophageal variceal hemorrhage with gastroesophageal balloon tamponade. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2008, with permission.)

V. PROCEDURE

A. Preprocedure considerations

1. Endotracheal intubation

a. Any patient who will undergo balloon tamponade should have the trachea intubated for airway protection.

b. Suctioning of pulmonary secretions and blood accumulated in the hypopharynx is facilitated in patients with endotracheal intubation.

c. Administration of sedatives and analgesics in intubated patients is safer and may be required often because these tubes are poorly tolerated in most patients.

d. The incidence of pulmonary complications is significantly lower when endotracheal intubation is routinely used.

2. Hemodynamics and resuscitation

a. Adequate intravenous access should be obtained with large-bore venous catheters and fluid resuscitation undertaken with crystalloid and colloid fluids.

b. A central venous catheter or pulmonary artery catheter may be required to monitor intravascular filling pressures, especially in patients with severe cirrhosis, advanced age, or underlying cardiac and pulmonary disease.

c. Four to six units of packed red cells should always be available in case of severe recurrent bleeding that commonly occurs in these patients.

d. Coagulopathy should be treated acutely with fresh frozen plasma and platelets.

3. Diagnostic endoscopy and gastric lavage

a. Placement of an Ewald tube and aggressive lavage and suctioning of the stomach and duodenum facilitates endoscopy, diminishes the risk of aspiration, and may help control hemorrhage from causes other than esophageal varices.

b. The diagnostic endoscopic procedure should be done as soon as the patient is stabilized after basic resuscitation. Endoscopy is performed in the intensive care unit or operating room under controlled monitoring and with adequate equipment and personnel. An endoscope with a large suction channel should be used.

c. Octreotide or combination vasopressin and nitroglycerin should be administered as part of initial resuscitation.

B. Equipment

1. Although several studies have published combined experience with tubes such as the Linton and Nachlas tube, the techniques described here are limited to the use of the Minnesota (Fig. 14-2) and Sengstaken–Blakemore (Fig. 14-3) tubes. When using a Sengstaken–Blakemore tube, a No. 18 Salem sump is attached above the esophageal balloon and inserted through the mouth. Suctioning above the esophageal balloon and hypopharynx diminishes, but does not eliminate, the risk of aspiration pneumonia.

2. The Minnesota tube has a fourth lumen that allows intermittent suctioning of saliva, blood, and pulmonary secretions in the hypopharynx (Fig. 14-2).

C. Technique

1. The universal protocol should be followed.

2. All lumens should be patent, and the balloons should be inflated and checked for leaks. If using the Sengstaken–Blakemore tube, a No. 18 Salem sump should be secured above the esophageal balloon with surgical ties. The tube should be generously lubricated with lidocaine jelly.

3. The tube can be inserted through the nose or mouth; however, the nasal route is not recommended in patients with coagulopathy. The tube is passed into the stomach (Fig. 14-4).

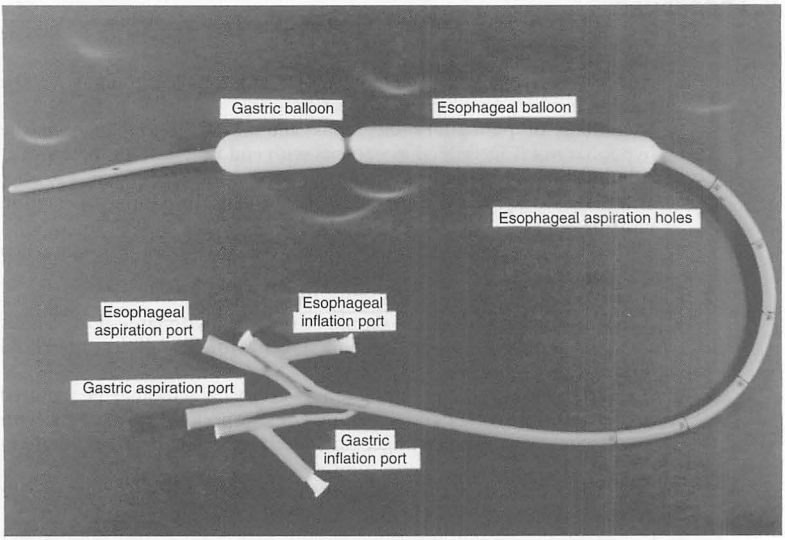

Figure 14-2. Minnesota tube. (From Pavini MT, Puyana JC. Management of acute esophageal variceal hemorrhage with gastroesophageal balloon tamponade. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2008, with permission.)

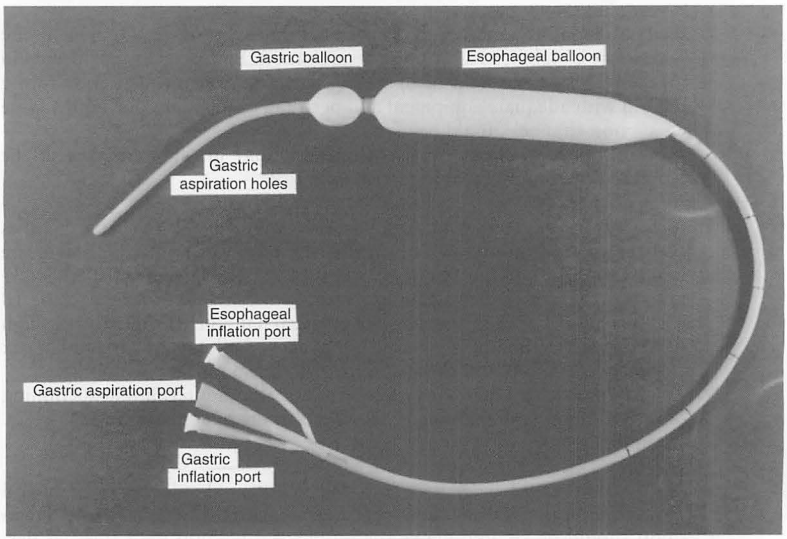

Figure 14-3. Senstaken–Blakemore tube. (From Pavini MT, Puyana JC. Management of acute esophageal variceal hemorrhage with gastroesophageal balloon tamponade. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2008, with permission.)

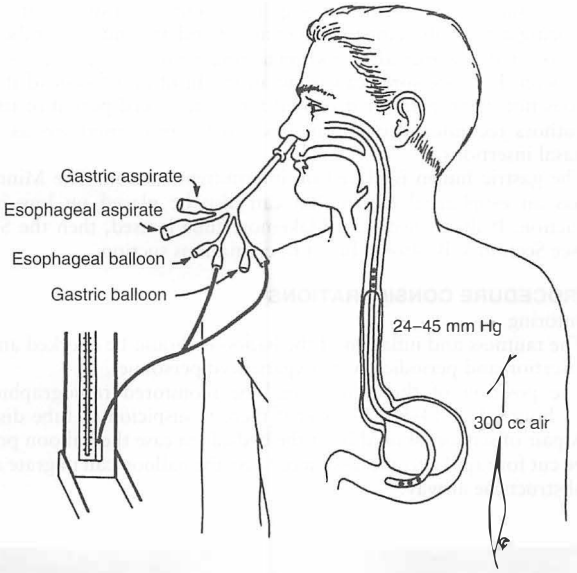

Figure 14-4. Proper positioning of the Minnesota tube. (From Pavini MT, Puyana JC. Management of acute esophageal variceal hemorrhage with gastroesophageal balloon tamponade. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2008, with permission.)

4. Auscultation in the epigastrium while air is injected through the gastric aspiration port verifies the position of the tube, but the position of the gastric tube must be confirmed radiologically at this time.
5. The gastric balloon is inflated with no more than 80 mL of air, and a portable radiograph is obtained that includes the upper abdomen and lower chest. Ultrasonography has been described as an alternative method of verification of tube placement.
6. When it is documented that the gastric balloon is below the diaphragm, it should be further inflated slowly to a volume of 250 to 300 mL. The gastric balloon of the Minnesota tube can be inflated to 450 mL. Tube inlets should be clamped with rubber-shod hemostats after insufflation.
7. Hemorrhage is frequently controlled with insufflation of the gastric balloon alone without applying traction; but, in patients with torrential hemorrhage, it is necessary to apply traction (*vide infra*). If the bleeding continues, the esophageal balloon should be inflated to a pressure of approximately 45 mm Hg (bedside manometer). This pressure should be monitored and maintained. Some authors advocate inflation of the esophageal balloon immediately after insertion (see Section VI.C).
8. When the nasal route is used, traction should not be applied against the nostril because this can easily cause skin and cartilage necrosis. When traction is required, the tube should be attached to a cord that is passed over a pulley in a bed with an overhead orthopaedic frame and aligned directly as it comes out of the nose to avoid contact with the nostril. This system allows maintenance of traction with a known weight (500 to 1,500 g) that is easily measured and constant.

9. When the tube is inserted through the mouth, traction is better applied by placing a football helmet on the patient and attaching the tube to the face mask of the helmet after a known weight (500 to 1,500 g) is applied for tension. Pressure sores can occur in the head and forehead if the helmet does not fit properly or it is used for a prolonged period of time. Several authors recommend overhead traction for oral insertions as well as for nasal insertions.
10. The gastric lumen is placed on intermittent suction. The Minnesota tube has an esophageal lumen that can also be placed on low intermittent suction. If the Sengstaken–Blakemore tube is used, then the Salem sump (see Section V.B) should be set to continuous suction.

VI. POSTPROCEDURE CONSIDERATIONS

A. Monitoring

1. The tautness and inflation of the balloons should be checked an hour after insertion and periodically by experienced personnel.
2. The position of the tube should be monitored radiographically every 24 hours (Fig. 14-5) or sooner if there is suspicion of tube displacement. A pair of scissors should be at the bedside in case the balloon port needs to be cut for rapid decompression because the balloon can migrate and acutely obstruct the airway.

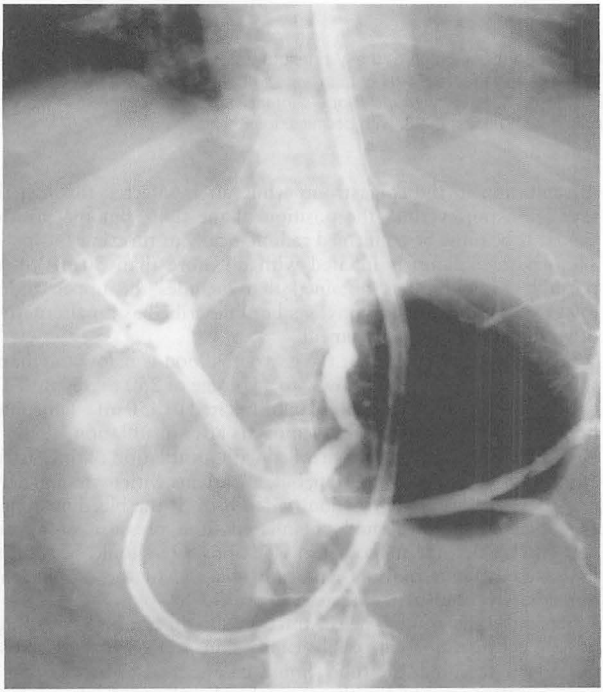

Figure 14-5. Radiograph showing correct position of the tube; the gastric balloon is below the diaphragm. (Courtesy of Ashley Davidoff, MD.) (From Pavini MT, Puyana JC. Management of acute esophageal variceal hemorrhage with gastroesophageal balloon tamponade. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2008, with permission.)

B. Weaning and removal
1. The tube should be left in place for a minimum of 24 hours. The gastric balloon tamponade can be maintained continuously up to 48 hours. The esophageal balloon, however, must be deflated for 30 minutes every 8 hours.
2. Once hemorrhage is controlled, the esophageal balloon is deflated first; the gastric balloon is left inflated for an additional 24 to 48 hours. If there is no evidence of bleeding, the gastric balloon is deflated, and the tube is left in place 24 hours longer. If bleeding recurs, the appropriate balloon is reinflated. The tube is removed if no further bleeding occurs.

C. Complications
1. The incidence of complications that are a direct cause of death in published reports ranges from 0% to 20%.
2. Tube migration (inadequate gastric balloon inflation or excessive traction).
   a. Acute laryngeal obstruction
   b. Tracheal rupture
3. Perforation of the esophagus.
4. Aspiration pneumonia (0% to 12%).
5. Mucosal ulceration of the gastroesophageal junction is related to prolonged traction time (>36 hours).
6. Impaction—inability to deflate the balloon. Occasionally, surgery is required to remove the balloon.
7. Necrosis of the nostrils.
8. Nasopharyngeal bleeding.

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15 PLACEMENT OF FEEDING TUBES

J. Matthias Walz and Thomas W. Felbinger

I. GENERAL PRINCIPLES

A. Introduction

1. Enteral nutrition (EN) in the critically ill patient compared to parenteral nutrition:
   - **a.** Maintains the integrity of the intestinal mucosal barrier
   - **b.** Decreases infectious morbidity and improves wound healing
   - **c.** Reduces cost
   - **d.** EN should be instituted if possible within 24 to 48 hours of admission to the critical care unit

B. Classification

1. Administration of EN can be distinguished according to anticipated duration or anatomic location of the feeding tube:
   - **a.** Short-term administration (<4 weeks)
     - **i.** It can be applied through nasogastric (NG) (polyvinyl chloride tube, 16- or 18-Fr), nasoduodenal, or nasojejunal fine bore tubes (silicone or polyurethane feeding tube, 6 to 14 Fr).
     - **ii.** Multi-lumen tubes allow gastric decompression while delivering feeding formula into the jejunum.
   - **b.** Long-term administration (>4 weeks)
     - **i.** Access routes for long-term EN include esophagostomy, gastrostomy, duodenostomy, and jejunostomy.
2. Anatomic location of the feeding tube:
   - **a.** Gastric feeding is a physiologic route for EN, but is often poorly tolerated due to gastric dysmotility with delayed emptying.
   - **b.** Feeding into the duodenum decreases the occurrence of regurgitation; infusion into the jejunum is associated with the lowest risk of aspiration.

C. Routes of insertion of feeding tubes

1. Small-bore nasoenteric tubes are inserted blindly or by using fluoroscopy, electromagnetic guidance, or endoscopy. Larger bore sump tubes are also commonly used for feeding and should be inserted through the mouth to reduce the risk of developing sinusitis.
2. Options for the creation of gastrostomy, duodenostomy, or jejunostomy include:
   - **a.** Open surgery or laparoscopy
   - **b.** Percutaneously using either endoscopy (percutaneous endoscopic gastrostomy [PEG]), ultrasonography, fluoroscopy (percutaneous fluoroscopic gastrostomy [PFG]) or computed tomographic (CT) guidance
3. Advancing jejunal tubes through an existing PEG tube (PEGJ, G to J-tube) is also possible (sizes range from 20 to 28 Fr).

D. Contraindications for tube placement

1. Absolute contraindications include coagulopathy, strictures of pharynx or esophagus (contraindication for placement of gastroscope), and abdominal wall infections.
2. Relative contraindications include severe ascites, gastric cancer, gastric ulcer, and recent banding of bleeding esophageal or gastric varices.

E. Contraindications for tube feeding

1. Absolute contraindications include intestinal obstruction, severe upper gastrointestinal hemorrhage, and severe mesenteric ischemia.
2. Relative contraindications include:
   a. Gastric feeding in patients with increased risk of pulmonary aspiration
   b. Enterocutaneous fistulas, severe inflammatory bowel disease, severe malabsorption, and severe short gut syndrome

II. PROCEDURE

A. Placement of nasoenteral feeding tubes

1. Appropriate length of the feeding tube: stomach, 30 to 36 in.; duodenum, 43 in.; jejunum, at least 48 in. (most tubes are radiopaque and have a tungsten-weighted tip or a stylet to facilitate passage into the duodenum). Use of an electromagnetic system that allows real-time tracking of insertion of the feeding tube will minimize the risk of placement of the tube within the tracheobronchial tree.
2. The universal protocol should be followed. With the patient in the right lateral decubitus position (if not contraindicated; supine if the electromagnetic systems is used), the tube is lubricated and advanced through the patient's nose into the stomach. Use of a carbon dioxide detector will also alert the clinician to tracheal misdirection of the tube.
3. Confirmation of correct placement must be made by x-ray.
4. A prokinetic agent such as erythromycin (500 mg IV) may facilitate passage of the tube into the small bowel; metoclopramide has been shown to be ineffective.
5. The tube is securely taped to the patient's forehead or cheek without tension.
6. If the tube is placed for duodenal or jejunal feeding, a loop 6 to 8 in. long may be left extending from the nose, and the tube may be advanced 1 to 2 in. every hour.
7. If the tube does not migrate into the duodenum over several hours, endoscopic assistance or fluoroscopic guidance can be attempted:
   a. After sedation and topical anesthesia, a nasoenteric feeding tube (43 to 48 in.) with an inner wire stylet is passed transnasally into the stomach.
   b. The endoscope is then advanced into the gastric lumen and endoscopy forceps are passed through the biopsy channel to grasp the tip of the enteral feeding tube.
   c. The endoscope, along with the enteral feeding tube, is advanced into the duodenum as far as possible; the endoscopy forceps and feeding tube remain in position as the endoscope is withdrawn back into the stomach.
   d. The forceps are opened and withdrawn carefully back into the stomach. The feeding tube is usually lodged in the second portion of the duodenum.
   e. The portion of the feeding tube that is redundant in the stomach is advanced slowly into the duodenum with the endoscopy forceps.

B. Placement of percutaneous feeding tubes

1. PEG. The three methods for placement of PEG-tubes are pull, push, and introducer techniques.
   a. Pull technique (supine position):
      i. After adequate sedation and prophylactic antibiotics (e.g., first-generation cephalosporin), the posterior pharynx is anesthetized and a fiber optic gastroscope is inserted into the stomach, which is insufflated with air.
      ii. Digital pressure to the patient's anterior abdominal wall in the left subcostal area (2 cm below costal margin) identifies the area of brightest transillumination.

(a) The indentation in the stomach created by digital pressure must be identified endoscopically; otherwise, another site should be chosen.

iii. A polypectomy snare is introduced through the endoscope.

(a) After prepping, local anesthesia, and skin incision, a large-bore catheter-needle-stylet assembly is advanced into the stomach and through the snare.

(b) The snare is tightened securely around the catheter.

iv. After removal of the stylet, a looped insertion wire is introduced through the catheter into the stomach.

v. The cannula is withdrawn slowly, so that the snare grasps the wire.

vi. The gastroscope is removed from the stomach and the end of the transgastric wire exiting the patient's mouth is tied to a gastrostomy tube.

vii. The wire exiting from the abdominal wall is pulled, while the endoscopist guides the lubricated gastrostomy tube into the stomach and then out through the abdominal wall.

viii. The gastroscope is reinserted into the stomach to confirm adequate placement and rule out bleeding (the intraluminal portion of the tube should contact the mucosa, but excessive tension on the tube should be avoided).

ix. The tube is sutured to the abdominal wall.

b. Push (Sacks–Vine) technique:

i. The gastroscope is inserted into the stomach, pointing toward the anterior abdominal wall.

ii. A short, straight guidewire is introduced into the stomach and dilators of increasing size are advanced over the wire into the stomach to create a large enough stoma to accommodate the gastrostomy tube.

iii. A gastrostomy tube with a tapered end is "pushed" over the guidewire into the stomach and sutured into place.

c. Introducer (peel-away; Russell) technique:

i. The gastroscope is inserted into the stomach, and an appropriate position for placement of the tube is identified.

ii. After infiltration of the skin with local anesthetic, a 16- or 18-gauge needle is advanced into the stomach.

iii. A J-tipped guidewire is inserted into the stomach, and the needle is withdrawn.

iv. Using a twisting motion, a 16-Fr introducer with a peel-away sheath is passed over the guidewire into the gastric lumen.

v. The guidewire and introducer are removed, leaving in place the sheath that allows placement of a 14-Fr Foley catheter.

vi. The sheath is peeled away after inflating the balloon (10 mL of normal saline).

2. Percutaneous endoscopic jejunostomy (PEJ)

a. The PEJ tube allows for simultaneous gastric decompression and duodenal or jejunal enteral feeding if a small feeding tube is attached and passed through the gastrostomy tube and advanced endoscopically into the duodenum or jejunum.

b. When the PEG is in position, a guidewire is passed through the PEG, grasped using endoscopy forceps, and passed into the duodenum as distally as possible.

c. The jejunal tube is then passed over the guidewire through the PEG into the distal duodenum and is advanced into the jejunum, and the endoscope is withdrawn.

III. POSTPROCEDURE CONSIDERATIONS

A. Safety measures

1. A chest radiograph, ideally including the upper abdominal segments for nasoenteric tubes and an abdominal film for PEG/PEJ, must be obtained to confirm the position of the tube before feedings are started (intrabronchial positioning of feeding tubes can cause a pneumothorax; capnography can be useful to avoid this complication).
2. Inspect all cuffs to rule out malfunction before initiation of feeding.

B. Daily care of feeding tubes

1. Daily irrigation of feeding tubes with normal saline or distilled water may avoid occlusion.
2. Should occlusion occur, tubes could be cleared by irrigation with warm saline, carbonated liquid, or digestive enzymes (pancrelipase [Viokase and Pancrease]).

C. Delivering the feeding formula

1. EN through nasoenteric feeding tubes may be initiated immediately after radiographic confirmation of correct tube position.
2. EN through PEG/PEJ tubes can be started as early as 1 hour after uncomplicated procedures.
3. Jejunal feeding may be instituted as early as 12 to 24 hours postoperatively.
4. Continuous pump infusion results in decreased abdominal distention, less diarrhea, and lower gastric residuals when compared to bolus administration.

D. Complications associated with nasoenteric or percutaneous feeding tubes

1. Possible complications include local infection, pneumothorax, and instillation of tube feeds into the lung, peritonitis, significant hemorrhage (intra- and retroperitoneal, abdominal wall), dislocation, necrosis (pressure ulcer), colonic injury, small bowel injury, liver injury, splenic injury, enterocutaneous fistula, pneumoperitoneum, and death.

Suggested Reading

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Good review on techniques and complications of PEG-placement.

16 CEREBROSPINAL FLUID ASPIRATION

Raimis Matulionis

I. GENERAL PRINCIPLES

A. Cerebrospinal fluid (CSF) profile includes glucose and protein values, a cell count, a Gram stain, cultures, and a pressure reading.

1. CSF glucose

a. **Normally** equivalent to two thirds of serum glucose

b. Lags behind blood levels by approximately 2 hours

c. Increased CSF glucose is nonspecific and usually reflects hyperglycemia

d. Decreased levels—result of any inflammatory or neoplastic meningeal disorder

2. CSF protein

a. Content is usually <0.5% of that in plasma

b. Nonspecific

c. Elevated level in the CSF is an indicator of central nervous system (CNS) pathology

d. Low levels are seen in patients with pseudotumor cerebri, acute water intoxication, and leukemia

3. CSF cell count

a. Normal count includes no erythrocytes and a maximum of five leukocytes per milliliter

b. Helpful in identifying cells from CNS primary or metastatic tumors and differentiation from inflammatory disorders

II. INDICATIONS

A. CSF access for diagnostic purposes. A computed tomography (CT) scan of the head should be strongly considered before performing a lumbar puncture (LP) in patients with dilated or poorly reactive pupils, papilledema, ocular palsies, hemiparesis, a recent history of focal seizures, a rapid or major decrease in the level of consciousness, bradycardia, irregular respirations, tonic seizures, or decerebrate or decorticate posturing.

1. *Hemorrhage*

a. An LP is indicated if the CT scan of the head is not diagnostic

b. A clinical history and presentation—atypical

c. LP should not be performed without prior CT—if any focal neurologic deficits present, transtentorial herniation may occur

2. *Infection*

a. CSF evaluation is the most important aspect of the laboratory diagnosis of meningitis.

b. Includes a Gram stain, cell count with differential, protein and glucose levels, and aerobic and anaerobic cultures with antibiotic sensitivities.

c. If tuberculosis or fungal infection is suspected, the fluid is analyzed by acid-fast stain, India ink preparation, cryptococcal antigen, and then is cultured in appropriate media.

d. Immunocompromised patient requires more extensive cultures performed for rapid diagnosis and early specific treatment.

i. Immunoprecipitation tests to identify bacterial antigens for *Streptococcus pneumoniae, Streptococcus* group B, *Haemophilus influenzae, Neisseria meningitidis* (meningococcus)
ii. Viral cultures, immunoglobulin titers, or polymerase chain reaction tests for herpes simplex, eastern equine encephalitis, West Nile, Varicella zoster, cytomegalovirus, Epstein-Barr virus, *Toxoplasma, Mycobacterium tuberculosis*

3. *Shunt system failure*
   a. Ventriculoperitoneal (VP) shunt most common system.
   b. Consists of a ventricular catheter, reservoir, and valve complex at the skull and a catheter that continues subcutaneously into the peritoneum, jugular vein, pleura, or urinary bladder.
   c. Shunt failure is often due to obstruction, disconnection, or infection of the shunt system.
   d. If failure is suspected, a CT scan should be performed immediately.
   e. Aspiration from the reservoir or valve system performed to determine patency and to collect CSF to rule out an infectious process.
4. *Benign intracranial hypertension (pseudotumor cerebri)*
   a. Occurs in young persons, often obese women.
   b. Intracranial pressure (ICP) elevation without focal deficits.
   c. Absence of ventriculomegaly and mass lesions.
   d. Symptoms develop over several months: headache (most common), dizziness, blurred vision, diplopia, transient visual obscurations, abnormal facial sensations.
   e. Objective signs: visual impairment, papilledema, sixth nerve palsy, LP demonstrates elevated ICP (up to 40 cm H_2O).
   f. Serial daily punctures can be therapeutic, with CSF aspirated until closing pressure is within normal limits (<20 cm H_20).
5. *Neoplasms*
   a. The subarachnoid space can be infiltrated by various primary or secondary tumors.
   b. CSF cytology study can determine the presence of neoplastic cells.
   c. Complete identification is not always possible.
   d. Individual proliferating T and B lymphocytes may aid in the differentiation of an opportunistic infection from a leukemic infiltration.
   e. CSF analysis for autoantibodies could play a role in the diagnosis of some paraneoplastic syndromes.
6. *Other neurologic disorders*
   a. Multiple sclerosis: elevated immunoglobulin G and oligoclonal bands; antibodies against cardiolipin synthetic lecitin (CSL), a sensitive and specific diagnostic test
   b. Alzheimer's disease: elevated τ protein and decreased amyloid-β peptide
   c. Guillain-Barré syndrome: antiganglioside (anti-GM1) antibodies and cytoalbumin dissociation

B. CSF access for therapeutic intervention
1. *Fistulas*
   a. The most common presentation, following trauma. A basilar skull fracture that traverses the ethmoid bone, frontal sinus—causing CSF rhinorrhea.
   b. Fracture that follows the long axis of petrous bone, usually involves middle ear: a hemotympanum and CSF otorrhea present if the tympanic membrane is ruptured.
   c. Delayed leaks are common—fistula can be occluded with adhesions, hematoma, or herniated brain tissue.

d. Diagnosis—clinical examination.
e. If clinical examination is uncertain—laboratory characterization is necessary.
i. Testing for glucose—might be misleading as glucose is present in nasal secretions.
ii. Interpretation of higher chloride levels—is not accurate.
iii. Identification of β_2-transferrin—the most accurate diagnostic for CSF. β_2-transferrin is produced by neuraminidase in the brain and is uniquely found in the spinal fluid and perilymph.
f. First-line treatment of a leak consists of postural drainage by keeping the patient's head elevated for several days.
i. Nonoperative approaches should conservative therapy fail: placement of a lumbar drainage catheter (risk of contamination) and daily LPs.

C. *Intracranial hypertension*
1. Can cause significant neurologic morbidity and mortality.
2. Access to intracranial CSF space could be diagnostic and therapeutic.
3. Most common ICP monitor used for access and to measure ICP is ventriculostomy.
a. It could be used to treat intracranial hypertension by CSF drainage.
b. Indications include head trauma, ischemic cerebral insults, obstructive hydrocephalus, aneurysmal subarachnoid hemorrhage (SAH), spontaneous cerebral hematoma.

D. *Drug therapy*
1. Can be a route of administration for chemotherapeutic agents and antibiotics
a. Intrathecal injections of various agents through LP or intraventricular injections through an implant reservoir for treatment of lymphoma or leukemia
b. Intrathecal chemotherapy in an attempt to minimize agent neurotoxicity
c. Intrathecal antibiotics in addition to systemic therapy

III. PROCEDURE

A. *LP*
1. LP is a common procedure that rarely requires radiologic or other assistance.
2. Contraindications:
a. Skin infection at the entry site
b. Anticoagulation
c. Blood dyscrasias
d. Known spinal subarachnoid block
e. Known spinal cord arteriovenous malformations
f. Papilledema in the presence of supratentorial masses
g. Posterior fossa lesions
3. Steps for LP:
a. A time-out is performed and the universal protocol is followed.
b. The patient is placed in the lateral knee–chest position or is sitting while leaning forward over a table at the bedside.
c. The area around L3-4 is prepped with an aqueous chlorhexidine solution or equivalent.
d. A mask and sterile gloves are worn and a fenestrated sterile drape is placed at the site.
e. Local anesthetic is injected subcutaneously using a 25- or 27-gauge needle.
f. A 1.5-in. needle is then inserted through the skin wheal, and additional local anesthetic is injected along the midline.

- **g.** The point of skin entry is midline between the spinous processes of L3-4, at the level of the superior iliac crests.
- **h.** The needle is advanced with the stylet or obturator in place.
- **i.** The bevel of the needle should be parallel to the longitudinal fibers of the dura or to the spinal column and oriented rostrally at an angle of approximately 30 degrees to the skin and aiming toward the umbilicus.
- **j.** When properly oriented, the needle passes through the following structures: skin → superficial fascia → supraspinous ligament → interspinous ligament → ligamentum flavum → epidural space with its fatty areolar tissue and internal vertebral plexus → dura → arachnoid membrane.
- **k.** An 18- to 20-gauge spinal needle should be used for pressure measurement.
  - **i.** The opening pressure is best measured with the patient's legs relaxed and extended partly from the knee–chest position.
  - **ii.** Once collected, the closing pressure is measured before needle withdrawal.
  - **iii.** Measurements are not accurate if performed while the patient is sitting because of the hydrostatic pressure of the CSF column.
- **l.** Hemorrhage is uncommon but possible with bleeding disorders and anticoagulation.
- **m.** Spinal SAH can result in blockage of CSF outflow with subsequent back and radicular pain, sphincter disturbances, and even paraparesis.
- **n.** Spinal subdural hematoma is similarly infrequent, but it is associated with significant morbidity.
- **o.** Surgical intervention for clot evacuation must be prompt.
- **p.** Infection by introduction of skin flora in the subarachnoid spaces causing meningitis is uncommon and preventable if aseptic techniques are used.

4. Postdural puncture headache (PPH) is the most common post-LP complication
- **a.** A smaller, atraumatic (pencil point) needle, parallel orientation to the dural fibers, and a paramedian approach—associated with a decreased risk of this complication.
- **b.** Typically develops within 72 hours and lasts 3 to 5 days and typically gets worse when upright compared with the supine position.
- **c.** Conservative treatment consisting of bed rest, hydration, and analgesics.
- **d.** If the symptoms are more severe, methylxanthines (caffeine or theophylline) may be successful in up to 85% of patients.
- **e.** If PPH persists or is unaffected, an epidural blood patch is then recommended.

Suggested Reading

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Classic reading material, good for references on neurosurgical issues.

NEUROLOGIC AND INTRACRANIAL PRESSURE MONITORING

17

Raimis Matulionis

I. GENERAL PRINCIPLES

A. The brain uses more oxygen and glucose per 100 g of tissue than any large organ. Completely dependent on uninterrupted cerebral blood flow (CBF) (i.e., has no appreciable reserves of oxygen and glucose).

B. Clinical monitoring directed toward early detection and reversal of potentially dangerous conditions.

C. Neurologic monitoring falls into two distinct categories:

1. Electroencephalography (EEG) and evoked potentials (EPs)—define a qualitative threshold consistent with the onset of cerebral ischemia.
2. Monitors of intracranial pressure (ICP), CBF, and cerebral metabolism—provide quantitative physiologic information.

D. Cerebral ischemia, defined as cerebral oxygen delivery (C_{DO_2}) insufficient to meet metabolic needs.

E. C_{DO_2} components: CBF, hemoglobin concentration, arterial hemoglobin saturation (Sa_{O_2}).

II. TECHNIQUES

A. Systemic monitoring

1. Pulse oximetry and blood pressure provide clues about the adequacy of global brain oxygenation.
2. Cerebral perfusion pressure (CPP = mean arterial pressure [MAP] − ICP) does not alter CBF over a range of pressures of approximately 50 to 150 mm Hg.
3. Pa_{CO_2} regulates cerebral vascular resistance over a range of 20 to 80 mm Hg.
4. CBF is acutely halved if Pa_{CO_2} is halved, and it is doubled if Pa_{CO_2} is doubled.
5. A decreasing arterial O_2 content (Ca_{O_2}), resulting from a decrease in hemoglobin or in Sa_{O_2}, normally causes CBF to increase.

B. Neurologic examination

1. Neurologic examination quantifies three key characteristics: level of consciousness, focal brain dysfunction, and trends in neurologic function.
2. The Glasgow Coma Scale (GCS), originally developed as a prognostic tool, has become a quick, reproducible *estimate* of level of consciousness (Table 17-1).

C. Neuroimaging

1. Cerebral computed tomography (CT): provides valuable prognostic information about ultimate neurologic outcome and about the risk of subsequent intracranial hypertension and brain structure but not function.
2. Magnetic resonance: provides better resolution than CT, but has limited use in trauma due to incompatibility with ferrous material, a frequent component of life support systems.

D. CBF monitoring

1. Xenon 133 (^{133}Xe) clearance and CT: clinical use is limited because of cumbersome regulations governing the administration of radionuclides, the

TABLE 17-1 Glasgow Coma Score

Component	Response	Score
Eye opening	Spontaneously	4
	To verbal command	3
	To pain	2
	None	1
	Subtotal: 1–4	
Motor response (best extremity)	Obeys verbal command	6
	Localizes pain	5
	Exhibits flexion withdrawal	4
	Exhibits flexor response (decorticate posturing)	3
	Exhibits extensor response (decerebrate posturing)	2
	Shows no response (flaccid)	1
	Subtotal: 1–6	
Best verbal response	Oriented and converses	5
	Disoriented and converses	4
	Uses inappropriate words	3
	Makes incomprehensible sounds	2
	Has no verbal response	1
	Subtotal: 1–5	
	Total: 3–15	

technically demanding nature of the measurements, and the sustained stable conditions (5 to 15 minutes) required to perform a single measurement.

2. Transcranial Doppler flow velocity: used to identify vasospasm after traumatic and nontraumatic subarachnoid hemorrhage.
3. Thermal diffusion: the device determines CBF in one small region of cortex—could be a useful monitor of global CBF or of a specific region at risk of ischemia; surgical placement and maintenance of an invasive intracranial device carries a risk of infection.

E. ICP monitoring

1. ICP functions as the outflow pressure for the cerebral circulation.
2. Although CBF cannot be directly inferred from MAP and ICP, severe increases in ICP reduce both CPP and CBF.
3. ICP monitoring has been used for surveillance and goal-directed therapy.
4. The Brain Trauma Foundation and the American Association of Neurologic Surgeons have published guidelines for the management of traumatic brain injury, including standards, guidelines, and options for the use of ICP monitoring.
   a. ICP monitoring is appropriate:
      i. In all salvageable patients with severe head injury (GCS score of 3 to 8 after resuscitation) and abnormal CT scan
      ii. In patients with severe head injury and a normal CT scan if two or more of the following are noted at admission: age older than 40, unilateral or bilateral motor posturing, and systolic blood pressure <90 mm Hg
      iii. Not monitoring ICP while treating for elevated ICP can be deleterious and result in poor outcome

- **b.** Current data support 20 to 25 mm Hg as an upper threshold above which treatment to lower ICP should generally be initiated.
- **c.** Ranked devices based on their accuracy, stability, and ability to drain cerebrospinal fluid (CSF).
  - **i.** Intraventricular devices—fluid-coupled catheter with an external strain gauge
  - **ii.** Intraventricular devices—micro strain gauge or fiber optic
  - **iii.** Parenchymal pressure transducer devices
  - **iv.** Subdural devices
  - **v.** Subarachnoid fluid-coupled devices
  - **vi.** Epidural devices
- **d.** In addition to intracranial hypertension, other data that may prompt concern:
  - **i.** Widening of the pulse ICP (indicating diminishing intracranial compliance)
  - **ii.** Plateau waves (cyclic increases in ICP, often 50 mm Hg or greater and lasting as long as 15 to 30 minutes)
- **e.** Complications of ICP monitoring include:
  - **i.** Aggravation of cerebral edema
  - **ii.** Intracranial hemorrhage
  - **iii.** Cortical damage
  - **iv.** Infection
  - **v.** Device-related malfunction and injuries

F. Brain oxygenation monitoring—there is currently insufficient evidence to determine whether the information they provide is useful for patient management or prognosis.

1. Jugular venous saturation monitoring—episodes of desaturation (SjO_2 50% to 55%) are associated with worse outcomes.
2. Brain tissue oxygen tension—low values of PbO_2 (10 to 15 mm Hg) and the extent of their duration (>30 minutes) are associated with high rates of mortality.
3. Near-infrared spectroscopy—determines the relative concentrations of oxygenated and deoxygenated hemoglobin in brain tissue.
4. Neurochemical monitoring: microdialysis technique—recovered dialysate can be analyzed for neurotransmitters or metabolic intermediates.

G. Electrophysiologic monitoring

1. Used to detect potentially damaging cerebral hypoperfusion, isolated seizures, and status epilepticus and to define the depth or type of coma.
2. Has limited value as a precise diagnostic tool.
3. Quantitative EEG monitoring used to identify delayed ischemic deficits after subarachnoid hemorrhage, occasionally before clinical deterioration.
4. Sensory EPs, which include somatosensory evoked potentials (SSEPs), brainstem auditory evoked potentials (BAEPs), and visual evoked potentials (VEPs), can be used as qualitative threshold monitors to detect severe neural ischemia by evaluating characteristic waveforms to specific stimuli.
5. Obliteration of EPs occurs only under conditions of profound cerebral ischemia or mechanical trauma. EP monitoring is one of the most specific ways in which to assess neurologic integrity.
6. EPs are insensitive to less severe deterioration of cerebral or spinal cord oxygen availability and are modified by sedatives, narcotics, and anesthetics.

Suggested Reading

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PERCUTANEOUS SUPRAPUBIC CYSTOSTOMY

18

Kevin M. Dushay

I. ANATOMY

- **A.** Urinary bladder is anterior and inferior to peritoneal cavity, and posterior to pubic symphysis.
  - **1.** When distended with urine, bladder dome rises above the pubic symphysis.
- **B.** Anterior superior midline of the external surface of the urinary bladder is generally free of major blood vessels.
  - **1.** Major arterial supply to anterior superior surface is from internal iliac branches entering lateral walls of bladder.
  - **2.** Venous drainage flows inferiorly and laterally to reach internal iliac veins.

II. ALTERNATIVES TO PERCUTANEOUS SUPRAPUBIC CYSTOSTOMY

- **A.** Urethral catheterization
  - **1.** Patients with prior prostate surgery may be easier to catheterize with Coudé catheter.
  - **2.** For urethral stricture, passing filiform and followers to dilate stricture may allow passage of Foley.
  - **3.** Urology consult for bedside flexible cystoscopy with passage of guidewire followed by urethral catheter insertion using Seldinger technique.

III. INDICATIONS

- **A.** Unsuccessful urethral catheterization in the setting of:
  - **1.** Acute urinary retention
  - **2.** Need for accurate urinary output monitoring
  - **3.** Prostatic hyperplasia, cancer, or prior prostate surgery
  - **4.** Loss of or threat to skin integrity due to urinary incontinence
- **B.** Inability to tolerate urethral catheter:
  - **1.** Following prostate or pelvic surgery
  - **2.** Urethral pain, excoriation, necrosis
  - **3.** Dementia/delirium causing patient to repeatedly remove catheter
- **C.** Urethral disruption from pelvic trauma/fracture (requires emergent placement)
- **D.** Bladder drainage required in the presence of severe urethral, prostatic, or epididymal infection to avoid bacteremia
  - **1.** Alternative—pretreat with antibiotics before inserting indwelling Foley catheter.
- **E.** Neurogenic bladder dysfunction with autonomic hyperreflexia associated with acute bladder distension
- **F.** Spinal cord injury patients:
  - **1.** May be easier for patient or caregiver than indwelling Foley catheter or intermittent straight catheterization
  - **2.** May reduce frequency of urinary tract infections

IV. CONTRAINDICATIONS

- **A.** Nonpalpable bladder
- **B.** Previous lower abdominal surgery

C. Bladder cancer
D. Coagulopathy
E. Blood clot retention in bladder
F. Lower abdominal wall cellulitis
G. Not recommended as first-line treatment for prostatic obstruction

V. PROCEDURE

A. Equipment—a number of different kits and devices are available
   1. Two main types of devices
      a. Catheter over introducer needle or obturator
      b. Sheath over needle or introducer, through which catheter is inserted
B. Technique
   1. For both types of device:
      a. Bladder sufficiently full to allow localization by palpation and/or by ultrasound and to allow needle entry into bladder without trauma to adjacent structures
         i. Bedside ultrasound localization/guidance recommended to reduce complications, especially with prior abdominal or pelvic surgery, prior radiation therapy, women with bladder prolapse, and to exclude trapped bowel or abnormal location of bladder, or for less-experienced operators.
         ii. Have all supplies ready; kit may not include prep, lidocaine, catheter, or collection system.
         iii. Follow universal protocol.
         iv. Patient supine, Trendelenberg position; prepare site with clippers if necessary; sterile prep and drape, lay out equipment, check catheter balloon.
         v. Use 1% or 2% lidocaine for midline skin wheal 2 to 4 cm above pubic symphysis; anesthetize tract perpendicular to body axis or angled 20 degrees caudally through subcutaneous tissue and rectus abdominis fascia using finder/introducer needle until bladder entry confirmed by aspiration of urine; then use scalpel to make stab wound along axis of needle.
   2. Catheter over trocar
      a. Withdraw finder needle, holding device near skin surface insert it along prepared path until urine aspirated.
      b. Advance device slightly and slide catheter into bladder while fixing trocar in place.
      c. Then remove trocar and secure catheter in position.
   3. Seldinger technique
      a. Remove syringe.
      b. Pass guidewire through introducer needle to indicator mark.
      c. Withdraw needle and pass dilator(s) over guidewire holding dilator close to skin until introducer with preloaded catheter or sheath can be inserted into bladder.
      d. Pinch sheath as guidewire and introducer are withdrawn to avoid urine leakage.
      e. Pass catheter through sheath until urine obtained, deploy anchor/balloon, then withdraw and peel sheath away keeping catheter in place; secure catheter.
   4. Catheter with internal fixation device
      a. Gently withdraw until resistance felt
      b. Advance 2 cm before securing to avoid bladder spasms

VI. POSTPROCEDURE CONSIDERATIONS

- **A.** Complications
  - **1.** Hematuria most common
  - **2.** Bladder spasms also common
    - **a.** Can use oxybutynin (Ditropan), hyoscyamine (Cystospaz), or other antispasmodics
      - **i.** Stop medication before suprapubic tube removal to avoid urinary retention
  - **3.** Retropubic bleeding
  - **4.** Bowel perforation
  - **5.** Rectal, uterine, or vaginal injury
  - **6.** Peritoneal perforation with intraperitoneal urine extravasation
  - **7.** Ureteral catheterization
  - **8.** Catheter dislodgement or kinking
  - **9.** Cellulitis, deep wound infection, cystitis, pyelonephritis, bacteremia
  - **10.** Postobstructive diuresis
  - **11.** Hypotension
  - **12.** Retained catheter or guidewire fragment
  - **13.** Bladder stones

Suggested Reading

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Early description of this technique with a good set of illustrations, though they seem to exaggerate the distance between the symphysis pubis and the entry site.

19 ASPIRATION OF JOINTS

Harvey S. Reich

I. GENERAL PRINCIPLES

A. Overview

1. Arthrocentesis involves the introduction of a needle into a joint space to remove synovial fluid.
2. It is an essential diagnostic technique for the evaluation of arthritis of unknown cause.
3. The presentation of conditions, such as septic arthritis and crystalline arthritis, may be similar, yet treatment may be different.
4. Arthrocentesis and synovial fluid analysis are important for accurate diagnosis.
5. Arthritis can involve a single joint (monoarthritis).
6. Arthritis can involve multiple joints (oligoarthritis).

II. INDICATIONS

A. Principles

1. Arthrocentesis is performed for both diagnostic and therapeutic reasons.
2. The evaluation of arthritis of unknown cause is the main indication for arthrocentesis.
3. In the intensive care unit, arthrocentesis is most commonly performed to rule out septic arthritis in a patient with acute monoarthritis or oligoarthritis.
4. Before performing arthrocentesis, one must be certain that a true joint space inflammation with effusion is present rather than a periarticular inflammatory process, such as bursitis, tendinitis, or cellulitis.
5. In the knee, the presence of an effusion may be confirmed by the bulge test or patella tap.
   a. Bulge test—milk fluid from the suprapatellar pouch into the joint, slide the hand down the lateral aspect of the joint line, and watch for a bulge medial to the joint.
   b. Patellar tap—apply pressure to the suprapatellar pouch while tapping the patella against the femur to determine if the patella is ballottable, which indicates an effusion.
6. Arthrocentesis with ultrasound guidance for evaluation of the joint and surrounding soft tissues can be performed at the bedside to assess for joint fluid, bursal fluid, or other soft tissue fluid collections such as an abscess. This can allow evaluation of bursal or soft tissue collections that may go undetected by blind aspiration, and can prevent potential contamination of an aseptic joint during blind aspiration through overlying infected tissue. Sonographic evaluation may render aspiration unnecessary if no joint or soft tissue fluid is detected.
7. Arthrocentesis may also be used therapeutically, as in the serial aspiration of a septic joint for drainage and monitoring of the response to treatment.
8. Arthrocentesis allows for injection of corticosteroid preparations into the joint space, a form of therapy useful for various forms of inflammatory and noninflammatory arthritis (see subsequent text).

B. Etiology of inflammatory arthritis

1. Rheumatoid arthritis
2. Spondyloarthropathies
   a. Psoriatic arthritis
   b. Seronegative spondyloarthropathy
   c. Ankylosing spondylitis
   d. Ulcerative colitis/regional enteritis
3. Crystal-induced arthritis
   a. Monosodium urate (gout)
   b. Calcium pyrophosphate dehydrate (pseudogout)
   c. Hydroxyapatite
4. Infectious arthritis
   a. Bacterial
   b. Mycobacterial
   c. Fungal
5. Connective tissue diseases
   a. Systemic lupus erythematosus
   b. Vasculitis
   c. Scleroderma
   d. Polymyositis
6. Hypersensitivity
   a. Serum sickness

C. Etiology of noninflammatory arthritis

1. Osteoarthritis
2. Trauma/internal derangement
3. Avascular necrosis
4. Hemarthrosis
5. Malignancy
6. Benign tumors
   a. Osteochondroma
   b. Pigmented villonodular synovitis

D. Contraindications

1. Absolute contraindications to arthrocentesis include infection of the overlying skin or periarticular structures and severe coagulopathy.
2. If septic arthritis is suspected in the presence of severe coagulopathy, efforts to correct the bleeding diathesis should be made before joint aspiration.
3. Therapeutic anticoagulation is not an absolute contraindication.
4. Although known bacteremia is a contraindication to arthrocentesis given the potential for joint space seeding, joint aspiration is nonetheless indicated if septic arthritis is the presumed source of the bacteremia.
5. Articular damage and instability constitute relative contraindications to arthrocentesis.

III. PROCEDURE

A. Arthrocentesis equipment

1. Skin preparation
   a. Two percent chlorhexidine and 70% isopropyl combination antiseptic or equivalent (10% povidone iodine solution should be used only if the patient has a sensitivity to chlorhexidine)
   b. Alcohol swab
   c. Ethyl chloride spray
2. Local anesthesia
   a. 1% Lidocaine, 25-gauge, 1-in. needle, 22-gauge, 1.5-in. needle, 5-mL syringe
   b. Sterile sponge/cloth

3. Arthrocentesis
   a. Sterile gloves
   b. 10- to 60-mL syringe (depending on size of effusion)
   c. 18- to 20-gauge, 1.5-in. needle
   d. Sterile sponge/cloth
   e. Sterile clamp
   f. Adhesive bandage (Band-Aid)
4. Collection
   a. Fifteen milliliters anticoagulated tube (with sodium heparin or ethylene diamine tetra acetic acid, EDTA)
   b. Sterile tubes for routine cultures
   c. Slide, cover slip

B. Technique

1. Joint aspiration requires knowledge of the relevant joint and periarticular anatomy and strict adherence to aseptic technique.
2. Joints other than the knee should probably be aspirated by an appropriate specialist, such as a rheumatologist or an orthopedic surgeon.
3. Aspiration of some joints, such as the hip or sacroiliac joints, may require fluoroscopic, ultrasound, or computed tomographic guidance.
4. The technique for knee aspiration is as follows:
   a. Confirm the presence of an effusion with the patient supine and the knee extended.
   b. Obtain written informed consent from the patient or legal guardian if feasible.
   c. Collect the items required for the procedure (see Section III.A).
5. The superior and inferior borders of the patella are landmarks for needle placement.
6. Entry should be halfway between these borders just inferior to the undersurface of the patella, either from a medial or lateral approach, the former being more commonly used and preferable with small effusions.
7. Cleanse the area with a chlorhexidine–isopropyl alcohol antiseptic solution. Allow the area to dry, then wipe once with an alcohol swab.
8. Local anesthesia can be achieved either with sterile ethyl chloride spray or with infiltration of local anesthetic solution (e.g., 1% lidocaine) into the subcutaneous and deeper tissues.
9. To enter the knee joint, use an 18- to 20-gauge, 1.5-in. needle with a sterile 20- to 60-mL syringe.
10. Use a quick thrust through skin and capsule.
11. Avoid periosteal bone to minimize pain.
12. Aspirate fluid to fill the syringe. If the fluid appears purulent or hemorrhagic, try to tap the joint dry.
13. Drainage of large effusions may require additional syringes, which may be exchanged for the original one while leaving the needle in place.
14. When the fluid has been obtained, the needle is removed, and pressure is applied to the puncture site with sterile gauze.
15. Apply an adhesive bandage after cleaning the area with alcohol. Apply prolonged pressure if the patient has a bleeding diathesis of any type.
16. Document the amount, color, clarity, and viscosity of the fluid. Send the fluid for cell count with differential, Gram stain, routine culture; cultures for gonococcus, mycobacteria, and fungi, if indicated, and polarized microscopic examination for crystal analysis.
17. Anticoagulated tubes are needed for accurate assessment of fluid for cell count and crystal analysis.
18. Sodium heparin and EDTA are appropriate anticoagulants.
19. Fluid may be sent for Gram stain and culture in the syringe or in a sterile red-top tube.
20. Other tests, including glucose and complement levels, are generally not helpful.

TABLE 19-1 Joint Fluid Characteristics

	Normal	Noninflammatory	Inflammatory	Septic
Color	Clear	Yellow	Yellow or opalescent	Variable; may be purulent
Clarity	Transparent	Transparent	Transparent	Opaque
Viscosity	Very high	High	Low	Typically low
Mucin clot	Firm	Firm	Friable	Friable
WBC/mm^3	<200	200–2,000	2,000–100,000	>50,000, often >100,000
PNM%	<25	<25	>50	>75
Culture	Negative	Negative	Negative	Usually positive

C. Synovial fluid analysis (Table 19-1)

1. Synovial fluid is divided into noninflammatory versus inflammatory types based on the total nucleated cell count.
2. A white blood cell (WBC) count of 2,000/mm^3 defines an inflammatory fluid.

D. Color

1. Normal synovial fluid is colorless.
2. Noninflammatory and inflammatory joint fluid has a yellow hue.
3. Septic effusions often appear whitish to frankly purulent.
4. Hemorrhagic effusions appear red or brown.
5. A repeated aspiration from an alternate site may be required if there is a question of a traumatic tap.
6. In case of continued doubt, the hematocrit of the aspirate can be compared with that of peripheral blood.
7. The hematocrit in a hemorrhagic effusion is typically lower than that of a peripheral sample and is equal to it in the case of traumatic tap.

E. Clarity

1. The clarity of the synovial fluid depends on the amount of cellular or particulate matter within it.
2. On the basis of how well, if at all, black print on a white background can be read through a glass tube filled with synovial fluid, the fluid is categorized as being transparent, translucent, or opaque.

F. Viscosity

1. The viscosity of synovial fluid is a measure of the hyaluronic acid content.
2. Degradative enzymes such as hyaluronidase are produced in inflammatory conditions resulting in a thinner, less viscous fluid.
3. The string sign is a bedside measure of viscosity.
4. Normal synovial fluid forms at least a 6-cm continuous string when a drop of fluid is allowed to fall from the needle or syringe.
5. Inflammatory fluid drips like water and will not form a string.
6. The mucin clot, another measure of viscosity, is a test performed by mixing several drops of synovial fluid in 5% acetic acid.
7. A good, tenacious mucin clot forms only with normal, noninflammatory fluid, but not with an inflammatory sample.

G. Cell count and differential

1. The cell count should be obtained as soon as possible after arthrocentesis to avoid a falsely low WBC count caused by delayed analysis.
2. In general, the technique for the cell count is identical to that used with blood samples.
3. Viscous fluid with much debris may give erroneous results with automated counters, thereby making a manual count more accurate in these circumstances.

4. The total WBC count and polymorphonuclear (PMN) cell count increase with infection and inflammation.
5. Septic fluid typically has a differential of >75% PMN cells.

H. Crystals

1. As with the cell count, crystal analysis should be performed as soon as possible after arthrocentesis for optimal diagnostic yield.
2. Fluid is examined for crystals using a compensated polarized light microscope.
3. The presence of intracellular monosodium urate or calcium pyrophosphate dihydrate (CPPD) crystals confirms the diagnosis of gout or pseudogout, respectively.
4. Monosodium urate crystals are usually needle shaped, are negatively birefringent, and appear yellow when oriented parallel to the compensator axis.
5. CPPD crystals typically are smaller and rhomboid, weakly positively birefringent, and appear blue when parallel to the plan of reference.
6. If the fluid cannot be examined immediately, it should be refrigerated to preserve the crystals.
7. Even when crystals are found in a sample, infection must be considered, because crystals can occur concomitantly with a septic joint.

I. Gram stain and culture

1. The Gram stain is performed as with other body fluids.
2. Synovial fluid should routinely be cultured for aerobic and anaerobic organisms. Additional cultures for fungi and mycobacteria should be sent in some circumstances, such as in chronic monoarticular arthritis.
3. Special growth media are required when disseminated gonorrhea is suspected.
4. A positive culture confirms septic arthritis.

IV. POSTPROCEDURE CONSIDERATIONS

A. Complications

1. The major complications of arthrocentesis are bleeding and iatrogenically induced infection.
2. These complications are exceedingly rare with strict adherence to aseptic technique and with correction of significant coagulopathy before joint aspiration.
3. Direct cartilaginous damage by the needle is difficult to quantitate and likely is minimized by avoidance of excessive needle movement or complete drainage of the joint, as well as avoiding advancement of the needle any deeper than needed to obtain fluid.

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ANESTHESIA FOR BEDSIDE PROCEDURES

20

J. Matthias Walz and Mark Dershwitz

I. GENERAL PRINCIPLES

A. Managing pain in critical illness

1. Anesthesia for bedside procedures in the intensive care unit (ICU) is accomplished with total intravenous anesthesia (TIVA).
2. Selecting the proper dose of an analgesic to administer is challenging because of:
   - **a.** Difficulty in assessing the effectiveness of pain relief (delirium, obtundation, endotracheal intubation).
   - **b.** Pharmacokinetic (PK) differences between critically ill and other patients.
   - **c.** Physiologic changes associated with aging (decrease in lean body mass, increase in volume of distribution of lipid soluble drugs, decrease in drug clearance rates, increased sensitivity to hypnotics and analgesics).

B. Pharmacokinetic (PK) considerations

1. PK behavior in critically ill patients is unlike that in normal subjects for the following reasons:
   - **a.** ICU patients frequently have renal and/or hepatic dysfunction; therefore, drug metabolism and elimination may be significantly impaired.
   - **b.** Hypoalbuminemia, common in critical illness, decreases protein binding and increases free (active) drug concentration.
2. The doses of medications used for TIVA must therefore be individualized for a particular, critically ill patient (for more detailed PK considerations see Dershwitz, 2007 in Suggested Reading).

II. INDICATIONS

A. Selection of agent

1. Procedures performed in the ICU can be differentiated according to their associated levels of discomfort in:
   - **a.** Mild to moderately uncomfortable (esophagogastroscopy, paracentesis)
   - **b.** Moderately to severely uncomfortable (endotracheal intubation, thoracostomy, flexible bronchoscopy)
   - **c.** Extremely painful (rigid bronchoscopy, orthopedic manipulations, tracheotomy)
2. Specific disease states should be considered so that safety and effectiveness are maximized:
   - **a.** Head trauma.
     - **i.** Effective, yet brief anesthesia is desirable so that the capacity to assess neurologic status is not lost for extended periods.
     - **ii.** The technique should not adversely affect cerebral perfusion pressure.
     - **iii.** If the effects of the medications dissipate too rapidly, undesirable episodes of agitation and increased intracranial pressure (ICP) may occur.
   - **b.** Coronary artery disease: sufficient analgesia is necessary during and after invasive procedures to minimize tachycardia (which is a major

determinant of ischemia) and reduce plasma catecholamine and stress hormone levels.

c. Renal or hepatic failure:
   i. The risk of an adverse drug reaction is at least three times higher in patients with azotemia compared to those with normal renal function.
   ii. Liver failure alters the volume of distribution of many drugs by impairing synthesis of albumin and α_1-acid glycoprotein.
   iii. Reductions in hepatic blood flow and hepatic enzyme activity decrease drug clearance rates.

III. PROCEDURE

A. Hypnotics

1. The characteristics of commonly used hypnotics are listed in Table 20-1

B. Propofol

1. Propofol is an extremely popular hypnotic agent for the following reasons.
   a. Propofol is associated with pleasant emergence and little hangover.
   b. It is readily titratable and has more rapid onset and offset kinetics than midazolam.
   c. The rapid recovery of neurologic status makes propofol a good sedative in ICU patients, especially those with head trauma.
   d. Spontaneously breathing patients anesthetized with propofol may maintain normal end-tidal carbon dioxide values during minor surgical procedures.
2. Maintenance infusion rates of 100 to 200 μg/kg/minute are adequate in younger subjects, which should be reduced by 20% to 50% in elderly individuals.
3. Adverse effects of propofol administration include:
   a. Depressed ventricular systolic function and decreased afterload.
   b. In patients with coronary artery disease, propofol administration may be associated with a reduction in coronary perfusion pressure.
   c. The emulsion used as the vehicle for propofol supports bacterial growth; iatrogenic contamination leading to septic shock is possible.
   d. Hyperlipidemia with prolonged infusions can occur, particularly in infants and small children.
   e. Serum zinc levels should be measured daily during continuous propofol infusions (chelation of trace metals, particularly zinc, by ethylenediaminetetraacetic acid, the bacteriostatic agent in one formulation).

TABLE 20-1 Characteristics of Intravenous Hypnotic Agents

	Propofol	Etomidate	Ketamine	Midazolam
Bolus dose (mg/kg)	1–2	0.2–0.3	1–2	0.05–0.1
Onset	Fast	Fast	Fast	**Intermediate**
Duration	Short	Short	Intermediate	Intermediate
Cardiovascular effects	↓	**None**	↑	Minimal
Respiratory effects	↓	↓	**Minimal**	↓
Analgesia	None	None	**Profound**	None
Amnesia	Mild	Mild	**Profound**	**Profound**

↓, decrease; ↑, increase.
The listed doses should be reduced 50% in elderly patients.
Entries in bold type indicate noteworthy differences among the drugs.

C. Etomidate

1. Etomidate has onset and offset PK characteristics similar to those of propofol and lacks significant effects on myocardial contractility (even in the setting of cardiomyopathy).
2. Etomidate depresses cerebral oxygen metabolism and blood flow in a dose-dependent manner without changing the intracranial volume–pressure relationship.
3. Etomidate is particularly useful in patients with:
   a. Hypovolemia
   b. Multiple trauma victims with closed head injury
   c. Patients with low ejection fraction, severe aortic stenosis, left main coronary artery disease, or severe cerebrovascular disease
4. Adrenal suppression can occur.
   a. Prolonged infusion is not recommended because of adrenocortical suppression.
   b. A single induction dose of etomidate may be hazardous in patients with established or evolving septic shock.

D. Ketamine

1. Ketamine is unique among the hypnotic agents in that it has analgesic, sedative, and amnestic effects.
2. Ketamine has a slower onset and offset as compared to propofol or etomidate following intravenous (IV) infusion, and stimulates the cardiovascular system (i.e., raises heart rate and blood pressure by direct stimulation of the central nervous system [CNS]).
3. Ketamine may be safer than other hypnotics or opioids in nonintubated patients because it depresses airway reflexes and respiratory drive to a lesser degree.
4. In the usual dosage, ketamine decreases airway resistance.
5. The administration of ketamine can be associated with disorientation, sensory and perceptual illusions, and vivid dreams; these effects have been termed *emergence phenomena*. To avoid emergence phenomena after ketamine administration, pretreatment or concurrent treatment with a benzodiazepine or propofol should be considered.
6. The combination of ketamine with a benzodiazepines and/or an opioid is useful in patients with coronary artery disease to avoid myocardial ischemia (the use of ketamine alone increases myocardial oxygen consumption).
7. Ketamine is relatively contraindicated in patients with increased ICP.

E. Midazolam

1. Administration of midazolam produces anxiolysis, amnesia, and relaxation of skeletal muscle (ideally suited for brief, relatively painless procedures as well as for prolonged sedation).
2. Midazolam is highly (95%) protein bound, and recovery is prolonged in obese and elderly patients and after continuous infusion because it accumulates significantly.
3. In patients with renal failure, active conjugated metabolites of midazolam may accumulate and delay recovery.
4. Midazolam (0.15 mg/kg IV) causes respiratory depression and blunts the ventilatory response to hypoxia.
5. Midazolam has a stable cardiovascular profile and causes dose-dependent reductions in cerebral metabolic rate and cerebral blood flow.

F. Opioids

1. Opioids blunt pain by:
   a. Inhibiting pain processing by the dorsal horn of the spinal cord
   b. Decreasing transmission of pain by activating descending inhibitory pathways in the brainstem
   c. Altering the emotional response to pain by actions on the limbic cortex

G. Morphine

1. Morphine is an agonist at μ, κ, and δ receptors.
2. Morphine causes significant histamine release after IV bolus injection.
3. Adverse effects of morphine include:
   a. Gastrointestinal:
      i. Constipation, nausea, and/or vomiting
      ii. Reduced gastric emptying and bowel motility
   b. Cardiovascular: hypotension, especially if it is given rapidly (i.e., 5 to 10 mg/minute)
   c. Respiratory:
      i. Morphine decreases the ventilatory response to CO_2 and hypoxia.
      ii. Exaggerated ventilatory depression in patients with renal failure is possible because of the active metabolite, morphine-6-glucuronide.

H. Fentanyl and related drugs

1. Fentanyl, alfentanil, sufentanil, and remifentanil enter and leave the CNS much more rapidly than morphine (much faster onset of effect after IV administration).
2. They are selective μ-opioid receptors agonists (the only significant difference among these agents is their PK behavior).
3. Fentanyl may be useful when given by intermittent bolus injection (50 to 100 μg), but when given by infusion its duration becomes prolonged.
4. Remifentanil owes its extremely short duration to rapid metabolism by tissue esterases (primarily in skeletal muscle); its PK behavior is unchanged in the presence of severe hepatic or renal failure.
5. Sufentanil infusion for TIVA may be initiated with a 0.5 to 1.5 μg/kg bolus followed by an infusion at 0.01 to 0.03 μg/kg/minute.
6. Remifentanil infusion for TIVA may be initiated with a 0.5 to 1 μg/kg bolus followed by an infusion at 0.25 to 1 μg/kg/minute.
7. Adverse effects can include hypotension when administered as a bolus (medullary vasomotor center depression and vagal nucleus stimulation), increases in ICP and adverse effects on cerebral perfusion pressure (fentanyl and sufentanil) and chest wall rigidity with large doses (fentanyl).

I. Neuromuscular blocking agents

1. Succinylcholine

   a. Succinylcholine 1 mg/kg IV will result in excellent intubating conditions in less than a minute. It is the drug of choice when the airway must be secured quickly (full stomach or symptomatic gastroesophageal reflux) unless there are contraindications.
   b. Succinylcholine may trigger malignant hyperthermia in genetically susceptible persons.
   c. Succinylcholine may cause a malignant rise in the extracellular potassium concentration in patients with major acute burns, upper or lower motor neuron lesions, prolonged immobility, massive crush injuries, and various myopathies.

J. Nondepolarizing neuromuscular blocking (NMB) gents

1. Vecuronium (0.1 mg/kg), rocuronium (0.6 to 1.2 mg/kg), and cisatracurium (0.1 to 0.2 mg/kg) are often used to facilitate intubation in persons in whom succinylcholine is contraindicated and are essentially devoid of cardiovascular effects.
2. Pancuronium (0.1 mg/kg) is a longer-lasting NMB drug and is commonly used to facilitate mechanical ventilation.
3. Pancuronium has a vagolytic effect that may cause tachycardia.
4. Use of NMB agents may cause muscle weakness persisting for months afterward: risk factors include concomitant glucocorticoid therapy or prolonged NMB.

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21 ROUTINE MONITORING IN THE INTENSIVE CARE UNIT

Akshay S. Desai and Gisela Banauch

I. TEMPERATURE

A. General principles

1. Estimate core temperature (independent of ambient fluctuations because of hypothalamic regulation).

B. Indications

1. Pulmonary artery, bladder, and rectum are reliable measurement sites; axillary, sublingual, and tympanic sites underestimate.

C. Procedure

1. Measure at least every 4 hours; continuously when <36°C or >39°C, or temperature-altering interventions applied (cooling blanket, active rewarming). Pulmonary artery, rectum, or bladder for continuous monitoring.

D. Postprocedure considerations

1. Rectal site can transmit resistant enteral bacteria.

II. ARTERIAL PRESSURE

A. General principles

1. Assess perfusion pressure adequacy: assure sufficient circulation for substrate/oxygen delivery and metabolic waste/carbon dioxide (CO_2) removal.
   - **a. Catheter**
     - i. Fluid column continuously transmits arterial pressure to transducer, where it is converted into electrical signal through diaphragm deformation-induced resistance changes in a Wheatstone bridge.
   - **b. Automated oscillometric monitor**
     - i. Analyzes magnitude/shape of arterial pressure oscillations with intermittent, controlled, slow blood pressure cuff inflation/deflation.

B. Indications

1. High risk of tissue perfusion compromise: all critically ill patients
   - **a. Catheter**
     - i. Erroneously high pressures from small air bubbles/heart rates close to transducer system's resonant frequency (overshoot)
     - ii. Erroneously low pressures from large air bubbles, catheter thrombus/heart rates above transducer system's resonant frequency (damping)
   - **b. Automated oscillometric monitor**
     - i. Intermittent measurements do not reflect rapidly changing hemodynamics.
     - ii. Inadequately sized cuffs (width/length) overestimate.
     - iii. Poor correlation with intra-arterial values at pressure extremes.

C. Procedure

1. **Catheter**
   - a. Seldinger technique for most insertions (radial, femoral, axillary sites).
   - b. Pressure zeroing at right atrial level required.
2. **Automated oscillometric monitor**
   - a. Cuff bladder width should equal 40%, length should equal/exceed 60% of extremity circumference.
   - b. Position microphones over artery.

D. Postprocedure considerations

1. Catheter

a. Complications include distal vessel occlusion, hemorrhage, and infection.

2. Automated oscillometric monitor

a. Complications include distal limb ischemia, venous stasis with prolonged/frequent cuff inflation or deflation failure; do not perform on limbs with compromised arterial/venous/lymphatic circulation.

III. ELECTROCARDIOGRAPHY

A. General principles

1. Assure perfusing rhythm: detect malignant arrhythmias. Endogenous cardiac electrical impulses monitored; computerized arrhythmia detection based on heart rate, variability, electrocardiogram (ECG) intervals/segment lengths, morphology.

B. Indications

1. High likelihood of malignant arrhythmia and/or cardiac ischemia: all critically ill patients. Artifacts arise from muscle activity or poor transmission (obesity, poor skin preparation, improperly positioned electrodes)

IV. RESPIRATORY MONITORING

A. General principles

1. Assure adequate ventilation/gas exchange.

a. Impedance pneumography

i. Measures thoracic impedance changes due to respiration-induced alterations in thoracic geometry; therefore, quantifies respiratory rate.

b. Mechanical ventilator

i. Measures inhaled/exhaled airflow versus time; derives respiratory rates, tidal volumes, minute ventilation

c. Pulse oximetry

i. Measures difference in light absorption spectra of oxygenated/deoxygenated hemoglobin across pulsatile tissue bed over time; calculates absorption ratio change over time, which estimates arterial oxygen saturation.

B. Indications

1. High likelihood of ventilatory and/or gas exchange impairment: all critically ill patients

a. Impedance pneumography

i. Imprecise at respiratory rate extremes/with physical motion

b. Mechanical ventilator

i. Moisture on pneumotachograph overestimates flow/volume

ii. Circuit leaks over- or underestimate respiratory rate and flow/volume

c. Pulse oximetry

i. Erroneous measurements from poor tissue perfusion (hypothermia, vasoconstrictors, hypovolemia, hypotension)

ii. Falsely low measurements from ethylene blue and other intravascular dyes

iii. Falsely elevated measurements from carboxy- /methemoglobinemia

iv. Falsely low measurements at earlobe in severe tricuspid insufficiency (venous regurgitation into capillaries)

V. CARDIAC OUTPUT

A. General principles

1. Assess flow adequacy: assure sufficient circulating volume for substrate/oxygen delivery and metabolic waste/CO_2 removal.

a. Thermodilution

i. Measures temperature versus time curve of pulmonary venous blood after known volume of cold solution injected into right atrium.

Pulmonary venous measurement site allows complete mixing of cold indicator solution with circulating blood volume. Cardiac output inversely proportional to integral of time versus temperature curve.

b. Esophageal Doppler

i. Measures blood flow velocity in descending thoracic aorta. Stroke volume to lower body calculated from sum of all velocities during one systole (time velocity integral) and aortic cross-sectional area. Cardiac output calculated from heart rate and stroke volume, assuming constant upper/lower body blood flow partition.

c. Pulse contour analysis

i. Measures arterial pressure waveform. Stroke volume calculated from mathematical arterial tree model (parameters include arteriolar resistance, aortic impedance, arterial compliance/capacitance). Model parameters periodically adjusted/calibrated with indicator dilution cardiac output.

d. Carbon dioxide elimination

i. Measures change in transpulmonary CO_2 elimination during normal and intermittent partial rebreathing. Intermittent partial rebreathing eliminates need for mixed venous CO_2 measurement in arteriovenous CO_2 difference estimation. CO_2 production calculated from minute ventilation and instantaneous exhaled CO_2 concentration; arteriovenous CO_2 difference estimated from end-tidal CO_2. Cardiac output directly proportional to CO_2 production and inversely proportional to arteriovenous CO_2 difference.

B. Indications

1. High risk of tissue perfusion compromise: shock, sepsis, major surgery, trauma

a. Thermodilution

i. Assumes exclusively forward flow during cold indicator solution mixing: invalid if tricuspid/pulmonic valve moderately/severely regurgitant and with atrial/ventricular septal defect.

b. Esophageal Doppler

i. Assumes fixed angle between Doppler beam and descending thoracic aortic flow. Small angle variations can produce large errors.

ii. Assumes flat spatial velocity profile of descending thoracic aortic flow; therefore invalid in tortuous/aneurysmal aortas.

c. Pulse contour analysis

i. Frequent recalibration required for rapid arteriolar tone changes; therefore cumbersome in hemodynamic instability

ii. Invalid with cardiac arrhythmias

d. Carbon dioxide elimination

i. Invalid with rapidly changing hemodynamics.

ii. Measures portion of transpulmonary flow that participates in CO_2 elimination; therefore invalid in lung parenchymal disease, including atelectasis.

C. Procedure

1. Thermodilution

a. Pulmonary artery catheter required; room temperature or refrigerated saline injected.

2. Esophageal Doppler

a. Pulsed wave Doppler transducer at tip of flexible probe advanced into esophagus to midthoracic level; long-axis rotation and insertion depth manipulation achieve optimal position with highest speed and clearest signal for aortic flow; endotracheal intubation may be required for airway protection.

3. Pulse contour analysis

a. Radial/femoral arterial catheter for arterial waveform; calibration achieved with either transpulmonary thermodilution (requires

pulmonary artery catheter or central venous catheter and thermistor on arterial catheter) or lithium chloride dilution (requires peripheral/central venous catheter and arterial catheter with lithium ion-sensitive electrode); calibration required every 4 to 8 hours, and more often with rapidly changing hemodynamics.

4. Carbon dioxide elimination

a. Controlled mechanical ventilation with endotracheal intubation required: CO_2 sensor measures instantaneous and end-tidal CO_2, disposable airflow sensor (differential pressure pneumotachometer) measures minute ventilation; disposable rebreathing loop allows measurements under partial rebreathing conditions; pulse oximetry adjusts for intrapulmonary shunting.

D. Postprocedure considerations

1. Thermodilution

a. Complications include cardiac valvular avulsion, catheter knotting, peripheral catheter migration with pulmonary infarction or pulmonary arteriolar rupture/hemorrhage, arrhythmias, central venous access–related thrombosis/infection.

2. Esophageal Doppler

a. Complications include esophageal/gastric perforation, bleeding, and additional complications inherent in endotracheal intubation (trauma/perforation of pharynx, retropharynx, larynx, trachea; epistaxis, aspiration, arytenoid dislocation, laryngospasm with pulmonary edema, hypoxemia).

3. Pulse contour analysis

a. Complications include those inherent in arterial catheterization (arterial injury and hemorrhage, arterial thrombosis or spasm with distal ischemia, infection), and those due to pulmonary arterial or central venous catheterization if required for calibration.

4. Carbon dioxide elimination

a. Complications include those inherent in endotracheal intubation and arterial catheterization.

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22 ECHOCARDIOGRAPHY IN THE INTENSIVE CARE UNIT

Dennis A. Tighe, Gerard P. Aurigemma, and Dinesh Chandok

I. GENERAL PRINCIPLES

A. Echocardiography is a common technique performed on critically ill patients. The major advantages of echocardiography as a diagnostic technique relate to its portability, lack of patient exposure to ionizing radiation, and capability to provide real-time structural and functional (hemodynamic) information.

B. Structural information is provided by transmitting ultrasound energy (2 to 10 MHz) from the echocardiograph and receiving signals returning from the cardiac structures to create real-time, two-dimensional (2D) and three-dimensional (3D) images of the heart.

C. Using the Doppler principle, reflected ultrasound energy can be used to determine the velocity and direction of flowing blood in the heart and great vessels, thereby providing information about the hemodynamic effects of stenotic and regurgitant valve lesions and information about left heart filling pressures and stroke volumes. Instantaneous pressure gradients can be estimated by measuring peak flow velocity (V), and, with application of the modified Bernoulli equation, the pressure gradient (P) can be estimated as $P = 4V^2$. Color-flow Doppler, a pulsed-wave Doppler technique, provides a spatial velocity map of abnormal flow within the heart and great vessels and is most useful to estimate the degree of valvular regurgitation and identify turbulent blood flow. Tissue Doppler imaging adds to the ability to estimate left heart filling pressures.

D. A complete echocardiographic examination includes information provided by the 2D, Doppler, color-flow, and M-mode modalities. 3D echocardiography may add important structural and spatial information in selected cases.

E. Echocardiography methods:

1. Transducer placed directly on the patient's chest (transthoracic echocardiography [TTE])
2. Transducer mounted on a gastroscope passed into the patient's esophagus and stomach (transesophageal echocardiography [TEE])

II. INDICATIONS FOR ECHOCARDIOGRAPHY IN THE INTENSIVE CARE UNIT (ICU)

A. Evaluation of left ventricular (LV) and right ventricular structure and function

1. Rapid estimation of ejection fraction and assessment of parameters such as wall thickness, chamber sizes, and wall motion abnormalities.
2. Doppler echocardiography can provide an accurate assessment of LV filling pressures and stroke volumes.

B. Evaluation of hypotension/shock (Tables 22-1 and 22-2)

C. Evaluation of cardiac valves

1. Assessment of valvular stenosis or regurgitation requires a comprehensive echocardiographic examination utilizing the 2D, pulsed-wave and continuous-wave Doppler, and color-flow Doppler modalities.
2. Suspected infective endocarditis (IE):
   a. TTE has a sensitivity to identify valvular vegetations of 44% to 80% among patients with suspected IE. TTE is relatively insensitive to

TABLE 22-1 Echocardiographic Features of Various Causes of Hemodynamic Compromise

Diagnosis	LVFAC	RV size and function	E/A ratio	S/D ratio
Hyperdynamic shock (e.g. sepsis)	↑	Small, hyperdynamic	>/<1	>1
Cardiogenic shock	↓ or ↑	Dilated, hypokinetic	<1	>1
Hemorrhagic shock	↑	Small, hyperkinetic	<1	<1
Pulmonary embolism	↑ or ↓	Dilated, hypokinetic	<1	>1
Cardiac tamponade	↑	Small, diastolic collapse	<1	>1

↑, increase; ↓, decrease. LVFAC, left ventricular fractional area change; RV, right ventricle; E/A, ratio o fmitral inflow E-wave velocity to A-wave velocity; S/D, systolic to diastolic ratio of pulmonary vein flow velocities.

diagnose myocardial or aortic root abscesses and infection of prosthetic valves.

b. TEE has a sensitivity approaching 100% for vegetations as small as 2 mm. TEE can detect complications of IE, such as fistulous tracts, perforation, and abscess formation, in 90% to 95% of cases. It is the modality of choice with suspected prosthetic valve endocarditis or with suspected IE with highly invasive organisms like *Staphylococcus aureus* (*S. aureus*).

D. Evaluation of the aorta and great vessels

1. Aortic dissection

a. Detection of a mobile intimal flap, aortic regurgitation, pericardial effusion, and aortic rupture.

b. TEE has higher sensitivity and specificity than TTE and equivalent diagnostic accuracy compared to other imaging modalities (Table 22-3).

2. Intramural hematomas and penetrating ulcers, variants of aortic dissection which can cause acute aortic syndromes

3. Deceleration injury to aorta/aortic trauma/valvular injuries

E. Evaluation of hypoxemia

1. Acute pulmonary embolism (PE)—not a first-line test

2. Right-to-left shunting through a patent foramen ovale (bubble test)

3. Congenital heart lesions

F. Evaluation of cardiac source of embolism

TABLE 22-2 Estimation of Right Atrial Pressure from Assessment of Size and Respiratory Change in Diameter of the Inferior Vena Cava

IVC size[a]	Respiratory change	RA pressure (mm Hg)
Small (<1.5 cm)	Collapse	0–5
Normal (1.5–2.5 cm)	Decrease >50%	5–10
Normal	Decrease <50%	10–15
Dilated (>2.5 cm)	Decrease <50%	15–20
Dilated with dilated hepatic veins	No change	>20

IVC, inferior vena cava; RA, right atrium.
[a]Measured at RA–IVC junction.

TABLE 22-3 Diagnostic Performance of the Various Tests for Acute Aortic Dissection

Parameter	Helical CT	MR	TEE
Sensitivity	+++	+++	+++
Specificity	+++	+++	+++
Site of intimal tear	+	+++	+++
Presence of thrombus	++	+++	++
Presence of AR	–	++	+++
Pericardial effusion	++	+++	+++
Branch vessel involvement	+	++	–/+
Coronary artery involvement	–	–	++

CT, computed tomography; MR, magnetic resonance; TEE, transesophageal echocardiography; AR, aortic regurgitation.
+++, excellent; ++, good; +, fair; –, not detected.

II. ECHOCARDIOGRAPHY PROCEDURE

A. A standard TTE examination is performed by placing an ultrasound transducer on the chest and imaging from a variety of areas.

1. In approximately 30% of critically ill patients, the image quality of TTE may be inadequate to obtain appropriate diagnostic information. Administration of a microbubble contrast agent may improve the diagnostic utility of bedside TTE in this situation. When image quality remains an issue or a more detailed evaluation is necessary, a TEE will often be required.
2. Limitations of TTE relate primarily to the adequacy of the available acoustic windows: obesity, obstructive lung disease, chest wall injuries, surgical dressings, small rib spaces, inability to move the patient, or previous sternotomy.
3. Contraindications to microbubble contrast agents include known right-to-left shunts, unstable heart failure, respiratory failure, pulmonary hypertension (systolic pressure >40 mm Hg), acute coronary syndrome within 7 days, serious ventricular arrhythmias, and known hypersensitivity.

TABLE 22-4 Special Preparation for Transesophageal Echocardiography (TEE) Examination

Nothing per mouth >8 h
Assess for contraindications
Insert IV, nasal O_2, BP cuff, ECG monitor, saturation monitor
Topical anesthesia
Bite block
IV sedation
  Narcotic
  Benzodiazepine
  Paralytic (endotracheally intubated patients only)
Code cart available
No requirement for infective endocarditis prophylaxis

IV, intravenous; BP, blood pressure; ECG, electrocardiogram.

TABLE 22-5 Special Indications for Transesophageal Echocardiography (TEE)

Mitral valve disorders
Cardiac source of embolism/shunts
Cardiac mass lesions
Diseases of the thoracic aorta
Suspected infective endocarditis
Complicated infective endocarditis
Prosthetic valve dysfunction
Poor transthoracic images
Intraoperative monitoring/valve assessment

4. TEE requires intubation of the esophagus. Special patient preparations are required (Table 22-4). TEE is recognized as a superior imaging modality for certain specific indications (Table 22-5).
   a. Limitations of TEE relate to factors such as cooperation, existence of a large hiatus hernia (limit the ability to acquire adequate images), and inability to intubate the esophagus.
   b. Contraindications to TEE include the presence of significant esophageal pathology (strictures, varices, tumors, mediastinal radiation therapy), upper gastrointestinal bleeding, significant coagulopathy, inadequate airway, and lack of patient cooperation.
   c. Complications: untoward effects of sedation, hypoxia, bleeding, arrhythmia, angina, esophageal perforation, methemoglobinemia, and death.

IV. POSTPROCEDURE CONSIDERATIONS

A. No special postprocedure considerations are required when a TTE is performed.
B. If a microbubble contrast agent was used, monitor the electrocardiogram (ECG), oxygen saturation, and vital signs for 30 minutes following injection.
C. For TEE, postprocedure considerations include patient recovery from conscious sedation (or general anesthesia in rare instances) and care and cleaning of the probe.
   1. Monitoring for a period of no less than 30 minutes post procedure is required for all patients receiving conscious sedation. The patient should have nothing by mouth until swallowing, cough, and gag reflexes have returned appropriately.
   2. The TEE probe should be wiped down and transported expeditiously to the area where it can be immersed in an antimicrobial solution, such as Cidex, for 10 minutes.
   3. The probe should be stored in a protective sheath in an unflexed position.

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23 ARTERIAL PUNCTURE FOR BLOOD GAS ANALYSIS

Marie T. Pavini and Richard S. Irwin

I. GENERAL PRINCIPLES

A. Technical considerations

1. Arterial blood gas (ABG) analysis requires a sample of arterial blood for measurement of pH, partial arterial carbon dioxide pressure ($Paco_2$), partial arterial oxygen pressure (Pao_2), bicarbonate (HCO_3^-), and percent oxyhemoglobin saturation (Sao_2) to assess a patient's respiratory, metabolic, and acid–base status.
2. Given the shape of the oxyhemoglobin dissociation curve, oximetry alone for Sao_2 measurement may not be reliable because there must be a substantial fall in Pao_2 before oximetric Sao_2 is appreciably altered. However, the Sao_2 determined by pulse oximetry may be more accurate than calculated Sao_2 from the ABG because the latter value cannot be corrected for variables such as the binding characteristics of hemoglobin (Hb) and 2,3-diphosphoglycerate.
3. The HCO_3^- in an ABG is calculated in contrast to the HCO_3^- measured in venous chemistries.

B. Equipment

1. A glass syringe is the standard to which all other methods are compared. If a large enough needle is used, entry is apparent because the syringe fills by the pressurized arterial flow of blood, without the need for applying a vacuum or using a vacuum-sealed collecting tube.
2. Other plastic ABG kits are available, which have directions specific for the type of collection syringe offered (see Section IV.A).

C. Alternative procedures

1. Using correction values, a venous blood gas (VBG) is useful when oxygenation is not suspect (i.e., past ABGs have correlated well enough with oximetric saturations, and there is no suspicion of a substantial change in oxygenation).
2. Arterial catheterization is an option if frequent ABG measurements are needed (see Section V.A).

II. INDICATIONS

A. Diagnostic

1. Abnormal acid–base and blood oxygenation can quickly lead to unresponsiveness, serious cardiac arrhythmias, and death and can alert the physician to reversible causes of tissue hypoperfusion, metabolic derangements, and respiratory demise.
2. An ABG should be obtained when there is undiagnosed altered mental status, abnormal breathing pattern, suspicion regarding the accuracy of hypoxemia by oximetric saturations, or abnormal HCO_3^- on chemistry laboratory tests.
3. Discrepancy between Sao_2 by oximetry and that calculated by the ABG can aid in the diagnosis of carboxyhemoglobinemia and methemoglobinemia.
4. Pao_2 from an ABG is necessary for calculation of A-a gradient in the delineation of causes of respiratory acidosis and respiratory alkalosis.

5. Values from an ABG are necessary for determination of arterial content of oxygen (Ca_{O_2}), oxygen delivery (D_{O_2}), and oxygen consumption (V_{O_2}).

III. CONTRAINDICATIONS

A. Puncturing a surgically reconstructed artery may:

1. Result in a pseudoaneurysm
2. Compromise the integrity of the graft site
3. Seed the foreign body, rendering it a nidus for infection

IV. PROCEDURE

A. Cautions

1. If a plastic syringe is used, the following errors may occur:
   - **a.** Falsely low Pa_{O_2} as O_2 from the sample can diffuse to the atmosphere whenever the sample P_{O_2} exceeds 221 mm Hg.
   - **b.** Plastic syringes with high surface area to volume ratios (i.e., tuberculin syringes) worsen gas permeability errors compared to 3-mL syringes. For this reason, butterfly infusion kits with their long tubing should not be used.
   - **c.** Plastic syringes tenaciously retain air bubbles and extra effort is required to remove them.
   - **d.** Plastic impedes smooth movement of the plunger, making arterial blood behave like venous blood (i.e., low pressure flow) and raising suspicion that the sample may be venous.
   - **e.** If plunger retraction imparts suction, gas bubbles may be pulled out of solution. If they are expelled, measured Pa_{O_2} and Pa_{CO_2} tensions may be falsely lowered.
2. Too much heparin causes the concentration of dissolved gases to be closer to that of heparin (P_{O_2} 150 mm Hg; P_{CO_2} <0.3 mm Hg at sea level and room temperature). There is only a 4% dilution error when 0.2-mL heparin is used for 3- to 5-mL blood, but any less heparin risks a clotted specimen. Crystalline heparin is free of dilutional error but risks clotting.
3. If an ABG specimen is not analyzed within 1 minute of being drawn or not immediately cooled to 2°C, the P_{O_2} and pH fall and P_{CO_2} rises due to cellular respiration and consumption of O_2 by leukocytes and platelets. This is of particular concern if leukocytes are $>40 \times 10^9$/L or platelets of $1{,}000 \times 10^9$/L.
4. Unintentional sampling of the vein will result in a report of a low arterial P_{O_2}.
5. Breath holding in normal subjects for 35 seconds has been associated with a fall in Pa_{O_2} of 50 mm Hg and pH of 0.07 and a rise in Pa_{CO_2} of 10 mm Hg.

B. Site selection

1. It is best to select an artery that has good collateral circulation so that if spasm or clotting occurs the distal tissue is not malperfused. It is also best to select a superficial artery for ease of entry as well as to minimize pain. The radial artery is the preferred site for arterial puncture. The ulnar artery provides sufficient collateral blood flow in approximately 92% of normal adults. The Allen's test (or its modification) is not routinely necessary (see Chapter 3) before puncture to determine superficial palmar arch collateral flow.
2. If radial artery sites are not accessible, dorsalis pedis, posterior tibial, superficial temporal (in infants), brachial and femoral arteries are alternatives (see Chapter 3).
3. Brachial and femoral artery punctures are not advised in patients with coagulopathies because adequate vessel tamponade may not be possible.

4. Any vessel that has been reconstructed surgically should not be punctured (see Section III).

C. Technique

1. Observe universal precautions.
2. Face artery to be punctured. If radial artery is the target, supinate the arm, slightly hyperflex the wrist, and palpate the artery. Secure the patient's hand (i.e., with tape) in this position such that it is rendered immobile.
3. Cleanse the site with an alcohol swab or chlorhexidine/alcohol solution.
4. It is preferable to inject with a 25-gauge needle enough 1% lidocaine intradermally to raise a small wheal where the puncture will be made.
5. Attach a 22-gauge or larger needle to a glass syringe that can accept 5 mL of blood. Wet the needle and syringe with a sodium heparin solution (1,000 units/mL) and express all excess solution or use a regulation ABG kit.
6. With the needle, enter the artery at an angle of approximately 30 degrees to the long axis of the vessel to avoid painful scraping of the periosteum below the artery.
7. As soon as the artery is entered, blood appears in the syringe. Obtain at least 3 mL passively in the glass syringe or the prescribed amount for the commercial ABG kit.
8. Immediately after obtaining the specimen, expel any tiny air bubbles to ensure that the specimen will be anaerobic and that results will be accurate. Remove the needle and cap the syringe.
9. If using the glass syringe, have an assistant roll it between both palms for 5 to 15 seconds to mix the heparin with the blood.
10. Apply pressure to puncture site for approximately 5 minutes (longer if a coagulopathy is present). If the brachial artery is used, compress the vessel so that the radial pulse cannot be palpated.
11. Immerse the capped sample in a bag of ice and water/slush. (Some kits do not require this step.) Immediately transport the sample to the blood gas analyzer. Ensure that the sample is labeled with time of draw and ventilator settings (F_{IO_2} if not on ventilator) as well as the temperature of the patient.

V. POSTPROCEDURE CONSIDERATIONS

A. Complications

1. Using the conventional radial artery technique, complications are unusual. These include:
   a. Vasovagal episode (rare)
   b. Local pain with or without breath holding (rendering false results)
   c. Limited hematomas (<0.58% of the time)
   d. Expanding aneurysm (frequent punctures)
   e. Reflex sympathetic dystrophy (frequent punctures)
   f. Spasm
   g. Uncontrolled bleeding
   h. Clotting with possible ischemia and loss of limb
2. Brachial and femoral sites are more difficult to tamponade, making internal bleeding a possibility (especially in coagulopathy).

B. Normal values and corrections

1. pH: 7.35 to 7.45
2. $Paco_2$: 35 to 45 mm Hg
3. Pao_2 (in the normal, nonsmoking, upright person aged 40 to 90): 108.75 (0.39 × age in years) mm Hg
4. Temperature: by convention, ABG specimens are analyzed at 37°C. Although no studies have demonstrated that correction for the patient's temperature is clinically necessary, ABGs drawn at temperatures >39°C

should be corrected because the solubility of O_2 and CO_2 increases as blood is cooled rendering hyperthermic patients more acidotic and less hypoxemic than uncorrected values would indicate.

5. When measuring electrolytes from the same arterial collection, a lithium or electrolyte-balanced heparin should be considered as the anticoagulant because sodium-heparins may artificially increase sodium levels and lower potassium levels through binding. Dilutional error may still exist if excessive amounts of anticoagulant are used.

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24 INDIRECT CALORIMETRY

Nicholas A. Smyrnios and Frederick J. Curley

I. GENERAL PRINCIPLES

A. Indirect calorimetry (IC) measures inspired and expired gas flows, volumes, and concentrations and uses those to determine energy expenditure, respiratory quotient (RQ), and other values.

B. Indirect calorimetry measures the O_2 used and CO_2 produced when carbohydrate, protein, and lipid are oxidized to produce adenosine triphosphate (ATP). Therefore, it is the *production* of chemical energy that is indirectly measured by gas exchange parameters. Nevertheless, the energy activity determined by IC is typically referred to as *energy expenditure.*

II. ENERGY CALCULATIONS

A. Energy expenditures:

1. Basal energy expenditure (BEE)—the energy used by the body at complete rest and in the postabsorptive state (no active food absorption occurring). This occurs only in deep sleep.

2. Resting energy expenditure (REE)—the energy used by the body while awake at rest plus the energy used to metabolize foods. Usually this is approximately 10% more than BEE. Because IC is typically done at rest, its measurement is usually described as REE.

3. Total energy expenditure (TEE) is REE plus the energy used during activity.

B. Most IC systems use the modified de Weir equation to calculate REE. The de Weir equation is not experimentally determined, but is mathematically derived based on our knowledge of the metabolism of carbohydrate, fat, and protein.

1. Energy expenditure $= 3.9(\dot{\mathbf{V}}O_2) + 1.1(\dot{\mathbf{V}}CO_2) - 2.17$(UN g/day) where $\dot{\mathbf{V}}O_2$ is oxygen consumption, $\dot{\mathbf{V}}CO_2$ is carbon dioxide production and UN is urinary nitrogen.

C. Both oxygen consumption and carbon dioxide production are determined by comparing the amount of the gas going into the patient to the amount coming out. To do that, the machine needs to know the volume and concentrations of the inspired and expired airstream. The equations that describe them are:

$$\text{Oxygen consumption} = \dot{\mathbf{V}}O_2 = \dot{\mathbf{V}}I(FIO_2) - \dot{\mathbf{V}}E(FEO_2)$$

$$\text{Carbondioxide production} = \dot{\mathbf{V}}CO_2 = \dot{\mathbf{V}}E(FECO_2) - \dot{\mathbf{V}}I(FICO_2)$$

where FIO_2 and FEO_2 are the inspired and expired oxygen fractions, respectively; $FICO_2$ and $FECO_2$ are the inspired and expired carbon dioxide fractions, respectively; and VE and VI are the exhaled and inhaled minute volumes, respectively. However, most systems measure only the expired airstream volume and mathematically calculate the inspired volume from that. That is done through a mathematical formula called the *Haldane transformation.* The exact derivation of the equation is beyond the scope of this chapter. However, the Haldane transformation is particularly vulnerable to inaccuracy in the measurement of FIO_2 and expiratory volume. Also, it becomes more erroneous as the actual FIO_2 increases. Many oxygen sensors are less accurate at higher FIO_2. Therefore, IC studies are usually limited to patients on 60% O_2 or less. Recent national guidelines support the limitation of FIO_2 to 0.6.

D. IC may be used to determine the percentage of energy expenditure that comes from each of the major foodstuffs. Once CO_2 production and O_2 consumption have been measured, their relationship and a measure of protein metabolism can be used to solve mathematically for the percentage of calories burned, derived from fat or carbohydrate. The exact calculation of percentage of calories burned is beyond the scope of this chapter. However, important points to be remembered from this discussion include:

1. The amount of protein catabolized in a day is estimated to be the sum of urine nitrogen (UN) plus daily losses from skin and stool (assumed to be 4 g/day) multiplied by 6.25.
2. The RQ is the ratio of CO_2 produced to O_2 consumed, or $\dot{V}CO_2/\dot{V}O_2$.
3. The primary foodstuffs have established RQs: fat, 0.7; protein, 0.8; and carbohydrate, 1.0. The normal range of RQ is from 0.7 to 1.0 because a combination of processes is almost always occurring. RQs >1.0 indicate that the net outcome of all the reactions occurring is the synthesis of fat (lipogenesis). Values <0.7 may be encountered when ketones are the primary fuel.

III. INDICATIONS

A. Estimation of caloric needs. Studies have compared the practice of providing calories based on energy expenditure estimated by demographically based equations with the practice of providing calories based on energy expenditure determined by IC. These studies have yielded inconsistent results. Some conclude that estimates of energy expenditure routinely overestimate caloric need, others conclude that estimates of energy expenditure are inaccurate but in no consistent direction, and still others conclude that clinical estimates are as accurate as measured values. There is no clear explanation for the discrepancy between these results. In addition, there is no clear evidence that using an approach based on IC has any impact on outcomes.

B. Substrate utilization. An elevated RQ may indicate excessive levels of carbohydrate metabolism or net lipogenesis due to excess calorie intake. Although the impact of altering substrate composition has not been shown in most diseases, in complicated cases of hepatic or renal failure an analysis of substrate utilization may be used quickly to assess the efficacy of a change in diet.

IV. PROCEDURE

A. Methods of measurement

1. Oxygen sensors in commercially available systems are either zirconium or differential paramagnetic sensors. These analyzers typically have an accuracy of ±0.02% and a response time of 130 ms or less.
2. Most carbon dioxide analyzers are nondispersed infrared devices. These analyzers have an accuracy of ±0.02% with a response time of 110 ms. Some systems measure both inspired and expired carbon dioxide and some measure only expired, assuming the inspired value to be negligible.
3. Volume is measured by measuring flow and integrating the result over time to obtain volume. Flow can be measured with a pneumotach or a mass flow sensor or generated by the device and kept constant in response to changes in ventilation.
4. Gas concentrations are measured using one of three techniques: mixing chamber, breath by breath, or dilution.
   a. Mixing chamber is the best-established method. A mixing chamber mixes expired gases over a predetermined interval and provides the material to be sampled. A sample of mixed gas is withdrawn from the chamber, the gas concentrations analyzed, and the sample returned to the chamber. The concentrations of inspiratory gas are sampled from the inspiratory side of a mouthpiece or a ventilator circuit. A computer

compares mixed expired versus inspired concentrations and multiplies by volume to yield a measure of consumption or production. The results reflect the values of gases mixed over time and are reported as values per time interval of measurement (e.g., milliliters of oxygen consumed per minute).

b. Breath-by-breath method. The collection and analysis of gases in the breath-by-breath method is similar to that in the mixing chamber technique, but each breath is analyzed. A sample of gases is taken for analysis from each inspiration and expiration. These samples are coupled with flow measurements for each breath to calculate $\dot{V}O_2$, $\dot{V}CO_2$, and REE. The crucial component in these measurements is the alignment of various signals. Instruments that use breath-by-breath analysis align the signals automatically by computer. Improper alignment can render the measurements useless.

c. Dilution method. This method is the only technique that can be used in intubated patients as well as in those nonintubated patients who cannot use a mouthpiece. A predetermined flow of gas of known oxygen and carbon dioxide concentration passes through a face shield mask or a hood-like canopy. The exhaled gases are diluted into the stream of gas. The amount of gas the machine puts into the stream is adjusted to keep the flow constant as the patient alters his or her own ventilation. Samples of the diluted gases are removed for analysis and the values obtained multiplied by the flow rate to yield a measure of volume. Oxygen consumption and carbon dioxide production are calculated by comparing concentrations in and out of the system.

B. Factors affecting accuracy

1. All connections to the metabolic cart and in the ventilator circuit must be checked for leaks.

2. An error in measuring O_2 or CO_2 concentrations leads to larger errors in the subsequently calculated values.

3. Any change in inspired O_2 concentration during the study renders the measurements invalid until the inspired O_2 concentration is remeasured. Therefore, it should be measured and displayed frequently during a test.

4. Inspired and expired gas concentrations are typically sampled with long, narrow tubes. These can easily clog with patient secretions and invalidate the data.

5. Most systems also somehow condition the gas from sample tubes to standardize for temperature and water vapor. Failure to follow the manufacturer's advice on desiccant change or timing of tubing change alters the accuracy of the data.

6. Disruption of the normal ventilator circuit with inappropriately placed sampling devices may lead to ventilator malfunction or trigger alarms.

7. The use of positive end-expiratory pressure (PEEP) may variably alter the ventilator circuit compressible volume, leading to errors in volume and concentration measurements. Techniques to isolate the sensors from PEEP have been incorporated into newer generation machines.

8. Traditionally, IC has not been performed on children because of leaks due to uncuffed endotracheal tubes, frequent use of high-frequency ventilation, and the common use of high F_{IO_2} and low ventilator flows. However, because of recent literature that has emphasized the large difference between predicted and measured energy expenditures in critically ill children, IC is now looked upon more favorably in the pediatric population.

9. The presence of gases other than oxygen, carbon dioxide, or nitrogen can alter the calculations.

Suggested Reading

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McArthur CD. Metabolic measurement using indirect calorimetry during mechanical ventilation—2004 revision and update. *Respir Care* 2004;49:1073.
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II Cardiovascular Problems and Coronary Care

25 CARDIOPULMONARY RESUSCITATION

John A. Paraskos

I. **HISTORY.** The introduction of cardiopulmonary resuscitation (CPR) has changed the definitions of life and death. Although sporadic accounts of attempted resuscitations are recorded from antiquity, until the advent of CPR no rational quarrel could be found with the 6th century BCE poetic fragment of Ibycus, "You cannot find a medicine for life once a man is dead."

II. **EFFICACY.** CPR does not appear to promise more than the short-term sustaining of viability until definitive therapy such as defibrillation can be administered. Data from prehospital care systems in Seattle showed that 43% of patients found to be in ventricular fibrillation (VF) are discharged from the hospital if CPR (i.e., basic life support [BLS]) is provided within 4 minutes and defibrillation (as part of advanced cardiac life support [ACLS]) is administered within 8 minutes. Survival rates for patients in asystole or with pulseless electrical activity (PEA) are much lower. Even though patients experiencing cardiac arrest in the hospital can be expected to receive CPR and definitive therapy well within the 4- and 8-minute time frames, their chances of being discharged alive are in general worse than for out-of-hospital victims.

III. MECHANISMS OF BLOOD FLOW DURING RESUSCITATION

A. Cardiac compression theory. According to this theory, during sternal compression the intraventricular pressures rise higher than other intrathoracic pressures. With each sternal compression, the semilunar valves should open and blood be ejected into the aorta and pulmonary artery. Between compressions, the semilunar valves would close and the atrioventricular (AV) valves open, allowing the heart to fill from the lungs and systemic veins. There is some echocardiographic evidence that this mechanism is operative early in the course of CPR.

B. Thoracic pump theory. According to this theory, during CPR the heart serves only as a passive conduit. Forward flow is generated by a pressure gradient between intra- and extrathoracic vascular structures. This is likely the mechanism most operative during CPR. Interposed abdominal compression (IAC)-CPR assists in raising intrathoracic pressure and improving forward flow. IAC-CPR is now advised for in-hospital CPR when abdominal compression is not contraindicated (e.g., abdominal aneurysm). Active compression–decompression (ACD)-CPR and vest CPR are optional techniques for hospital personnel adequately trained in these techniques.

C. Open chest CPR. Open chest CPR involves direct cardiac compression. Patients with penetrating chest trauma are unlikely to respond to chest compression and are candidates for open chest CPR. If open chest CPR is to be used, it must be used early to succeed. This technique should not be attempted unless adequate facilities and trained personnel are available.

D. Cardiopulmonary bypass for unresponsive cardiac arrest. Cardiopulmonary bypass is not a form of routine life support; however, it represents a possible adjunct to artificial circulation. It is being used more frequently for sudden cardiac collapse during invasive procedures as a bridge to emergency surgery.

IV. INFECTIOUS DISEASES AND IMPLICATIONS FOR HEALTH CARE PROFESSIONALS.

Bag-valve-mask devices should be made available to health care personnel as initial ventilation equipment. Early endotracheal intubation should be encouraged when equipment and trained professionals are available. Masks with one-way valves and plastic mouth and nose covers with filtered openings provide some protection from transfer of oral fluids and aerosols. S-shaped mouthpieces, masks without one-way valves, and handkerchiefs provide little if any barrier protection and should not be considered for routine use.

A. Advanced cardiac life support in adults. The use of adjunctive equipment, more specialized techniques, and pharmacologic and electrical therapy in the treatment of cardiac or respiratory arrest is generally referred to as ACLS. These techniques and their interface with BLS and emergency medical services are taught in the American Heart Association (AHA)'s ACLS teaching programs (Fig. 25-1).

1. **Airway and ventilatory support.** Oxygenation and optimal ventilation are prerequisites for successful resuscitation. Supplemental oxygen should be administered as soon as it becomes available, beginning with 100%. Endotracheal intubation is required if the patient cannot be rapidly resuscitated or when adequate spontaneous ventilation does not resume quickly. Trained personnel should attempt intubation.
2. **Circulatory support.** Chest compression should not be unduly interrupted while adjunctive procedures are instituted. The carotid or femoral pulse should be evaluated every few minutes and compressions adjusted as needed. If a compression device or vest is being used, the rescuer

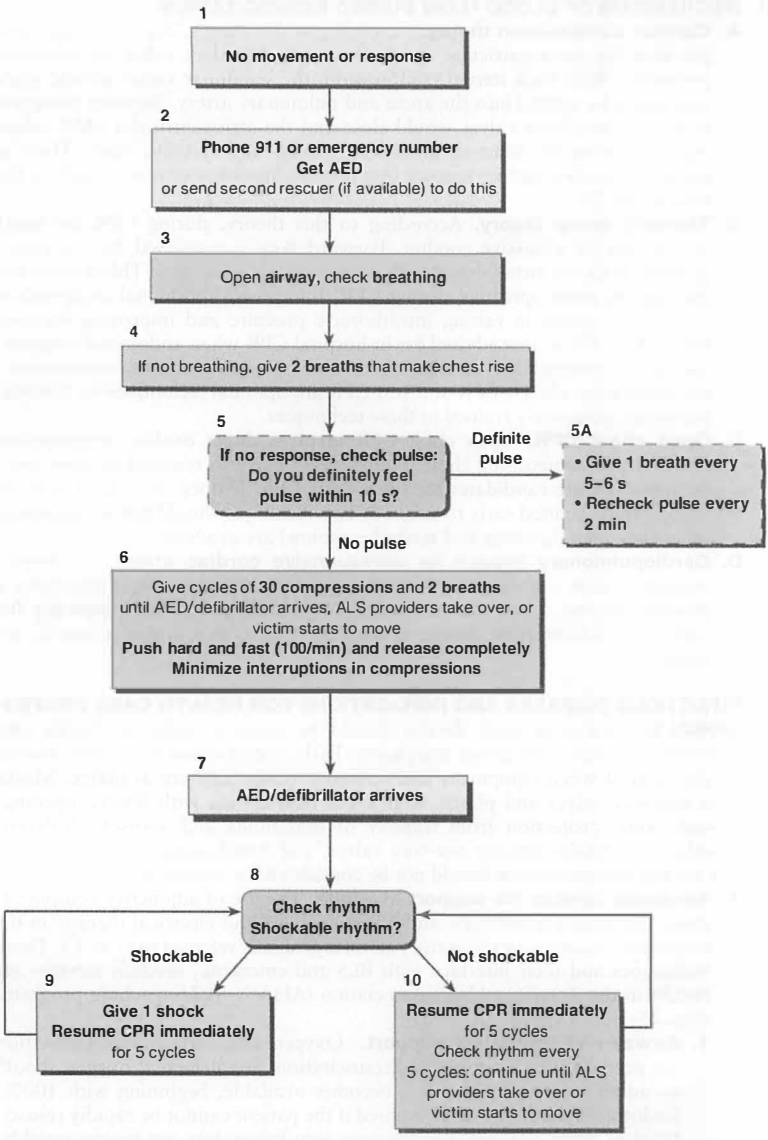

Figure 25-1. Adult basic life support health care provider algorithm. AED, automatic external defibrillator; CPR, cardiopulmonary resuscitation; ALS, advanced life support. (From American Heart Association. Guidelines 2005 for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005;112(Suppl 24):IV-29–IV-34, with permission. Copyright 2005.)

coordinating the resuscitation effort must ensure that adequate pulses are generated by the device.

3. **Defibrillation.** Electrocardiographic (ECG) monitoring is necessary during CPR to guide appropriate electrical and pharmacologic therapy. Until ECG monitoring becomes available, the victim should be assumed to be in VF or pulseless ventricular tachycardia (VT)/VF. Most defibrillators currently marketed (including automated external defibrillators) have built-in monitoring circuitry in the paddles that guide electrical therapy. Defibrillation is the definitive therapy for most cardiac arrests. It should be attempted as early as possible in a witnessed arrest and repeated as per Figure 25-2 until VF or pulseless VT has terminated. In an unwitnessed arrest, five cycles of CPR with simultaneous drug therapy may precede the first defibrillation attempt. Proper use of the defibrillator requires special attention to the following:
   a. **Selection of proper energy levels.** Biphasic defibrillators appear safer and more effective than monophasic defibrillators; 100 J initially and 200 maximum are usually recommended. If only a monophasic defibrillator is available, an initial energy of 200 J appears to be safer than higher energies and equally effective. If 200 J of a monophasic defibrillator has not succeeded on the second try, 300 J (or maximum output) can be used. Very obese victims may require higher energy levels.
   b. **Proper asynchronous mode.** Synchronization to the R wave must be deactivated to allow the defibrillator to fire during VF. During rapid VT (rates >150), it is best not to attempt synchronization with the R wave as this is likely to increase the chance of delivering the shock on the T wave and inducing VF.
   c. **Proper position of the paddles or electrode pads.** The anterolateral position requires that one paddle be placed to the right of the upper sternum, just below the clavicle and the other to the left of the nipple in the left midaxillary line. For the anteroposterior position preferred for pads, one pad is positioned under the left scapula with the patient lying on it. The anterior pad or paddle is positioned to the left of the left sternal border. The pad or paddle should not be placed directly over an implanted device. Self-adhering defibrillator electrode pads are preferable for use in the intensive care unit.
   d. **Adequate contact between paddles and skin.** If hand-held paddles must be used, the rescuer should hold the paddles firmly against the skin with approximately 25 lb of pressure. Electrical contact material must be adequately but not overly applied to the paddle surfaces.
   e. **No contact with anyone other than the victim.** The rescuer must be sturdily balanced on both feet and not standing on a wet floor. The rescuer's hands should not be wet. CPR and manual ventilation must be discontinued with no one remaining in contact with the patient.
   f. **Rechecking of equipment.** If no skeletal muscle contraction is noted, the equipment, contacts, and synchronizer switch used for elective cardioversion should be checked. *Care must be taken that the synchronizer switch is in the off position.*
   g. **Rhythm assessment.** The rhythm should be assessed after each countershock, and the patient checked for a pulse at appropriate times. *This should be done before proceeding with additional therapeutic interventions.*

B. Drug therapy

1. **Intravenous (IV) access.** Venous access through a reliable IV route should be established early in the course of the resuscitative effort to allow administration of necessary drugs and fluids. If reliable IV access has not yet been established, kits are available to establish intraosseous access in

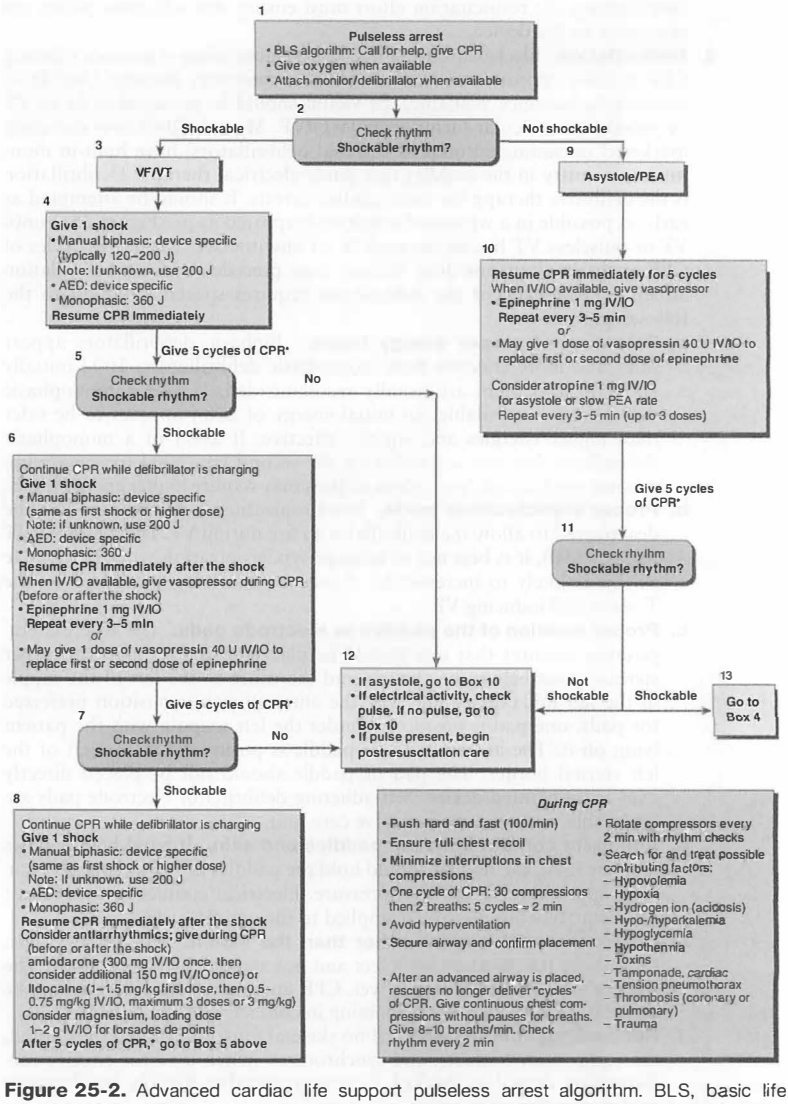

Figure 25-2. Advanced cardiac life support pulseless arrest algorithm. BLS, basic life support; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; AED, automatic external defibrillator; IV, intravenous; IO, intraosseous. (From American Heart Association. Guidelines 2005 for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005;112(Suppl 24):IV-58–VI-66, with permission. Copyright 2005.)

adults, as well as children. This modality is preferable to attempting dosing through an endotracheal tube.

2. **Correction of acidosis.** Correction of acidosis should be considered when the cardiac arrest has lasted for a prolonged period and adequate ventilation is being provided. The AHA guidelines suggest that sodium bicarbonate or other buffers be avoided until a perfusing rhythm has been reestablished. Exceptions include patients with known preexisting hyperkalemia or tricyclic overdose, for whom the administration of sodium bicarbonate is recommended.
3. **Volume replacement.** Increased central volume is often required during CPR, especially if initial attempts at defibrillation have failed. Simple crystalloids, such as 5% dextrose in water, are inappropriate for rapid expansion of the intravascular space. Isotonic crystalloids (0.9% saline, Ringer's lactate), colloids, or blood are necessary for satisfactory volume expansion.
4. **Sympathomimetic drugs and vasopressors.** Sympathomimetic drugs either act directly on adrenergic receptors or act indirectly by releasing catecholamines from nerve endings.
   a. **Epinephrine.** Epinephrine is the pressor agent used most frequently during CPR. It has both α and β activity. Indications for its use include all forms of cardiac arrest. Its β action is useful in asystole and bradycardiac arrest and has also been said to convert asystole to VF and "fine" VF to more easily converted "coarse" VF. An IV bolus of 1 mg is given every 3 to 5 minutes as needed to restore a perfusing rhythm.
   b. **Norepinephrine.** Norepinephrine is a potent α-agonist with β activity. There is no reason to select it over epinephrine during cardiac arrest. It appears to be most useful in the treatment of septic shock and neurogenic shock.
   c. **Isoproterenol.** This synthetic catecholamine has almost pure β-adrenergic activity. Its cardiac activity includes potent inotropic and chronotropic effects. Indications for its use include atropine-resistant, hemodynamically significant bradyarrhythmias as well as various forms of high-degree atrioventricular block. *It should not be used during cardiac arrest.*
   d. **Dopamine.** This naturally occurring precursor of norepinephrine has α, β, and dopaminergic-receptor activity. Indications for its use are primarily hemodynamically significant hypotension and cardiogenic shock.
   e. **Dobutamine.** This potent synthetic β agonist differs from isoproterenol in that tachycardia is less problematic. It is indicated primarily for the short-term enhancement of ventricular contractility in the patient with heart failure and cardiogenic shock.
   f. **Vasopressin.** Because endogenous vasopressin levels were noted to be higher in successfully resuscitated patients than in those who died, it has been argued that the administration of exogenous vasopressin may be beneficial in refractory cardiac arrest. Although early data suggested potential superiority to epinephrine in initial management of asystolic arrest, a recent randomized trial suggests that the combination of epinephrine and vasopressin is no more effective than epinephrine alone. According to the most recent AHA guidelines, if it is to be used, vasopressin should be administered once (40 IU, IV) before epinephrine. If return of pulse fails, epinephrine may then be used in usual doses. If epinephrine was utilized as the first agent without success, vasopressin may be used once, as the second agent.
5. **Antiarrhythmic agents.** Antiarrhythmics play an important role in stabilizing rhythm in many resuscitative situations.

a. **Amiodarone.** Amiodarone IV has been found successful in terminating a variety of reentrant and nonreentrant supraventricular and ventricular arrhythmias. It has replaced the use of lidocaine or bretylium during VT/VF arrest when defibrillatory attempts have failed. An IV dose of 300 mg is administered. An additional dose of 150 mg may be considered if VT/VF persists or recurs. The maximum cumulative dose is 2.2 g over 24 hours for recurrent VT/VF.

b. **Procainamide.** Procainamide is indicated for ventricular arrhythmias refractory to amiodarone. It is also useful in patients with supraventricular arrhythmias. An infusion is administered at 20 mg/minute until the arrhythmia is suppressed, hypotension develops, or the QRS interval is lengthened by 50% from its original duration. The maximum total dose is 17 mg/kg.

c. **Adenosine.** Adenosine depresses AV nodal conduction and sinoatrial node activity. It is effective in terminating arrhythmias that involve the AV node in a reentrant circuit. *It should not be used during cardiac arrest.*

d. **Verapamil and diltiazem.** These drugs are primarily useful in slowing the ventricular response during atrial fibrillation or flutter. *They should not be used during cardiac arrest.*

e. **Magnesium.** Magnesium is administered IV during VF in a patient with suspected hypomagnesemia. It also may be of value in patients with *torsade de pointes.* One to 2 g may be diluted to 100 mL of 5% dextrose in water and given over 1 to 2 minutes.

f. **Atropine.** Atropine is a vagolytic drug of use in increasing heart rate and facilitating AV conduction by suppressing vagal tone. It is indicated in hemodynamically significant bradycardias, in which case the initial dose may be as low as 0.4 mg. It is also used in asystole and bradycardic arrests for which 1 mg is given IV and repeated every 3 to 5 minutes, as needed, to a total dose of 0.04 mg/kg.

g. **Calcium.** Calcium is indicated only in calcium channel blocker toxicity, severe hyperkalemia, severe hypocalcemia, cardiac arrest after multiple transfusions with citrated blood, and fluoride toxicity, as well as hypotension in patients being removed from heart–lung bypass after cardioplegic arrest. *It is not indicated for routine use in cardiac arrest.*

C. Clinical settings. The procedures involved in resuscitation of a victim of cardiovascular or respiratory arrest are part of a continuum progressing from initial recognition of the problem and institution of CPR to intervention with defibrillation, drugs, pacemakers, transport, and postresuscitative evaluation and care. The following sections focus on the pharmacologic and electrical interventions appropriate to various clinical settings common in cardiac arrest.

1. **Ventricular fibrillation and pulseless ventricular tachycardia.** VF is the initial rhythm encountered in 50% to 70% of prehospital cardiac arrests and in 30% to 40% of in-hospital cardiac arrests. Pulseless VT is also found in a significant number of in-hospital arrests and in a smaller number of prehospital arrests. Electrical defibrillation is the most important intervention in treating these arrhythmias (Fig. 25-2). The sooner it is administered, the more likely it is to succeed. Repeated attempts are often necessary.

2. **Asystole.** Asystole is the first rhythm encountered in 30% to 40% of prehospital as well as in-hospital cardiac arrests. It is obviously the end result of any pulseless rhythm, and as such, when it is the presenting rhythm at an unwitnessed arrest it is unlikely to be reversible. Although some have advocated the early use of vasopressin in asystolic arrest, a recent randomized trial suggests that the combination of vasopressin and

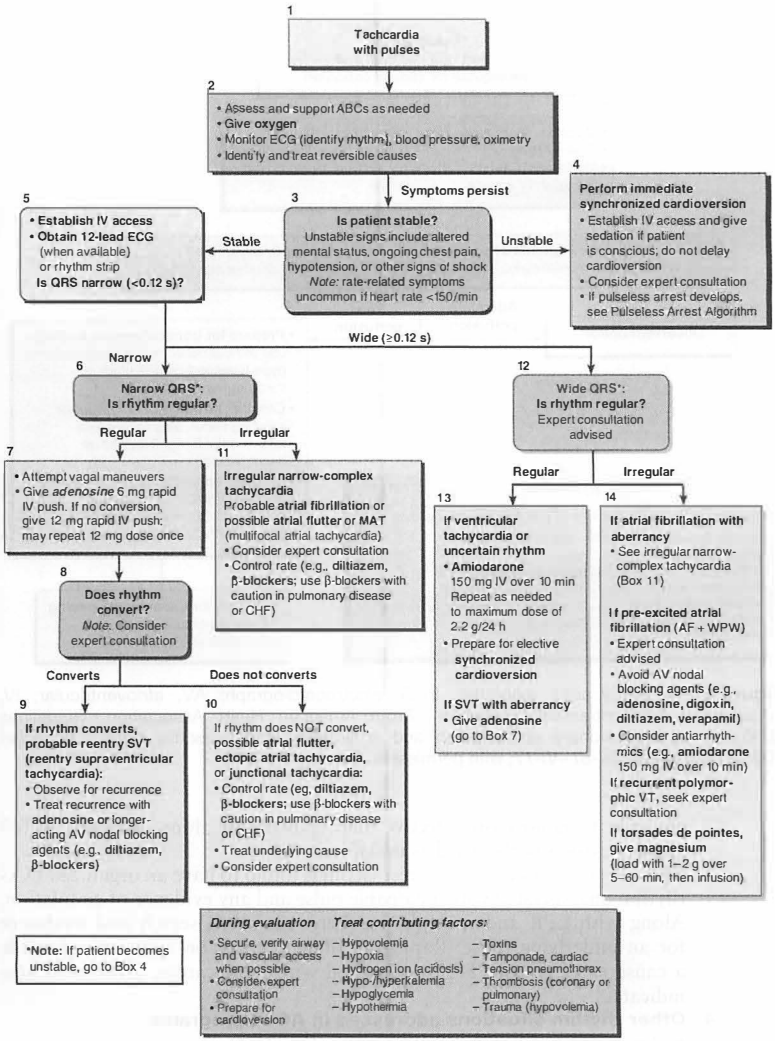

Figure 25-3. Advanced cardiac life support tachycardia algorithm. ABC, airway, breathing and circulation; ECG, electrocardiograph; IV, intravenous; MAT, multifocal atrial tachycardia; CHF, congestive heart failure; SVT, supraventricular tachycardia; AF, atrial fibrillation; WPW, Wolff-Parkinson-White syndrome; VT, ventricular tachycardia; AV, atrioventricular. (From American Heart Association. Guidelines 2005 for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005;112(Suppl 24):IV-67–VI-77, with permission. Copyright 2005.)

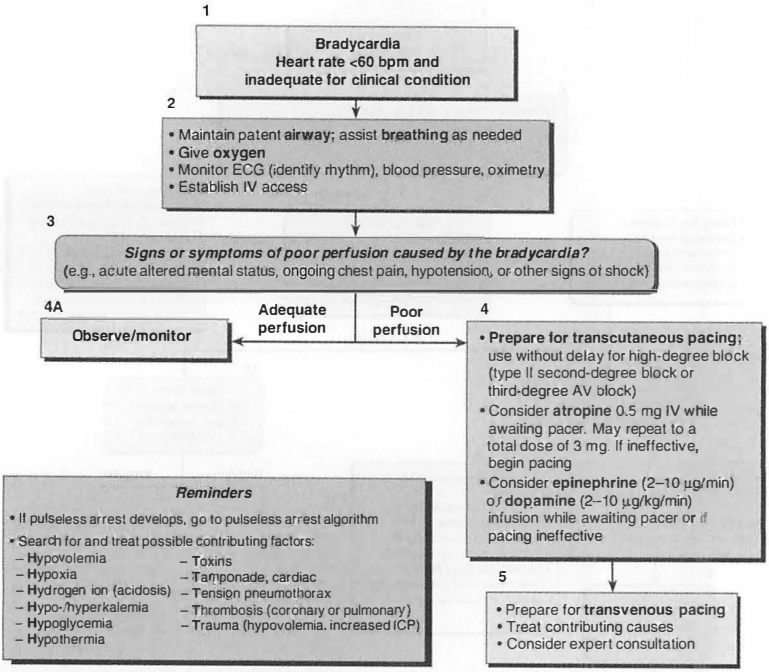

Figure 25-4. Bradycardia algorithm. ECG, electrocardiograph; AV, atrioventricular; IV, intravenous; ICP, intracranial pressure. (From American Heart Association. Guidelines 2005 for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005;112(Suppl 24):IV-67–VI-77, with permission. Copyright 2005.)

epinephrine is no more effective than epinephrine alone. Atropine in full vagolytic doses is also used as initial intervention.

3. **PEA.** PEA occurs when an arrest victim is found to have an organized ECG rhythm unassociated with a palpable pulse and any evidence of circulation. Along with CPR and epinephrine, there must be a search and treatment for an underlying cause. Rapid IV volume expansion is warranted while a cause is sought. If PEA is associated with bradycardia, atropine is also indicated.
4. **Other rhythm situations addressed in ACLS programs**
   - **a.** Sustained tachycardias with a pulse (Fig. 25-3)
   - **b.** Unstable and stable supraventricular tachycardias (Fig. 25-4)
   - **c.** Bradycardia with a pulse (Fig. 25-4)

Suggested Reading

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Wenzel V, Krismer AC, Arntz HR, et al. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med* 2004;350:105.
Vasopressin was as effective as epinephrine as first line drug in out-of-hospital cardiac arrest and improved survival to hospitalization among patients initially found to be in asystole.

26 PHARMACOLOGIC MANAGEMENT OF THE HYPOTENSIVE PATIENT

Michael M. Givertz

I. GENERAL PRINCIPLES

A. Background

1. Hypotension is frequently encountered in the intensive care setting as the final result of a heterogeneous group of disorders.
2. End-organ perfusion generally becomes compromised when the systolic arterial pressure falls below 90 mm Hg, or when mean arterial pressure falls below approximately 60 mm Hg.
3. Although definitive management requires therapy directed at the underlying cause of hypotension (e.g., antibiotics for sepsis, corticosteroids for adrenal insufficiency, blood transfusion for bleeding), intravenous (IV) vasoactive agents are at times necessary to maintain perfusion to vital organs while the underlying etiology of hypotension is investigated and definitive measures have been instituted.

B. Adrenergic receptor physiology

1. With few exceptions, vasopressors and positive inotropes are sympathomimetic amines that bind to and stimulate adrenergic receptors. The characteristic hemodynamic effects of individual agents depend to a great extent on selective binding to various adrenergic receptors.
   - **a.** α_1-Adrenergic receptors
     - **i.** Present in smooth muscle cells of many vascular beds, including the arterioles supplying the skin, mucosa, skeletal muscles, and kidneys, as well as peripheral venules.
     - **ii.** Stimulation causes vasoconstriction and is the most common mechanism of vasopressor action.
     - **iii.** Receptors in the myocardium appear to mediate a modest positive inotropic effect with little change in heart rate (HR).
   - **b.** β_1-Adrenergic receptors
     - **i.** Predominant adrenergic receptors in the heart.
     - **ii.** Stimulation causes a positive inotropic and chronotropic response.
   - **c.** β_2-Adrenergic receptors
     - **i.** Stimulation causes relaxation of smooth muscle in the bronchial tree, gastrointestinal tract, and uterus.
     - **ii.** Mediate vasodilation of arterioles supplying skeletal muscle.
   - **d.** Dopaminergic receptors (DA_1 and DA_2)
     - **i.** Mediate renal, coronary, cerebral, and mesenteric vasodilation.
     - **ii.** Stimulate natriuresis.
2. Receptor selectivity of vasoactive drugs can be dose dependent (e.g., dopamine).
3. Overall clinical effects of a drug include both the direct sequelae of adrenergic receptor stimulation and the reflex response of homeostatic forces (e.g., norepinephrine-mediated α_1-adrenergic stimulation induces increased vagal tone, which opposes the positive chronotropic effects of β_1-adrenergic stimulation, resulting in little overall change in HR).

TABLE 26-1 **Dose Range, Receptor Activity, and Predominant Hemodynamic Effects of Vasoactive Drugs Commonly Used to Treat Hypotension**

Drug	Dose range	DA	α_1	β_1	β_2	HR	CO	SVR
Dobutamine	2–15 μg/kg/min	–	+	+++	++	↔↑	↑↑	↔↓
Dopamine	1–5 μg/kg/min	+++	–	–	–	↔	↔	↔
	5–10 μg/kg/min	++	+	++	–	↑	↑↑	↔↑
	10–20 μg/kg/min	++	+++	++	–	↑↑	↔↑	↑↑
Epinephrine	1–10 μg/min	–	+++	++	++	↑↑	↑	↑↑
Norepinephrine	0.5–30 μg/min	–	+++	++	–	↔	↔	↑↑
Phenylephrine	40–180 μg/min	–	+++	–	–	↔↓	↔	↑↑
Vasopressin	0.01–0.05 units/min	–	–	–	–	↔	↔↓	↑↑

HR, heart rate; CO, cardiac output; SVR, systemic vascular resistance.

II. TREATMENT

A. Commonly used vasopressors and positive inotropes (Table 26-1)

1. Epinephrine (Adrenalin)
   - **a.** An endogenous catecholamine which is the least selective of the vasopressor agents, and a potent agonist of α- and β-adrenergic receptors.
   - **b.** Clinically used doses (1 to 10 μg/minute) result in α-mediated venous and arterial constriction and β-mediated increased HR and myocardial contractility. The latter effect is mitigated by increased afterload.
   - **c.** Blood flow to skeletal muscles is increased owing to β_2-mediated vasodilation.
   - **d.** Used to reverse hypotension with or without bradycardia following cardiopulmonary bypass.
   - **e.** Because of adverse effects on renal and splanchnic blood flow, and potential for inducing myocardial ischemia and tachyarrhythmias, epinephrine is considered a second-line agent in the management of hypotension secondary to septic shock.
2. Norepinephrine (Levophed)
   - **a.** An endogenous catecholamine with potent α_1- and β_1-adrenergic activity, but little β_2-agonism.
   - **b.** Predominant effect is dose-dependent vasoconstriction of arterial resistance vessels and veins. Cardiac effects of β_1-stimulation are counterbalanced by increased afterload and reflex vagal activity induced by elevated systemic vascular resistance (SVR).
   - **c.** Clinically used doses (0.5 to 30 μg/minute) result in potent vasoconstriction. Generally infused as a second-line agent in cases of severe distributive shock, but several small studies suggest that in adults with septic shock, use of norepinephrine as the initial agent is more likely to result in improved blood pressure and survival compared to dopamine.
   - **d.** Adverse effects include increased myocardial oxygen consumption, and excessive renal and mesenteric vasoconstriction. Renal ischemia may be of particular concern in patients with hemorrhagic shock.
   - **e.** Extravasation causes tissue necrosis and should be managed with local infiltration of phentolamine.
3. Dopamine (Intropin)
   - **a.** An endogenous catecholamine that functions as a central neurotransmitter and synthetic precursor to norepinephrine.

- **b.** Stimulates dopaminergic and adrenergic receptors in a dose-dependent manner; also stimulates release of norepinephrine from nerve terminals.
  - **i.** Low dose (<5 μg/kg/minute): predominantly stimulates dopaminergic receptors in renal, mesenteric, and coronary vessels. In normal subjects, low-dose dopamine augments renal blood flow with little effect on blood pressure. The strategy of using low-dose dopamine as a renoprotective agent in critically ill patients has not been shown to be effective in controlled studies.
  - **ii.** Moderate dose (5 to 10 μg/kg/minute): predominant effect is β_1-mediated augmentation of myocardial contractility and HR.
  - **iii.** High dose (>10 μg/kg/minute): overall hemodynamic effect resembles that of norepinephrine and is mediated by α_1-adrenergic receptor stimulation.
- **c.** As an agent with both inotropic and vasopressor activity, moderate-to high-dose dopamine has the versatility to be used as a first-line agent in hypotension of unknown etiology. However, in the setting of severe hypotension due to septic shock, a more potent α-adrenergic agonist such as norepinephrine may be more effective in restoring perfusion pressure.
- **d.** By itself or in combination with other inotropes such as dobutamine, moderate-dose dopamine may be used in the management of hypotensive patients with acute decompensated heart failure.
- **e.** Adverse effects include dose-dependent tachycardia, tachyarrhythmias, and excessive vasoconstriction, which in patients with coronary artery disease can result in myocardial ischemia.

4. Dobutamine (Dobutrex)

- **a.** A synthetic sympathomimetic amine that causes potent nonselective β- and mild α-adrenergic stimulation. Its mechanism of action is complex and involves two stereoisomers with distinct affinities for different adrenergic receptors (see main text).
- **b.** Clinically used doses (2 to 15 μg/kg/minute or higher) increase cardiac contractility and HR. The positive chronotropic effect occurs to a lesser extent than with dopamine. SVR is modestly reduced or may remain unchanged.
- **c.** Useful in the temporary inotropic support of hypotensive patients with acute decompensated heart failure, and patients with concomitant septic shock and depressed cardiac function.
- **d.** In patients with marked hypotension, the initial effect on blood pressure may be unpredictable. In this setting, dobutamine should be administered in combination with a vasopressor such as dopamine.
- **e.** As with other positive inotropic agents, increased myocardial oxygen consumption may worsen cardiac ischemia, and tachycardia or arrhythmias may limit dose titration. In patients with acute decompensated heart failure, inotropic response may be variable and short-term or intermittent dobutamine therapy has been associated with excess mortality.

5. Phenylephrine (Neosynephrine)

- **a.** A synthetic sympathomimetic amine that selectively stimulates α_1-adrenergic receptors, causing dose-dependent arterial vasoconstriction. Increased blood pressure activates vagal reflexes, causing slowing of the HR.
- **b.** Although there are little data regarding its relative efficacy compared to older vasopressors, phenylephrine is frequently infused at 40 to 180 μg/minute to treat vasodilatory or hyperdynamic septic shock. The absence of β-agonist activity at usual doses has made

phenylephrine an attractive agent in clinical situations where tachycardia or tachyarrhythmias limit the use of other agents.

c. High-dose phenylephrine can cause excess vasoconstriction, and patients with left ventricular systolic dysfunction may not tolerate the α_1-mediated increase in afterload.

d. Compared to epinephrine and norepinephrine, phenylephrine is less likely to decrease microcirculatory blood flow in the gastrointestinal tract.

6. Vasopressin (Pitressin)

a. An endogenous antidiuretic hormone that has recently been added to the armamentarium of agents used to treat hypotension. The mechanism of pressor action has not been fully elucidated, but involves binding to V_1 receptors on vascular smooth muscle.

b. Minimal effect on blood pressure in healthy subjects, but increases blood pressure in patients with septic shock or vasodilatory shock following cardiopulmonary bypass, and has been shown to facilitate the tapering of adrenergic agents in these settings.

c. It remains unclear whether hemodynamic benefits are confined to a subset of patients with relative vasopressin deficiency, hypersensitivity, or both.

d. Currently recommended in doses of 0.01 to 0.05 units/minute as an adjunctive agent in the treatment of vasodilatory septic shock that is poorly responsive to traditional adrenergic agonists. Also, may be given as a one-time dose of 40 units IV to replace first or second dose of epinephrine in pulseless cardiac arrest (see Chapter 25). Use as a stand-alone vasopressor has not been well studied.

e. Potential adverse effects include excess vasoconstriction causing end-organ hypoperfusion including myocardial ischemia. Cardiac output (CO) may also worsen due to excessive afterload.

B. Adjunctive agents

1. Methylene blue (Urolene Blue)

a. Inhibits guanylate cyclase the target enzyme of endothelium-derived nitric oxide (NO).

b. Administered as a one-time IV bolus in a dose of 1 to 2 mg/kg to treat refractory hypotension (or vasoplegia syndrome) following cardiopulmonary bypass or cardiac transplantation.

c. Potential adverse effects include hypertension, cardiac dysrhythmias, malignant hyperthermia, and hemolytic anemia.

2. Drotrecogin alfa (Xigris)

a. A recombinant form of human activated protein C that exerts potent anti-inflammatory and antithrombotic effects *in vitro*.

b. Indicated for sepsis syndrome associated with organ dysfunction and high risk of death (Apache II score >25) in the absence of bleeding. Standard IV dosing is 24 mg/kg/hour for 96 hours at a cost of approximately $8,000.

c. In a large, phase III study, serious bleeding events occurred in 2.4% of patients treated with drotrecogin alfa and in 1% of those receiving placebo.

3. Hormones

a. Several hormones including cortisol and thyroxine play important roles in the maintenance of vascular tone, and their absolute or relative deficiency may contribute to hypotension in the critically ill patient (see Chapters 89 and 90).

C. Choosing an agent (Table 26-2)

1. There are no large adequately controlled trials to guide the pharmacologic management of hypotension. Consensus recommendations are based on

TABLE 26-2 Hemodynamic Profiles of Selected Causes of Hypotension and Commonly Used First-Line Agents

Cause of hypotension	PAOP	CO	SVR	Preferred agent(s)
Unknown	?	?	?	Dopamine
Hypovolemia	↓	↓	↑	None[a]
Acute decompensated heart failure	↑	↓	↑	Dopamine Dobutamine
Cardiogenic shock	↑ ↔	↓	↑	Dopamine
Hyperdynamic sepsis	↓ ↔	↑	↓	Norepinephrine Dopamine
Sepsis with LV dysfunction	?	↓	↓	Dopamine Norepinephrine plus dobutamine
Anaphylaxis	?	?	↓	Epinephrine
Anesthesia-induced hypotension	?	?	↓	Phenylephrine

↓, decrease; ↑, increase; ?, unknown.
[a]Volume resuscitation with intravenous fluids and/or blood products recommended.
PAOP, pulmonary artery occlusion pressure; CO, cardiac output; SVR, systemic vascular resistance; LV, left ventricle.

animal studies and small clinical trials. The selection of an appropriate agent should be made on a case-by-case basis, with attention to the known or suspected underlying cause.

2. Given its combined pressor and inotropic properties, moderate-dose dopamine is a reasonable choice for the initial treatment of hypotension of unknown etiology. For the treatment of severe hypotension (systolic blood pressure <70 mm Hg), a more potent α_1-adrenergic agonist such as norepinephrine should be considered.
3. Norepinephrine may be the pressor of choice in the treatment of vasodilatory shock related to sepsis. In cases where tachycardia, tachyarrhythmias, or both limit dose titration of other agents, phenylephrine is a useful alternative. Epinephrine can be added for refractory septic shock.
4. For the mildly hypotensive patient with left ventricular systolic dysfunction, dobutamine is the drug of choice. With frank cardiogenic shock or combined vasodilation and pump failure, dopamine can be used as a single agent or in combination with other drugs such as dobutamine.
5. In patients with septic shock and associated myocardial dysfunction, dobutamine can be added to norepinephrine for added positive inotropic support.
6. Vasopressin has emerged as a useful adjunctive agent for treatment of the septic patient with hemodynamic collapse resistant to traditional sympathomimetic agents.

III. MONITORING AND COMPLICATIONS

A. Vasopressors and positive inotropes are potent agents with considerable potential for toxicity mediated by the same mechanisms that increase blood pressure. They should be used with extreme caution and at the lowest dose required to maintain end-organ perfusion.

1. Tachycardia and tachyarrhythmias result from β_1-stimulation and can limit the use of these agents in patients with underlying cardiovascular disease.
2. Depressed left ventricular systolic function may develop as a result of increased afterload or secondary to ischemia.

3. Myocardial ischemia may be caused by coronary vasoconstriction or more commonly by increased myocardial oxygen demand.
4. Excessive arterial vasoconstriction can compromise splanchnic and renal perfusion. Similarly, peripheral limb ischemia and even necrosis may occur.

B. Monitoring
1. Patients should be treated in an intensive care setting with continuous monitoring of cardiac rhythm, urine output, and arterial oxygenation.
2. Intra-arterial cannulation and direct monitoring of blood pressure is suggested during prolonged vasopressor use.
3. Fluid resuscitation and careful attention to intravascular volume are paramount as many patients with hypotension can be stabilized with fluids alone, and the administration of vasopressors to hypovolemic patients can worsen end-organ perfusion. The use of central venous or pulmonary artery catheters to monitor filling pressures can be helpful in selected cases, but the routine use of invasive hemodynamic monitoring is not necessary and may be harmful.
4. Although a mean arterial pressure of >60 mm Hg is usually required to maintain autoregulatory blood flow to vital organs, some patients may require higher or lower pressures. It is essential to monitor carefully other indicators of global and regional perfusion such as mental status and urine output. Following mixed venous oxygen saturation and serum lactate levels, and intramucosal pH monitoring by gastric tonometry may be useful, but are not advocated for routine use.

C. With few exceptions these drugs are short-acting agents with rapid onset and offset of action. They are generally initiated without a bolus and can be titrated frequently. Abrupt lowering and discontinuation of vasoactive drugs should be avoided to prevent rebound hypotension.

D. There is considerable variation in the initial dose required to restore adequate hemodynamics. Moreover, an individual patient's responsiveness to a given agent may diminish over time owing to several mechanisms including adrenergic receptor desensitization.

E. Careful attention should be paid to potential drug–drug interactions.
1. Recent or current treatment with β-adrenergic antagonists can cause resistance to the action of dobutamine and other β-agonists.
2. The administration of less selective adrenergic agonists such as epinephrine to patients treated with β-blockers can cause unopposed α-adrenergic stimulation.
3. Patients taking monoamine oxidase inhibitors will experience an exaggerated response to some catecholamines and should be treated with a very low (<10%) starting dose.

F. Drugs should generally be administered through central venous catheters using volumetric infusion pumps that deliver precise flow rates. In the event of vasopressor extravasation, an α_1-adrenergic antagonist (e.g., phentolamine 5 to 10 mg diluted in 10 to 15 mL of saline) can be infiltrated into the area to limit local vasoconstriction and tissue necrosis.

Suggested Reading

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Martin C, Viviand X, Leone M, et al. Effect of norepinephrine or dopamine on the outcome of septic shock. *Crit Care Med* 2000;28:2758–2765.
Observational study suggesting a possible survival benefit when patients with septic shock are treated initially with norepinephrine rather than dopamine.

THE CARDIOMYOPATHIES: DIAGNOSIS AND ICU MANAGEMENT

27

G. William Dec

I. BACKGROUND

A. The cardiomyopathies are a diverse group of diseases characterized by primary involvement of the myocardium.

B. They are classified by anatomic appearance and physiologic abnormalities (Table 27-1) as:

1. Dilated cardiomyopathies (DCMs)

2. Hypertrophic cardiomyopathies (HCMs)

3. Restrictive cardiomyopathies (RCMs)

C. Echocardiography is the most useful initial test to differentiate between the three types and to assess the extent of systolic and diastolic ventricular dysfunction.

II. DILATED CARDIOMYOPATHIES

A. Background

1. Cardiac enlargement (left ventricular [LV] end-diastolic dimension >55 mm) and decreased contractile function (left ventricular ejection fraction [LVEF] <45%) are the principal hallmarks of the disease.

2. Reversible causes should always be considered and carefully evaluated (Table 27-2).

3. A familial/genetic pattern is present in 50% of cases; clinical clues often include:

a. Concomitant skeletal myopathy

b. Sensorineural hearing loss

B. Pathophysiology

1. Impaired systolic contractile function leads to progressive ventricular dilatation through the Frank–Starling mechanism.

2. Functional mitral and/or tricuspid regurgitation (TR) are common due to annular displacement secondary to progressive ventricular dilatation.

3. Chronic exertional dyspnea due to elevated filling pressures is the most frequent symptom. Acute pulmonary edema is uncommon except during periods of stress (e.g., infection, change in cardiac rhythm, surgical procedures).

4. Physical findings:

a. Jugular venous distension (50% to 60%); hepatojugular reflux (approximately equal to 20%).

b. S4 and S3 gallops may wax and wane in intensity.

c. Mitral or TR murmurs (1 to 3/6 in intensity) are often audible.

d. Clear lungs are most common due to enhanced pulmonary lymphatic drainage.

e. Liver enlargement and peripheral edema are seen in fewer than 50% of cases.

C. Prognosis

1. Prognosis is highly dependent on disease etiology.

a. Idiopathic DCM: 5-year survival rate approximately 75%

b. Anthracycline cardiomyopathy: 5-year survival rates <25%

TABLE 27-1 Hemodynamic and Morphometric Features of the Cardiomyopathies

Features	Dilated	Hypertrophic	Restrictive
LV ejection fraction	<45%	65–90%	50–70% <40% (late)
LV cavity size	Increased	Normal or decreased	Normal Increased (late)
Stroke volume	Markedly decreased	Normal or increased	Normal or increased
Volume:mass ratio	Increased	Decreased	Markedly decreased
Diastolic compliance	Normal to decreased	Markedly decreased	Markedly decreased
Other features	Mild/moderate MR/TR are common	Dynamic obstruction	Often mimics constrictive pericarditis

LV, left ventricular; MR, mitral regurgitation; TR, tricuspid regurgitation.

TABLE 27-2 Causes of Potentially Reversible Dilated Cardiomyopathy

Toxins
Ethanol
Cocaine
Antiretroviral agents (AZT, ddI, ddC)
Phenothiazines
Metabolic abnormalities
Nutritional (thiamine, selenium, carnitine, and taurine deficiencies)
Endocrinologic (hypothyroidism, acromegaly, thyrotoxicosis, pheochromocytoma)
Electrolyte disturbances (hypocalcemia, hypophosphatemia)
Inflammatory/infectious/infiltrative
Infectious
Viral (coxsackievirus, adenovirus, cytomegalovirus)
Parasitic (toxoplasmosis)
Spirochetal (Lyme disease)
Inflammatory/infiltrative
Collagen vascular disorders (sarcoidosis)
Hypersensitivity myocarditis
Hemochromatosis
Sarcoidosis
Miscellaneous
Tachycardia induced
Idiopathic
Peripartum

AZT, zidovudine (azidothymidine); ddI, didanosine (dideoxyinosine); ddC, zalcitabine (dideoxycytidine).

TABLE 27-3 High-Risk Features in Dilated Cardiomyopathy

Clinical features
NYHA class IV symptoms on admission
Recent onset of illness (<6 mo)
Active myocardial ischemia (angina or ischemic ECG abnormalities)
History of syncope
Persistent S_3 gallop
Right-sided heart failure signs
Inability to tolerate ACE inhibitors
Hemodynamic and ventriculographic findings
Left ventricular ejection fraction <20%
Right ventricular dysfunction
Pulmonary hypertension
Right atrial pressure >8 mm Hg
Pulmonary capillary wedge pressure >20 mm Hg
Cardiac index <2.0 L/min/m^2
Neurohormonal abnormalities
Hyponatremia (serum sodium <137 m Eq/L)
Enhanced sympathetic tone (elevated plasma norepinephrine or resting sinus tachycardia)
Persistent elevation of B-type natriuretic peptide or troponin
Histologic features
Active lymphocytic or granulomatous myocarditis on endomyocardial biopsy
Arrhythmia pattern
History of prior cardiac arrest
Symptomatic or asymptomatic nonsustained runs of ventricular tachycardia
Second- or third-degree AV block

NYHA, New York Heart Association; ECG, electrocardiogram; S_3, third heart sound; ACE, angiotensin-converting enzyme; AV, atrioventricular.

2. Spontaneous improvement occurs in 20% to 40% of cases, particularly if symptom duration is short (<6 months).
3. Clinical, echocardiographic, and laboratory findings help identify high-risk patients (Table 27-3).

D. Diagnosis

1. Echocardiography is the most useful noninvasive modality as it assesses systolic and diastolic function, chamber dimensions, ventricular wall thickness, and excludes hemodynamically significant valvular disease (Table 27-4).
2. Patients with known DCM and stable symptoms require little additional diagnostic testing during hospitalization. Typical testing will include:
   a. Serum electrolytes, renal function, and magnesium level.
   b. Twelve lead electrocardiogram (ECG) and chest x-ray (CXR).
   c. Preoperative echocardiography is generally *unnecessary* in patients who have been clinically stable at home.
   d. Preoperative pharmacologic stress testing with cardiac perfusion imaging should be considered for patients with ischemic cardiomyopathy and either worsening heart failure or anginal symptoms or in whom a major surgical procedure is planned.

TABLE 27-4 Diagnostic Evaluation of New-Onset Dilated Cardiomyopathy

Class I studies (*usually indicated, always acceptable*)
CBC and urinalysis
Electrolytes, renal function, glucose, phosphorus, calcium, albumin, TSH level
Chest film, electrocardiogram
Transthoracic Doppler echocardiogram
Noninvasive stress testing in patients who lack angina but who have a high probability of underlying ischemic heart disease, a known prior myocardial infarction, or extensive areas of hibernating myocardium (Note: Patients should be suitable candidates for revascularization if extensive ischemia is detected.)
Class II studies (*acceptable but of uncertain efficacy; controversial*)
Serum iron/ferritin
Noninvasive stress testing in all patients with unexplained dilated cardiomyopathy
Coronary angiography in all patients with unexplained dilated cardiomyopathy
Endomyocardial biopsy in patients with:
Cardiomyopathy of recent onset (generally <6 mo) and rapid deterioration in ventricular function
Clinically suspected myocarditis
Cardiomyopathy and a systemic disease known to involve the myocardium (e.g., sarcoidosis, hemochromatosis)
Class III studies (*generally not indicated*)
Routine 24-h ambulatory ECG monitoring
Serial echocardiography in clinically stable patients
Routine right-heart catheterization to guide medical therapy
Endomyocardial biopsy in chronic dilated cardiomyopathy
Cardiac catheterization in patients who are not candidates for revascularization, valve replacement, or cardiac transplantation

CBC, complete blood count; TSH, thyroid-stimulating hormone; ECG, electrocardiogram.
(Adapted from American College of Cardiology/American Heart Association Task Force Report: Guideline update for the diagnosis and management of chronic heart failure in the adult: summary article. *Circulation* 2005;112:1825–1852).

E. Treatment

1. Elective surgery should be postponed for patients with newly diagnosed DCM to initiate and optimize pharmacologic therapy and allow sufficient time for spontaneous recovery of systolic function.
2. Heart failure decompensation is the most frequent complication during an acute noncardiac hospitalization.
3. Individuals whose LVEF is <20% are at increased risk for developing perioperative heart failure, atrial fibrillation, ventricular arrhythmias, and cardiorenal syndrome.
4. The cornerstones of pharmacologic therapy should include:
   a. A loop diuretic (furosemide, bumetanide, or torsemide)
   b. An ACE-inhibitor or angiotensin-receptor blocker (ARB)
   c. A β-adrenergic receptor blocker
   d. Digoxin and aldosterone antagonists are generally reserved for patients with chronic advanced (New York Heart Association (NYHA) class III or IV) heart failure symptoms
5. Acute volume expansion should be avoided as it will exacerbate mitral regurgitation (MR)/TR and lead to decreased forward stroke volume and cardiac index.

6. Hemodynamic monitoring with a pulmonary artery catheter should be considered for major surgical procedures in DCM patients who have:
   a. Recent decompensation in heart failure symptoms
   b. Myocardial infarction (MI) within the previous 3 months
   c. Moderate/severe stenotic valvular heart disease
7. Hemodynamic goals for DCM management in intensive care unit (ICU) setting should include:
   a. Pulmonary capillary wedge (PCW): 15 to 18 mm Hg
   b. CI >2.2 L/minute/m^2
8. For hemodynamically unstable patients, oral vasodilators should be replaced with short-acting intravenous agents (e.g., nitroprusside, nitroglycerin, or nesiritide). Occasionally, a β-agonist (dobutamine) or a phosphodiesterase III inhibitor (milrinone) may be required for management of a persistent low-output state.
9. Rapid atrial fibrillation is not uncommon during acute hospitalization due to enhanced sympathetic tone. Acceptable agents to control heart rate may include digoxin, β-blockers, and intravenous amiodarone. Calcium antagonists should be avoided.
10. Asymptomatic ventricular arrhythmias generally do not require pharmacologic suppression. Intravenous amiodarone or lidocaine are the agents of choice for symptomatic ventricular tachyarrhythmias.

III. HYPERTROPHIC CARDIOMYOPATHIES

A. Background

1. Hereditary condition characterized by LV hypertrophy, hyperdynamic systolic contractile function, and markedly impaired diastolic function.
2. HCM in adults must be differentiated from hypertensive concentric left ventricular hypertrophy (LVH), which is commonly seen in the elderly.
3. Clinical manifestations:
   a. Dyspnea on exertion (secondary to impaired diastolic filling and elevated filling pressures) is the most common symptom and often quite limiting.
   b. Angina-like chest pain (due to increased LV mass, wall stress, and concomitant atherosclerotic coronary disease in older patients) may occur.
   c. Syncope, near-syncope (due to outflow tract obstruction, ventricular arrhythmias, or inadequate diastolic filling) is less commonly seen.

B. Pathophysiology

1. HCM is inherited in >60% of cases as autosomal dominant trait.
2. Specific single-point missense mutations in genes that encode key sarcomeric contractile and regulatory proteins include:
   a. β-Myosin heavy chain (35%)
   b. Troponin T (15%)
   c. Myosin-binding protein (15%)
   d. Tropomyosin (<5%)
3. The pathologic hallmark is unexplained myocardial hypertrophy; the intraventricular septum is typically much greater than ventricular free wall but concentric LVH can also occur.
4. HCM may have obstructive or nonobstructive physiology, depending on the presence/absence of a dynamic subaortic outflow tract pressure gradient.
5. Physical findings are dependent on presence or absence of outflow tract obstruction, its severity, and the presence or absence of MR.
   a. Precordial palpation typically reveals a hyperdynamic systolic apical impulse.
   b. Carotid upstroke is very rapid; if obstruction occurs, a bisferiens character (rapid initial upstroke, slow second carotid impulse) may be palpable.
   c. Prominent S4 gallop is virtually always present.

TABLE 27-5 Bedside Maneuvers to Differentiate the Murmur of Obstructive Hypertrophic Cardiomyopathy from that of Valvular Heart Disease

Maneuver	Response of murmur		
	HCM	Aortic stenosis	Mitral regurgitation
Hypovolemia Tachycardia Valsalva Venodilators (nitrates) (*decreased LV cavity size*) Volume expansion	Increased	Decreased	Decreased
Passive leg elevation Isometric hand grip Vasopressors (*increased cavity size*)	Decreased	No change or small increase	No change or small increase

HCM, hypertrophic cardiomyopathy; LV, left ventricular.

d. Systolic murmur(s) may be due to outflow obstruction and/or MR.
e. Bedside maneuvers help differentiate HCM from aortic stenosis or MR (Table 27-5).

C. Prognosis

1. High-risk patients can be identified by clinical, ECG, and echocardiographic findings:
a. Young age (younger than 30 years) at time of initial diagnosis
b. Family history of HCM and sudden cardiac death
c. Syncopal history
d. Asymptomatic or symptomatic nonsustained ventricular tachycardia on ECG monitoring
e. Marked LVH (wall thickness >30 mm)
f. Fall in blood pressure during exercise testing

D. Diagnosis

1. ECG generally demonstrates:
a. LVH with strain pattern
b. "Pseudo-MI pattern": QS waves due to marked LV hypertrophy
2. Echocardiogram is the most useful diagnosis tool:
a. Asymmetrical hypertrophy of the intraventricular septum with septal-to-ventricular free wall ratio greater than or equal to 1.3:1 is highly suggestive.
b. Doppler interrogation at rest and during provocative maneuvers (PVCs, Valsalva) is critical to assess presence/severity of dynamic outflow obstruction and presence/absence of MR.

E. Treatment

1. Noncompliant LV is poorly equipped to handle sudden preload shifts.
2. Hypovolemia will worsen dynamic outflow obstruction and increase the degree of MR.
3. Transesophageal echocardiographic (TEE) or continuous hemodynamic monitoring is recommended for patients with marked LV hypertrophy and/or significant outflow tract obstruction (>50 mm Hg) undergoing surgical procedures associated with:
a. Significant blood loss
b. Decreased vascular tone
c. Need for transient inotropic support

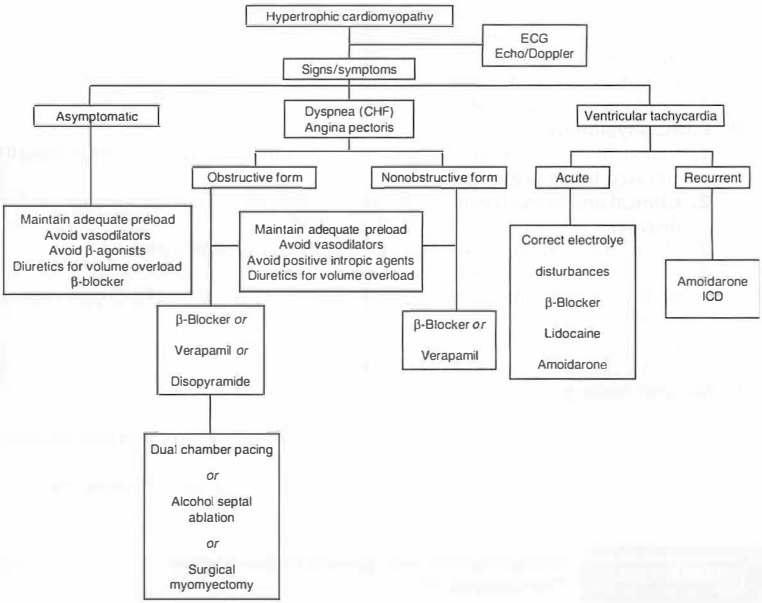

Figure 27-1. Treatment algorithm for the management of patients with known hypertrophic cardiomyopathy. ECG, electrocardiogram; CHF, congestive heart failure; ICD, implantable cardioverter defibrillator. (From Irwin JS, Rippe JM. *Irwin and Rippe's intensive care medicine*, 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2003:310, with permission.)

4. Pharmacologic therapy.
   - **a.** Diuretics should be used judiciously (if at all)
   - **b.** β-Blockers are most frequently utilized in patients with symptomatic HCM (Fig. 27-1).
     - **i.** High doses are often required
     - **ii.** Sustained release preparations should be replaced with shorter acting agents during periods of hemodynamic lability.
   - **c.** Calcium channel blockers, particularly verapamil, are useful in patients with persistent symptoms or intolerance to β-blockers.
   - **d.** Catecholamines, particularly β-agonists like dobutamine, should be avoided whenever possible as they will increase dynamic LV outflow obstruction.
   - **e.** Atrial fibrillation management may include:
     - **i.** β-Blocker or calcium channel blocker for rate control
     - **ii.** Intravenous amiodarone
     - **iii.** Prompt cardioversion if poorly tolerated
     - **iv.** Systemic anticoagulation (very high risk of emboli)
   - **f.** Surgical septal myectomy or alcohol septal ablation improves symptoms for patients with NYHA class III or IV angina or dyspnea and marked outflow tract obstruction despite optimized pharmacologic therapy.

IV. RESTRICTIVE CARDIOMYOPATHIES

A. Background

1. Least common type (<5%) of heart muscle disease.

2. Hallmarks include:
   a. Severe diastolic dysfunction ("restrictive" echocardiographic pattern)
   b. Normal systolic function and cavity size
   c. Substantial biatrial enlargement
3. Etiologies are shown in Table 27-6

B. Pathophysiology

1. Ventricular myocardium is rigid and noncompliant, resulting in chronically elevated filling pressures.
2. Clinical and hemodynamic features can often mimic constrictive pericardial disease.
3. Heart failure is the most common initial clinical manifestation.
4. Physical finding may include:
   a. Increased jugular venous pressure (JVP) (often >20 cm H_2O), prominent Y descent
   b. Positive Kussmaul's sign in JVP
   c. Moderate (1 to 2/6) MR/TR murmurs

C. Natural history

1. Cardiac amyloidosis is the prototypical disease:
   a. Cardiac involvement is common in immunologic (AL) and transthyretin (TT) types
   b. Survival of <24 months from the onset of heart failure symptoms

TABLE 27-6 Classification and Causes of Restrictive Cardiomyopathy

Myocardial
Noninfiltrative
Idiopathic[a]
Scleroderma
Pseudoxanthoma elasticum
Diabetic cardiomyopathy
Infiltrative
Amyloidosis[a]
Sarcoidosis[a]
Gaucher's disease
Hurler's disease
Fatty infiltration
Storage diseases
Hemochromatosis
Fabry's disease
Glycogen storage diseases
Endomyocardial
Endomyocardial fibrosis[a]
Hypereosinophilic syndrome
Carcinoid heart disease
Metastatic malignancies
Radiation-induced myocardial injury
Anthracycline toxicity[a]
Drugs causing fibrotic endocardial changes (serotonin, methysergide, ergotamine)

[a] Conditions more likely to be encountered in clinical practice.
(From Wynne J, Braunwald E. The cardiomyopathies. In: Braunwald E. (ed.): *Heart disease*. 7th ed. Philadelphia: WB Saunders, 2005:1682.)

2. Idiopathic restrictive disease
   a. Disease of elderly
   b. Five-year survival rate currently averaging 65%

D. Diagnosis

1. Evaluation centers on differentiating: (a) RCM from constrictive disease and (b) idiopathic origin from infiltrative disease etiologies.
2. Echocardiography will typically show concentric LVH, normal ventricular size, biatrial enlargement, and Doppler evidence of restrictive physiology.
   a. Prominent mitral E wave (E/A ratio >1.5)
   b. Short isovolumetric relaxation time
   c. Short mitral deceleration time (DT <140 ms)
   d. Reduced mitral annular relaxation velocity (E′) on Doppler tissue imaging (DTI)
3. Increased myocardial echogenicity ("speckling") suggests an infiltrative process such as amyloidosis, which can be confirmed by:
   a. Rectal biopsy (70% sensitivity)
   b. Abdominal fat pad biopsy (80% sensitivity)
   c. Endomyocardial biopsy (>99% sensitivity)
4. Cardiac MR or high-resolution CT imaging should be performed to exclude pericardial constriction, if the correct diagnosis remains uncertain based on clinical and/or hemodynamic features.

E. Treatment

1. General measures include:
   a. Low dose of diuretics to decrease "congestive" symptoms.
   b. PCW should generally exceed 15 mm Hg if hemodynamic monitoring is undertaken to avoid inadequate preload during periods of instability.
   c. Angiotensin-converting enzyme (ACE) inhibitors and β-blockers are generally ineffective but may be used if systolic dysfunction (LVEF <40%) develops.
2. Cardiac amyloidosis may respond to:
   a. Prednisone and melphalan immunosuppression
   b. Heart transplantation followed by autologous bone marrow transplantation
3. Atrial fibrillation is poorly tolerated and may require urgent cardioversion and initiation of amiodarone or β-blocker treatment.

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VALVULAR HEART DISEASE

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28

I. AORTIC STENOSIS

A. Principles: irrespective of how acute or severe its presentation, severe aortic stenosis (AS) should always be considered a surgical disease.

B. Etiology and natural history:

1. **Etiology.** Principally degenerative, with progressive, age-related calcification of normal trileaflet valve. Calcification of congenitally bicuspid valve may lead to presentation earlier in life. Rheumatic disease is increasingly less common.
2. **Progression.** On average, steady decrease of 0.1 cm^2/year in valve area, and increase of 7 mm Hg/year in mean transvalvular gradient per year, due to calcification. However, rate of progression is highly variable and difficult to predict in individual patients. Older age, renal failure, hypertension, smoking, and hyperlipidemia associated with more rapid progression.
3. **Clinical natural history.** Poor once symptoms (even mild) occur.

C. Pathophysiology

Progressive obstruction to left ventricular (LV) outflow, characterized by increased transvalvular velocity and pressure gradient and reduced effective aortic orifice. High afterload leads to compensatory, concentric LV hypertrophy, diastolic dysfunction, enhanced wall stress, and ultimate failure due to "afterload mismatch". Timely intervention to relieve the mechanical obstruction often reverses ventricular dysfunction.

D. Clinical presentation

1. **Acute presentation.** Chest discomfort (angina), syncope, or heart failure.
2. **Prognosis.** Average survival 1 to 3 years from symptom onset without surgical intervention.
3. **Clinical examination.** Slow rising, late-peaking, low-amplitude carotid pulse (*parvus et tardus*). Harsh, late-peaking basal systolic ejection murmur and decreased (or absent) aortic component of S2; radiation of murmur to apex may mimic mitral regurgitation (MR) (Gallavardin phenomenon). Murmur may be diminished or absent in patients with reduced ejection fraction (EF) and progressive LV failure.

E. Investigations

1. Electrocardiogram (ECG) and chest radiograph: LV hypertrophy nonspecific and not always present.
2. Echocardiography:
   a. **Two-dimensional echocardiography** allows accurate definition of valve anatomy, assessment of severity of valve calcification, and evaluation of LV hypertrophy and systolic function.
   b. **Doppler echocardiography** permits measurement of the transaortic jet velocity, pressure gradient, and effective aortic orifice area (severe if 4 m/s or greater, 40 mm Hg [mean] or greater, and $<1.0\ cm^2$, respectively).
   c. Patients with suspected AS, severe LV dysfunction, and low cardiac output (and hence low transvalvular pressure gradient) may benefit from dobutamine stress to clarify severity. With dobutamine, "true" severe AS gradient increases with unchanged valve area. Contractile

reserve (>20% increase in stroke volume with dobutamine) predicts better outcome following aortic valve replacement.

3. Computed tomography measures the large amount of aortic valve calcium in severe AS and permits evaluation of aortic root dimensions.
4. Cardiac catheterization verifies severity of AS in difficult cases and provides preoperative coronary angiography.

F. Management

1. Intensive care unit management: cautious use of diuretics for patients with severe volume overload; avoid hypovolemia or excessive preload reduction which may further compromise cardiac output. Support blood pressure by all means in hypotensive patients. Caution with use of vasodilators, given propensity for hypotension (limited ability to augment cardiac output).
2. Aortic valve replacement is the lifesaving intervention and is almost never contraindicated.
3. Percutaneous intervention with balloon valvuloplasty is rarely useful, except as a palliative measure (risky and only transiently effective). Percutaneous aortic valve replacement is currently under evaluation as an alternative for patients who are not candidates for surgery.

II. AORTIC REGURGITATION

A. Etiology: primary valvular aortic regurgitation (AR) may be a sequela of endocarditis, bicuspid aortic valve, rheumatic heart disease, or calcific degeneration (in tandem with AS). It may also present as secondary complication of aortic root disease, aortic dissection, or aortic trauma. Chronic AR of any cause may present acutely with heart failure.

B. Pathophysiology: over time, chronic AR leads to both increased preload (increased end-diastolic volume) and increased afterload (increased systolic pressure and wall stress) with associated eccentric ventricular hypertrophy and LV cavity dilation. Progressive rise in end-systolic wall stress ultimately results in afterload mismatch, decline in systolic function, and heart failure. Acute, severe AR abruptly reduces ventricular compliance, generating high filling pressures and heart failure despite low-intensity murmur.

C. Clinical presentation

1. Symptoms: exertional dyspnea, heart failure; angina prominent late in course.
2. Physical examination: classically, wide pulse pressure reflecting large stroke volume, with associated diastolic decrescendo murmur at the base. Severity of AR correlates better with duration than intensity of murmur. Chronic, severe AR may be associated with a number of characteristic signs or arterial hyperpulsatility on physical examination including a "water hammer" (Corrigan) pulse, capillary pulsations (Quincke sign), and a variety of other auscultatory findings of wide pulse pressure. Functional mitral stenosis (MS) may be audible as an apical diastolic rumble (Austin-Flint murmur). Acutely, these signs may be absent, and the diastolic murmur is often unimpressive or short due to rapid equalization of aortic and LV end-diastolic pressures.

D. Investigations

1. ECG and chest radiograph: acutely, pulmonary edema may contrast with normal heart size and lack of ventricular hypertrophy. Chronic AR is associated with prominent ventricular enlargement (*cor bovinum*). Severe aneurysmal dilation of the aorta may suggest primary disease of the aortic root as a mechanism for AR.
2. Echocardiography:
   a. May be helpful in evaluation of leaflet anatomy and motion as well as size and shape of the aortic root, to identify the cause of AR. Ventricular chamber dimensions, volumes, EF, and mass can also be assessed. Transesophageal echocardiography (TEE) may provide more detailed assessment where transthoracic imaging is inadequate.

b. Doppler and color-flow imaging show the regurgitant jet. AR may be quantified by calculating the effective regurgitant orifice area and regurgitant volume (severe if $\geq 0.30\,cm^2$ and ≥ 60 mL/beat, respectively).

3. Cardiac catheterization: may permit assessment of AR severity by aortography, and coronary angiography may be performed in older patients (if no large vegetations) as a prelude to surgical intervention.

E. Management

1. Afterload reduction with intravenous or oral vasodilators is central to the acute medical treatment of severe AR. Intra-aortic balloon counterpulsation and β-blockade are contraindicated.

2. Surgical valve replacement is indicated in chronic AR for symptomatic patients and those with evidence of LV dysfunction (EF $\leq 55\%$) or severe LV cavity dilation (end-diastolic dimension ≥ 75 mm Hg, end-systolic dimension ≥ 55 mm or $\geq 25\ mm/m^2$). Valve replacement may be urgently required in patients with acute, severe AR and heart failure. Aortic valve repair is sometimes possible. Periannular repair is necessary for perivalvular abscesses in patients with endocarditis.

3. For patients with AR secondary to aortic root disease, progressive aortic enlargement (beyond 50 mm in those with a bicuspid valve and beyond 55 mm in those with a tricuspid valve) may be an independent indication for surgical intervention to prevent rupture. In some patients, a structurally normal aortic valve may be preserved during surgical repair or replacement of the enlarged aortic root.

III. MITRAL REGURGITATION

A. Etiology and mechanism

1. Primary mitral valve (MV) disease. Due most commonly to myxomatous degeneration (e.g., MV prolapse), rheumatic heart disease, infective endocarditis, and annular calcification.

2. Ischemic or functional MR. Most commonly due to valve tenting, secondary to chordal traction following progressive ventricular remodeling in patients with cardiomyopathy or previous myocardial infarction. Rarely a consequence of acute papillary muscle rupture, for example, following acute myocardial infarction.

B. Pathophysiology

1. Chronic, severe MR increases LV end-diastolic volume and promotes progressive eccentric hypertrophy, further distortion of the papillary muscle architecture, and additional MR. Progressive volume loading, with attendant rises in wall stress, overwhelms compensatory mechanisms and leads to myocardial failure.

2. Acute onset of severe MR (e.g., in the context of myocardial infarction with papillary muscle rupture or endocarditis with leaflet perforation) causes a marked reduction of forward stroke volume and abrupt increase in end-diastolic volume. In contrast to chronic MR, the regurgitant volume is tolerated poorly due to small left–atrial (LA) size with diminished LA compliance. Abrupt rise of LA pressure leads to pulmonary edema, marked elevation of pulmonary vascular resistance, and biventricular heart failure.

C. Clinical presentation

1. Symptoms

a. Nature and severity of symptoms related to severity of MR, rate of progression, level of filling pressures, and presence of atrial arrhythmias or associated valvular, myocardial, or coronary artery disease.

b. Exertional dyspnea and symptoms of low cardiac output (weakness, fatigue) are common in patients with chronic, severe MR.

c. Patients with acute, severe MR typically present with abrupt onset of pulmonary edema in a suggestive clinical context (e.g., acute myocardial

infarction, endocarditis). Hypotension and frank cardiogenic shock may develop, requiring urgent or emergent surgical intervention.

2. **Physical examination.** Classically, apical holosystolic murmur radiating to the left axilla and infrascapular area (though anterior radiation may occur with posterior leaflet problems). P2 component of S2 may be increased if associated pulmonary hypertension is present. S3 and S4 gallops are frequently audible. Diastolic rumble may occasionally be audible in severe MR (functional MS). Murmur of acute MR may be lower pitched and softer than the murmur of chronic MR.

D. Investigations

1. ECG and chest radiograph: in chronic MR, principal ECG findings are of LA enlargement and, frequently, atrial fibrillation (AF). Chest radiography reveals cardiomegaly with LV and LA enlargement. In acute, severe MR, atrial enlargement and cardiomegaly are often absent.
2. Echocardiography and Doppler:
   a. Two-dimensional (2D) echocardiography provides important clues to (i) etiology and mechanism (e.g., ruptured chord or papillary muscle); (ii) ventricular function, global and regional. Given superior ability to assess the detailed anatomy of the MV and severity of regurgitation, TEE is often useful when transthoracic images are suboptimal. Live three-dimensional echocardiography shows the entire valve anatomy.
   b. Doppler and color-flow show the jet, direction (septal-superior for posterior leaflet, lateral for anterior leaflet, central for functional or bileaflet) and quantifies MR (effective regurgitant orifice, regurgitant volume, severe if $\geq 0.40\,cm^2$ and ≥ 60 mL/beat, respectively).
3. Cardiac catheterization may verify severity of MR, hemodynamics, and LV function but mostly is used to assess coronary lesions and need for revascularization.

E. Management

1. Medical treatment
   a. Pharmacologic therapy with vasodilators generally ineffective for management of chronic severe MR since afterload is not excessive. Without surgical treatment, prognosis for patients with severe MR and heart failure is poor.
   b. Surgical treatment should be considered for patients with symptoms or functional disability related to MR or for asymptomatic patients with progressively deteriorating LV function or increasing chamber dimensions.
   c. Acute severe MR may require medical stabilization with afterload reducing agents (e.g., nitroprusside), inotropes (e.g., dobutamine), or intra-aortic balloon counterpulsation. Diuretics, nitrates, and mechanical ventilation may be useful in the management of associated pulmonary edema.
2. Surgical treatment
   a. Outcome depends on clinical and hemodynamic status of patient, age of patient, comorbidities, and skill/experience of surgical team. Also strongly influenced by severity of LV dysfunction and presence of concomitant coronary artery disease. Recent decrease in operative mortality allows consideration of surgery even in patients elderly or with advanced heart failure.
   b. Approach varies according to mechanism. MV repair preferred to replacement where possible; repair typically possible in those with degenerative disease or leaflet perforation, but more difficult in those with significant rheumatic deformity or calcification of the subvalvular apparatus.
   c. Hemodynamic stabilization with medical therapy is optimal before surgical intervention, but emergent surgical intervention may be indicated (despite high perioperative mortality) for those with acute papillary

muscle rupture and shock or for infective endocarditis complicated by refractory congestive heart failure or recurrent emboli.

IV. MITRAL STENOSIS (MS)

A. Etiology. Predominantly rheumatic.

B. Pathophysiology. The fixed orifice due to commissural fusion leads to large gradient with increases in flow (pregnancy, anemia) and to heart failure.

C. History. Most commonly, presenting symptoms are fatigue, dyspnea, and diminished effort tolerance. Usually a slowly progressive disease, though those with critical MS may experience attacks of sudden pulmonary edema precipitated by AF, pregnancy, fever, effort, or other physical/emotional stress. Some experience sequelae of severe pulmonary hypertension (chest pain, hemoptysis) and massive LA remodeling (peripheral emboli, compression of recurrent laryngeal nerve).

D. Physical examination. Typically, irregular pulse secondary to AF with signs of left and right heart failure. Characteristic auscultatory features include accentuated S1 with opening snap; low-pitched apical diastolic rumble (best heard in left lateral decubitus position). Parasternal (right ventricular [RV]) lift, accentuation of P2 and narrowed splitting of second heart sound are notable as pulmonary hypertension develops. S3 absent unless significant MR or AR coexists. Of note, diastolic murmur sometimes is inaudible in low-flow MS of the elderly.

E. Investigations

1. ECG and chest radiograph: LA enlargement is usually present in sinus rhythm; AF common with progressive disease; RV hypertrophy may develop in setting of associated pulmonary hypertension. Chest radiograph frequently demonstrates evidence of LA enlargement (occasionally severe) and may rarely show MV calcification.
2. Echocardiography and Doppler
   a. 2D-echocardiography for (i) assessment of MV anatomy; (ii) planimetry of reduced orifice; and (iii) quantification of valvular and subvalvar calcification with scoring to assess suitability for balloon valvuloplasty.
   b. Doppler echocardiography and color flow for (i) assessment of MS severity (mean transmitral gradient and valve area, severe if ≥ 10 mm Hg and $\leq 1.5\ cm^2$, respectively) at rest and with exercise; (ii) identification of associated MR; (iii) assessment of hemodynamics (pulmonary hypertension, filling pressures) and evaluation of aortic valve (affected in approximately one third of patients with MS).
   c. TEE: may provide additional information regarding (i) LA (appendage) thrombus; (ii) MR presence and severity.
3. Cardiac catheterization: permits detailed hemodynamic assessment of the MV (usually necessary only when echocardiography is nondiagnostic) and coronary angiography. Most commonly done in tandem with an attempt at percutaneous balloon mitral valvuloplasty.

F. Management

1. Acute management of heart failure symptoms may include oxygenation, diuretics, β-blockers/calcium channel blockers for control of heart rate, and mechanical ventilation. Warfarin anticoagulation should be considered for prevention of systemic embolism in patients with AF, prior embolic events, and those with known LA thrombus.
2. Surgical or percutaneous intervention should be considered in patients with severe, symptomatic MS, or those with moderately severe MS and new-onset AF or significant pulmonary hypertension.
3. In patients with favorable valve morphology, mild MR, and no evidence for LA thrombus, percutaneous balloon mitral valvuloplasty is the preferred treatment with results equivalent to surgical commissurotomy; can be done in pregnant women with low risk.

4. Surgical MV repair/replacement reserved primarily for those with heavily calcified valves or with significant concomitant MR who are not candidates for a percutaneous procedure.

V. PROSTHETIC VALVE COMPLICATIONS

A. Prosthetic valve thrombosis

1. Clinical presentation: stroke due to systemic embolism or heart failure due to obstruction of a mechanical heart valve. Suspect in patients with new dyspnea in association with muffled valve closure sounds or new murmurs on auscultation.
2. Investigations: echo to assess severity of prosthetic obstruction; transesophageal echo may be useful to better define thrombus size and degree of limitation in movement of mobile element. Fluoroscopy may provide superior visualization of valve leaflets due to acoustic shadowing on ultrasound.
3. Treatment
   a. Reoperation: preferred for left-sided valve thrombosis with symptomatic heart failure and large clot burden.
   b. Thrombolysis: risk of embolism and secondary recurrence, but reasonable to consider for poor surgical candidates or as primary therapy for those with right- or left-sided valve thrombosis with small clot burden and mild symptoms. Fibrinolytic therapy with Streptokinase or recombinant tissue plasminogen activator (r-TPA) followed by intravenous heparin and aspirin until international normalized ratio (INR) is therapeutic.

B. Prosthetic valve endocarditis

1. Clinical presentation: infection, embolism, heart failure. May affect both mechanical and bioprosthetic valves.
2. Investigations: blood cultures and TEE are key to diagnosis. TEE also shows abscesses, fistula, and intraprosthetic and periprosthetic regurgitation.
3. Treatment antibiotics: early reoperation to remove infected tissue and foreign material, especially if heart failure is present.

C. Structural failure

1. Bioprosthesis: frequent, progressive due to degeneration. Reoperation after stabilization.
2. Mechanical valve: rare, sudden due to defective material. Urgent reoperation.

D. Prosthetic regurgitation

1. Presentation: heart failure or anemia due to hemolysis. Murmur may not be audible.
2. Investigations: echocardiography, particularly TEE, is key to diagnosis.
3. Treatment by reoperation (urgency determined by severity of heart failure and infectious cause). Percutaneous treatment of periprosthetic regurgitation is possible.

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29 CRITICAL CARE OF PERICARDIAL DISEASE

Sunil Mankad

I. GENERAL PRINCIPLES

A. Definition

There is a wide spectrum of pericardial disease seen in critical care, but the clinicopathologic processes involved are relatively few and include:

1. Pericarditis, with or without pericardial effusion, with or without myocardial involvement (myopericarditis)
   - a. Acute
   - b. Subacute
   - c. Chronic, fibrinous, noneffusive, or exudative
2. Pericardial effusion and cardiac tamponade
3. Constrictive pericarditis
   - a. Acute
   - b. Subacute
   - c. Chronic adhesive
   - d. Fibrocalcific

B. Anatomy

1. The pericardium is a double-layered fibroserous sac that surrounds the heart and is made up of a ***visceral*** layer that adheres firmly to the epicardium and a tough, fibrous outer ***parietal*** layer.
2. Importantly, the pericardium reflects over the origin of the great vessels; therefore, a hemorrhagic pericardial effusion may develop with ascending aorta dissection/rupture.
3. A small amount of fluid (up to 50 mL) normally exists between these two pericardial layers in the ***pericardial space***, and there is enough slack in the parietal pericardium to usually accommodate 100 to 200 mL of fluid between the layers and in two pericardial recesses, the oblique and transverse sinuses, before causing hemodynamic compromise.
4. From a histologic standpoint, the pericardium is made up of compact collagen layers interspersed with elastin fibers, which help provide mechanical viscoelastic function.

C. Etiology (of pericarditis with or without effusion)

1. Idiopathic
2. Owing to living agents (viral or bacterial)
3. Related to myocardial infarction
4. Secondary to connective tissue disease/vasculitis
5. Immunopathic or associated with "hypersensitivity" states including postcardiotomy related
6. Secondary to diseases of contiguous structures
7. Secondary to disorders of metabolism
8. Neoplastic
9. Traumatic
10. Radiation induced
11. Uremic

D. Pathophysiology

1. The unique anatomy of the pericardium allows for the pressure–volume relation of the pericardium to be nonlinear, with an initially flat response (little change in pressure despite large changes in volume) and a subsequent "threshold" critical volume at which point a steep slope develops (large change in pressure with small changes in volume).
2. The pericardium serves several important, albeit subtle, functions although it is not essential for life and no major clinical problems usually develop if there is congenital absence of the pericardium or with surgical removal:
   a. The pericardium limits distention of the cardiac chambers.
   b. This facilitates interaction, interdependence, and coupling of the ventricles and atria such that changes in pressure/volume in the right heart influences pressure/volume in the left heart and *vice versa*.
   c. The thin-walled right ventricle is usually affected more by this restraint than is the thick-walled left ventricle.
3. Excessive fluid in the pericardium increases the normal pericardial effect on ventricular interaction and exaggerates the normal inspiratory decrease in systemic blood pressure, thereby leading to pulsus paradoxus (inspiratory drop in blood pressure >10 mm Hg).
4. Although pulsus paradoxus is the hallmark of tamponade, at the bedside it must be borne in mind that it is common to other disorders, including obstructive lung disease (including severe asthma), pulmonary embolism, tense ascites, obesity, mitral stenosis with right heart failure, right ventricular infarction, hypovolemia, and cardiogenic shock.
5. Beyond pericardial stretch, compensatory mechanisms for tamponade are mainly adrenergically mediated, including tachycardia, peripheral vasoconstriction, and maintained ejection fraction (in pure tamponade without heart disease, the ejection fraction is normal or increased); eventually, these compensatory mechanisms fail and cardiac output or stroke volume fall.
6. Like tamponade, constriction severely limits ventricular filling, with equalization of left and right heart diastolic pressures; systolic right ventricular pressure rises, but usually to <50 mm Hg, and the ratio of right ventricular end-diastolic pressure to systolic pressure is usually >0.3.
7. Unlike in cardiac tamponade, the heart is not compressed in early diastole and relaxes normally or abruptly (rubber bulb effect) as filling proceeds until it reaches its pericardial limit.

II. PERICARDITIS

A. Diagnosis

1. Acute pericarditis may be asymptomatic, but more often the patient has central, sharp, positional (worse when patient is supine and reduced when patient sits up) chest pain with a pleuritic component; however, chest pressure that may approximate angina may also occur.
2. Chest pain may migrate to anywhere in the chest, but frequently radiates to one or both of the trapezius ridges.
3. True dyspnea does not occur in the absence of a large pericardial effusion, but shallow, rapid breathing due to pleurisy is often present.
4. Odynophagia (pain on swallowing) occasionally occurs.
5. The pericardial friction sound (rub) is pathognomonic, but varies from faint to very loud (especially in uremic pericarditis) and may be transient; a fully developed rub has three components: atrial late diastolic rub, ventricular systolic rub, and an early diastolic rub.
6. The white blood cell count, sedimentation rate, and other acute phase reactants vary according to the etiologic agent or primary illness; serum levels

of cardiac enzymes vary depending on coexistent myocardial involvement (myopericarditis).

7. Acute pericarditis is most often an inflammatory, fibrinous disease without an increase in the normal amount of pericardial fluid; cardiomegaly on chest radiography will occur only if >200 to 250 mL of pericardial fluid has accumulated.
8. Typically, four potential electrocardiographic (ECG) stages are noted, with the entire ECG evolution occurring in a matter of days or weeks:
   a. Stage I (Fig. 29-1): diffuse concave upward ST (J-point) elevation with ST depression in lead AVR consistent with epicardial inflammation.
   b. Stage II: ST (J) segments return to baseline more or less "in phase," with little change in T waves. The PR segments may be depressed in either stage I or, more often, stage II, and rarely in stage III. T waves progressively flatten and invert in all or most of the leads that showed ST segment elevations.
   c. Stage III: T-wave inversions appear and are not distinguishable from those of diffuse myocardial injury, myocarditis, or biventricular injury.
   d. Stage IV: T waves return to their prepericarditis configuration.

B. Treatment

1. The treatment of clinically noneffusive pericarditis or pericarditis without a compressing effusion is symptomatic, aimed at pain control, treatment of malaise, and fever reduction.
2. Initial treatment is usually with nonsteroidal anti-inflammatory drugs (NSAIDs) usually resulting in prompt pain relief; typical regimens include ibuprofen (400 to 800 mg every 8 hours) or indomethacin (25 to 50 mg every 6 hours); aspirin (up to 900 mg every 6 hours) may be utilized if there is no response to the NSAIDs.
3. Intractable pericarditis may be treated with corticosteroid therapy, but at the lowest dose possible with appropriate tapering; however, this may lead to chronic recurrent pericarditis symptoms with attempts at weaning.
4. For postmyocardial infarction pericarditis, steroids and NSAIDS should not be utilized due to experimental work demonstrating reduced coronary

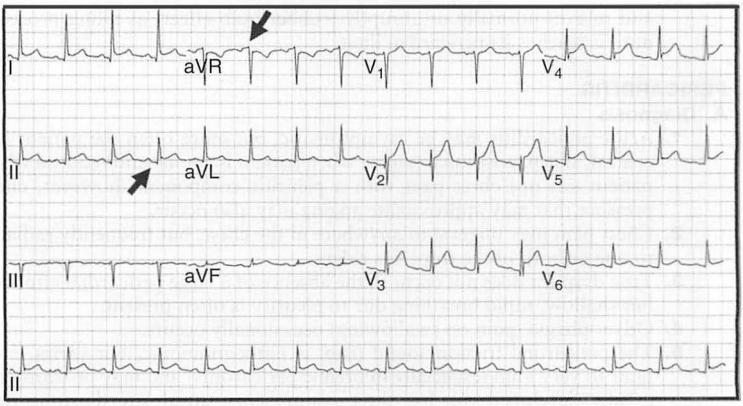

Figure 29-1. Shown are the characteristic electrocardiographic (ECG) stage I findings of acute pericarditis including diffuse concave upward ST (J-point) elevation in leads I, aVL, aVF, V_2, V_2–V_6 with ST depression in lead accelerated ventricular rhythm (AVR) consistent with epicardial inflammation; also shown is PR segment depression/elevation in leads II and aVR, respectively (*black arrows*). (ECG courtesy of Dr. Stephen C. Hammill, MD.)

blood flow, increased myocardial infarction size, increased blood pressure, and increased incidence of myocardial rupture.

III. PERICARDIAL EFFUSION AND CARDIAC TAMPONADE

A. Diagnosis

1. Noncompressing effusions may produce no clinical manifestations and may be the only sign of pericardial disease; if a systemic or extrapericardial disease is responsible for the pericarditis, signs and symptoms of that condition may dominate the picture.
2. Extremely large noncompressing effusions may produce precordial discomfort and symptoms resulting from pressure on adjacent structures, such as dyspnea (from reduced lung capacity), cough, hoarseness, dysphagia, and hiccups; heart sounds may be muffled with massive effusions.
3. The ECG may show low-voltage QRS complex and T waves with nearly always normal P-wave voltage; electrical alternans may be present (Fig. 29-2).
4. Cardiac tamponade is defined as hemodynamically significant cardiac compression resulting from accumulating pericardial contents that overcome compensatory mechanisms and must be considered in any patient with cardiogenic shock and systemic congestions; the pericardial effusion may be fluid, blood, pus, or gas (including air).
5. Cardiac tamponade may appear insidiously as the first sign of pericardial injury or intrapericardial bleeding, especially in conditions such as neoplasia, trauma, and connective tissue disorders.
6. Most patients are hypotensive and tachycardic; in patients with rapid tamponade, such as procedural-related perforation or hemorrhage, the dominant picture is one of shock.
7. Heart sounds may be distant; neck veins are typically engorged, even with the patient sitting erect; forehead, scalp, and retinal venous engorgement are common.

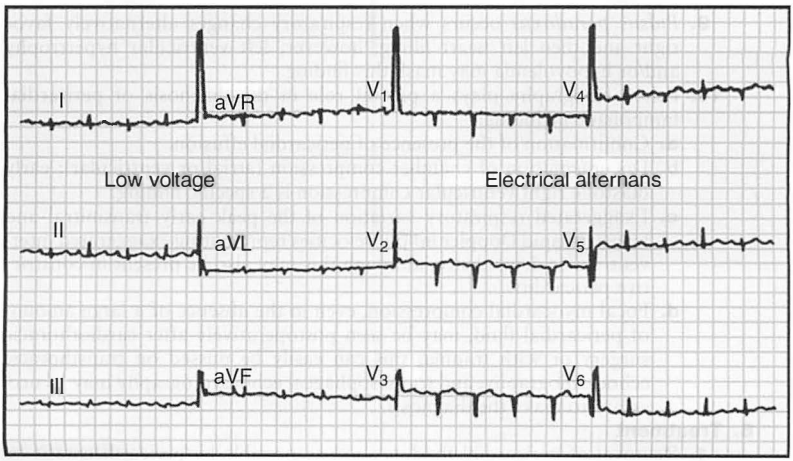

Figure 29-2. Shown is a typical electrocardiograph (ECG) in a patient with a large pericardial effusion; the limb leads show low voltage and electrical alternans (beat-to-beat change in QRS axis) is demonstrated in leads aVR, V_1, V_4, and V_5. (ECG courtesy of Dr. Stephen C. Hammill, MD.)

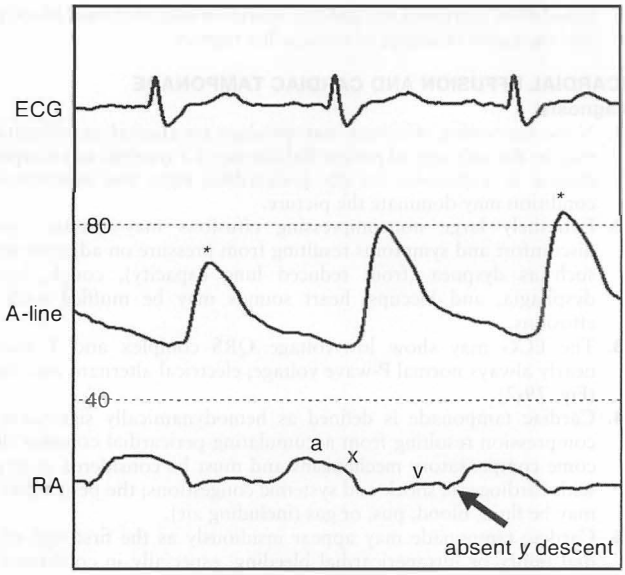

Figure 29-3. Shown are electrocardiograph (ECG), arterial line (a-line), and right atrial (RA) tracings in a patient with pericardial tamponade; note the pulsus paradoxus demonstrated on the a-line tracing (*asterisks* *) as well as the blunted y descent seen on the RA-trace (*black arrow*).

8. If the jugular venous pattern can be discerned, a single negative systolic phase in mid-systole, x-descent, with absence of the y-descent can be a valuable finding (Fig. 29-3).
9. *Pulsus paradoxus* occurs when respiratory changes alternatively favor right and then left heart filling; however, left ventricular hypertrophy and/or hypovolemia may mask this finding.
10. Echocardiography plays a pivotal role in the diagnosis of pericardial tamponade including:
    a. Confirmation of the presence of pericardial effusion.
    b. Documentation of chamber compression (atrial or ventricular); early diastolic right ventricular compression is a specific finding.
    c. Exaggerated respiratory variation of the peak early transmitral and transtricuspid Doppler inflow velocities representing exaggerated interventricular dependence, although this may also be present in constrictive pericarditis.
    d. Focal myocardial compression, even in the absence of a large amount of pericardial fluid, may be seen postoperatively after cardiothoracic surgery or with trauma; this can easily be missed on transthoracic echocardiography, and transesophageal echocardiography may be necessary to make the diagnosis.

B. Treatment

1. Removal of pericardial fluid as soon as possible by pericardicentesis or surgical drainage is the definitive treatment.
2. Emergency echocardiographic-guided pericardiocentesis is a well-established, safe, effective, and readily accessible management strategy for tamponade—especially those resulting from catheter perforation

secondary to invasive catheter-based procedures; echocardiography can help establish the safest and most direct site for needle aspiration.

3. Surgical drainage is optimal for focal myocardial compression related to intrapericardial hematoma/thrombus, traumatic tamponade, or tamponade resulting from pericarditis caused by pyogenic organisms.

IV. CONSTRICTIVE PERICARDITIS

A. Diagnosis

1. Patients usually have one or more of the following signs and symptoms of systemic congestion (usually with clear lung fields) and a normal or slightly enlarged (rarely small) cardiac size:
   - **a.** Easy fatigability.
   - **b.** Dyspnea on exertion, usually with orthopnea.
   - **c.** Pedal edema, ascites, or both.
   - **d.** Hepatomegaly (and, in some cases, splenomegaly).
   - **e.** Distension of the neck veins in which the x- and y-descents, both are prominent venous; the y-descent tends to be deeper and precipitous as it corresponds to the ventricular pressure dip when the atrioventricular valves are open.
   - **f.** Respiratory changes in cardiac pressures are minimal, and jugular venous pressure increases during inspiration (Kussmaul's sign, also seen in right ventricular infarction, acute cor pulmonale, and tricuspid stenosis).
   - **g.** Inspiratory decrease in arterial pressure in pure constriction is slight, nearly always <10 mm Hg.

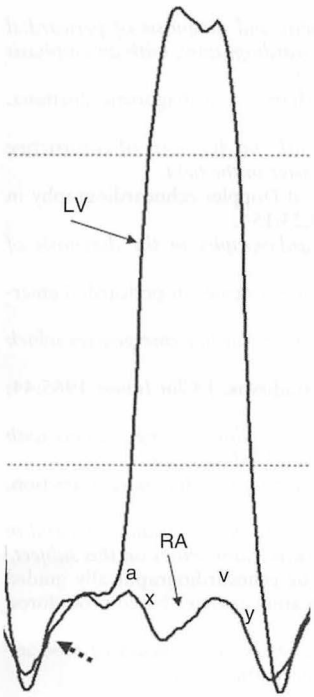

Figure 29-4. Shown are the simultaneous left ventricular (LV) and right atrial (RA) pressure curves' tracings during cardiac catheterization demonstrating the classic "dip and plateau" diastolic pressure curve (*dashed arrow*) and prominent x and y descents of the RA tracing seen in constrictive pericarditis. (Tracing courtesy of Dr. Paul Sorajja, MD.)

2. In conjunction with the clinical presentation, Doppler echocardiography can reliably confirm the diagnosis of constrictive pericarditis most cases of constrictive pericarditis by illustrating exaggerated interventricular dependence; findings of a dilated inferior vena cava with decreased respiratory variation and increased expiratory diastolic flow reversals in the hepatic veins are also noted.
3. Noninvasive establishment of a thickened pericardium may also be useful using cardiac magnetic resonance or computed tomographic imaging.
4. If the diagnosis remains uncertain, simultaneous right and left heart catheterization can be performed; findings include equal and elevated right and left diastolic pressures including a "square-root" configuration to the diastolic pressure (not seen in tamponade, particularly when measured by manometer tip catheters; Fig. 29-4); importantly discordance of right and left ventricular pressures with respiration is seen (during peak inspiration, there is a decrease in left ventricular pressure and a concomitant increase in right ventricular pressure).

B. Treatment

1. Medical treatment of constrictive pericarditis includes diuretics for volume overload; if a significant inflammatory component is present in acute or subacute constrictive pericarditis, then a course of anti-inflammatory medications may be helpful.
2. The definitive treatment of constrictive pericarditis is surgical removal of as much of the pericardium as possible

Suggested Reading

Hoit BD. Pericardial disease and pericardial tamponade. *Crit Care Med* 2007;35: S355.
This contemporary paper reviews the pathogenesis and diagnosis of pericardial disease, focusing on the diagnostic utility of echocardiography, with an emphasis on those areas of greatest interest to the intensivist.

Nishimura RA. Constrictive pericarditis in the modern era: a diagnostic dilemma. *Heart* 2001;86:619.
This is a state of the art review on how to establish the diagnosis of constrictive pericarditis in the modern era by a recognized master in the field.

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This study illustrates the pivotal role of echocardiography in the diagnosis of constrictive endocarditis.

Sefrović PM, Ristć AD, Imazio M. et al. Management strategies in pericardial emergencies. *Herz* 2006;31:891.
This contemporary reviews the natural history of pericardial emergencies which require prompt critical care intervention.

Shabetai R, Fowler NO, Fenton JC. et al. Pulsus paradoxus. *J Clin Invest* 1965;44: 1882.
The physiology of pulsus paradoxus, an important finding among patients with pericardial effusions and tamponade is outlined in a landmark study.

Spodick DH. Pericarditis, pericardial effusion, cardiac tamponade, and constriction. *Crit Care Clin* 1989;5:455.
The different manifestations of pericardial disease are systematically reviewed in this classic review article by one of the world's leading authorities on this subject.

Tsang TSM, Freeman WK, Barnes ME. et al. Rescue echocardiographically guided pericardiocentesis for cardiac perforation complicating catheter-based procedures. *J Am Coll Cardiol* 1998;32:1345.
This important review focuses on the technique, safety, and efficacy of echocardiographically guided pericardiocentesis in emergent situations.

THE ACUTE AORTIC SYNDROMES

Piotr Sobieszczyk, Heather L. Gornik, and Joshua A. Beckman

30

I. OVERVIEW. The acute aortic syndromes are rare yet morbid entities with variable clinical presentation. Mortality due to these disorders increases rapidly with delayed treatment, requiring a high index of suspicion to allow early recognition and management.

II. AORTIC DISSECTION

A. Background

1. Epidemiology of aortic dissection (AD)
   a. Most common acute aortic syndrome.
   b. Estimated US annual incidence of 3.5/100,000 may be an underestimate as many patients die before diagnosis is made.
   c. Incidence increases with age.
2. Stanford classification system
   a. Type A involves the ascending or proximal aorta.
   b. Type B involves the aorta distal to the origin of the left subclavian artery.

B. Pathophysiology

1. Tear in the aortic intima exposes underlying media to blood flow at systemic pressure. The intimal tear propagates, forming a second or "false" lumen.
2. Etiology of AD is variable (Table 30-1). Processes that weaken the medial layers of the aorta, such as hypertension, or intrinsic connective tissue disorders, may eventually result in intramural hemorrhage, aortic dissection, or rupture. Iatrogenic causes include previous aortic surgery or catheterization.

C. Prognosis

1. Without intervention, the risk of death approaches 1%/hour in the first 24 hours after AD. For untreated cases, mortality rates are approximately 50% at 1 week, and upwards of 90% beyond 3 months.
2. Type A: 30-day mortality with medical management approaches 50%, but 20% with surgical repair.
3. Type B: 30-day mortality rate 10% with medical therapy.

D. Diagnosis

1. Clinical presentation is variable and depends on the aortic segment involved. No pathognomonic physical findings secure the diagnosis. Clinical index of suspicion must be high.
   a. Common symptoms: chest pain (73%), back pain (53%), syncope (10%).
   b. Common sign: hypertension (77% type B cases, 36% type A cases).
   c. Less common signs: murmur of aortic insufficiency (31%); hypotension and shock; pericardial tamponade; myocardial ischemia (3%); congestive heart failure (4% to 7%); malperfusion syndromes (e.g., limb ischemia, neurologic impairment or paraplegia, mesenteric ischemia, or renal insufficiency).
2. Diagnostic testing
   a. No reliable blood test at this time for rapid detection of AD.
   b. Chest radiography has limited diagnostic utility.

TABLE 30-1 Factors Associated with Predisposition to Aortic Dissection

Degeneration of the aortic wall
Advanced age
Chronic hypertension
Connective tissue disorders
Marfan's syndrome
Ehlers–Danlos syndrome
Familial aortic dissection syndromes
Inflammatory disorders
Giant cell arteritis
Takayasu arteritis
Iatrogenic injury
Catheterization
Intra-aortic balloon
Aortic surgery
Congenital disorders
Bicuspid aortic valve
Aortic coarctation
Turner's syndrome
Noonan's syndrome
Pregnancy
Cocaine use

c. Electrocardiogram nonspecific (normal in 31% of cases). Ischemic changes may be seen if type A dissection involves the coronary arteries.

d. Noninvasive imaging of the aorta establishes the diagnosis. Three available modalities provide similar diagnostic accuracy (Table 30-2). Invasive angiography is rarely required.

i. Contrast-enhanced computed tomography (CT)

ii. Transesophageal echo (TEE)

iii. Magnetic resonance angiography (MRA).

E. Treatment (Fig. 30-1)

1. Early surgical consultation is critical. Initial management of hemodynamically stable patient must focus on reducing adrenergic tone and lowering heart rate and dP/dt (Table 30-3).

2. Type A dissection is a surgical emergency.

3. Type B dissection is managed medically. Surgery carries high mortality and is reserved for patients with limb or visceral ischemia or contained rupture. Endovascular treatment is a viable alternative to surgery in selected high-risk patients.

4. Long-term management after initial stabilization requires control of hypertension; β-blocker therapy is central to any strategy to prevent aortic expansion. Periodic imaging of the aorta is essential to detect aneurysm formation, extension of dissection, and impending rupture.

III. INTRAMURAL HEMATOMA

A. Background

1. Intramural hematoma (IMH) comprises up to 20% of cases of acute aortic syndromes.

2. Categorized by Stanford classification system (type A and type B).

TABLE 30-2 Advantages, Disadvantages, and Performance of Aortic Imaging Modalities for Aortic Dissection

Modality	Findings	Advantages	Disadvantages	Sensitivity (%)	Specificity (%)
Transthoracic echocardiography	Diagnostic: Undulating intimal flap in proximal aorta Suggestive: Aortic root dilatation Aortic insufficiency Pericardial effusion	Easy to obtain Performed at bedside Noninvasive	Visualization of aorta limited to aortic root Poor image quality in many patients	70–90 (Type A) 30–40 (Type B)	80
Transesophageal echocardiography	Diagnostic: Undulating intimal flap in aorta Differential flow in true and false lumens Intramural hematoma Suggestive: Aortic root dilatation Aortic insufficiency Pericardial effusion	Quick to perform Performed at bedside Descending aorta can be assessed Valvular and ventricular functional assessment possible	Specially trained personnel needed to perform test Aortic arch may be obscured from overlying bronchus	90–100	70–80
Computed tomography	Diagnostic: Intimal flap within aorta Presence of dual lumens with differential contrast enhancement Suggestive: Aortic root dilatation Pericardial effusion	Readily available at most centers	Limited visualization of branch vessels Requires intravenous iodinated contrast Unable to assess aortic valve, ventricular function	90–100	80–90
Magnetic resonance imaging	Diagnostic: intimal flap within aorta Presence of dual lumens Suggestive: Aortic root dilatation Pericardial effusion	Excellent sensitivity and specificity No need for contrast agents Assessment of branch vessels	Not uniformly available Long scanning times Difficult to monitor patients during exam	95–100	95–100
Aortography	Diagnostic: Intimal flap within aorta Presence of dual lumens Suggestive: Aortic root dilation Aortic insufficiency	Excellent branch vessel visualization	Requires assembly of angiography team Requires iodinated contrast agents Invasive Unable to detect IMH Limited sensitivity if dual lumens equally opacified	80–90	90–96

IMH, Intramural hematoma.

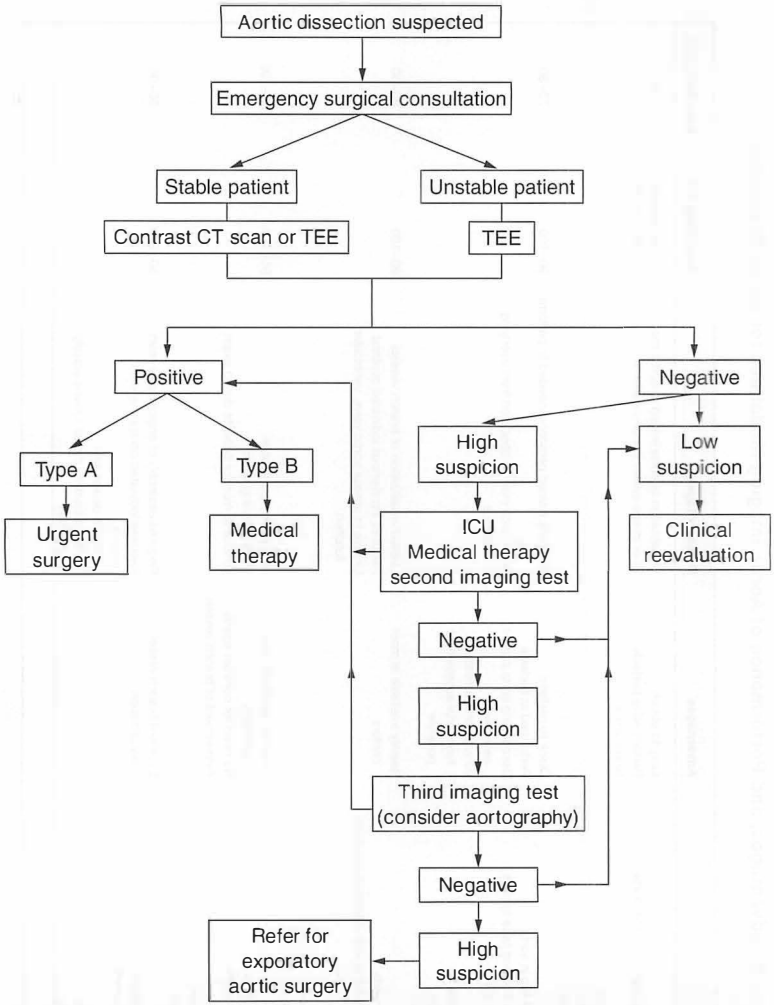

Figure 30-1. Suggested diagnostic and therapeutic algorithm for patients presenting with suspected acute aortic dissection or related entity. CT, computed tomography; TEE, transesophageal echocardiogram; ICU, intensive care unit. (From Shah PB, Beckman JA. Acute aortic syndromes. In: Irwin RS, Rippe JM, eds. *Irwin and Rippe's intensive care medicine*, 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2003, with permission.)

B. Pathophysiology

1. Variant of AD.
2. Spontaneous hematoma within the medial layer of the aorta without an identifiable intimal flap. Rupture of the vaso vasorum into the medial layer is most likely mechanism.

C. Prognosis

1. Dependent on Stanford classification and similar to that of AD.

TABLE 30-3 **Medical Therapy for Hemodynamically stable Acute Aortic Dissection**

Therapeutic goal	Medication	Suggested dose	Desired response
Pain relief	Morphine sulfate	1–2 mg IV q 3–5 min	Pain relief resulting in reduction of sympathetic tone
Heart rate reduction	Metoprolol	2.5–5.0 mg IV q 2 min up to three doses. Follow with 5–10 mg IV q 4–6 h	Maintenance of heart rate to between 60 and 70 beats per min
	Esmolol	500 μg/kg IV bolus followed by continuous infusion of 50 μg/kg/min. Titrate up to maximum of 300 μ/kg/min.	Maintenance of heart rate to between 60 and 70 beats per min
	Propranolol	1 mg IV q 3–5 min. (not to exceed 10 mg). Follow with 2–6 mg IV q 4–6 h	Maintenance of heart rate to between 60 and 70 beats per min
Heart rate/blood pressure reduction	Labetalol	20 mg IV over 2 min followed by 40–80 mg IV q 10–15 min to a maximum of 300 mg. Start IV infusion at 2 mg/min and titrate to 10 mg/min	Maintenance of heart rate to between 60 and 70 beats per min; maintenance of systolic blood pressure between 100 and 110 mm Hg
Blood pressure reduction	Sodium nitroprusside	0.25–0.3 μg/min IV infusion and titrate to 10 μg/kg/min	Maintenance of systolic blood pressure between 100 and 110 mm Hg
Blood pressure reduction in setting of renal artery involvement	Enalaprilat	0.625–1.25 mg IV q 6 h	Maintenance of systolic blood pressure between 100 and 110 mm Hg

D. Diagnosis

1. Clinical presentation indistinguishable from AD.
2. Pericardial effusion, hemothorax, and hemoperitoneum from rupture of the adventitia herald impending rupture.
3. Diagnosis is made by one of the imaging modalities used to diagnose AD (i.e., CT, TEE, and MRA).

E. Treatment

1. Initial management identical to that of AD (Fig. 30-1 and Table 30-3).
2. Surgical repair is recommended for type A IMH (surgical mortality rate of 8% vs. 55% with medical therapy).
3. Type B IMH can be managed medically but warrants careful clinical follow-up and serial imaging. Late progression of IMH to dissection, aneurysm, or rupture can be as high as 21%.

IV. PENETRATING ATHEROSCLEROTIC ULCER

A. Background

1. Penetrating atherosclerotic ulcer (PAU) more common in elderly patients with hypertension and severe aortic atherosclerosis.
2. Preferentially involves the descending thoracic and abdominal aorta.

B. Pathophysiology

1. Severe atherosclerotic lesion ulcerates, penetrates through the intimal layer, and results in a discrete ulcer crater.
2. Propagation to dissection can occur, but is rare: ulceration can extend through the adventitia resulting in pseudoaneurysm formation or frank aortic rupture. Symptomatic ulcers or ulcers with deep erosion are more likely to rupture. Stable PAU will often progress to aneurysmal dilatation of the aorta.

C. Clinical presentation

1. Occurs in patients with multiple atherosclerotic risk factors and marked systemic atherosclerosis.
2. Most patients, if they have symptoms, present with the acute onset of pain in the chest and/or the back and hypertension.
3. Pericardial tamponade, myocardial ischemia, and aortic insufficiency are uncommon because the ascending aorta is a very unusual location for PAU.

D. Diagnosis

1. Diagnosis can be established with contrast computed tomographic angiography (CTA, TEE, or MRA).

E. Treatment

1. Optimal treatment strategy of patients with PAU is unknown. Medical therapy is initial choice in absence of false aneurysm formation, frank rupture, or recurrent pain.
2. Blood pressure must be controlled to reduce the shear stress and pulse pressure against the ulcer (Table 30-2).
3. Patients with hemodynamic instability, evidence of aortic rupture, or pseudoaneurysm should undergo immediate surgical therapy.
4. Elective surgical repair indicated in patients with intractable pain, distal embolization from thrombus within the ulcer, or progressive aneurysmal dilatation of the aorta. Endovascular stent grafting can be used safely in selected patients.
5. Stable patients with PAU must be followed-up with serial imaging studies.
6. Risk factor modification includes lipid-lowering therapy and smoking cessation.

V. RUPTURED AORTIC ANEURYSM

A. Background

1. Annual incidence of ruptured abdominal aortic aneurysm (AAA) and thoracic aortic aneurysm (TAA) is estimated at 5 to 7 and 3.5 per 100,000 persons, respectively.
2. Owing to the progressive risk of rupture with increasing aneurysm diameter, elective repair is recommended when the diameter of the thoracic aorta reaches 6 cm (5 cm in patients with Marfan's syndrome) and that of the abdominal aorta reaches 5 to 5.5 cm.

B. Prognosis

1. Prognosis of ruptured TAA or AAA is grim. Of patients who develop rupture, 60% will die before presentation to medical attention.
2. Operative mortality for patients reaching medical attention is approximately 50%; however, mortality is 100% without surgical intervention.

C. Diagnosis

1. Clinical presentation
   a. Diagnosis should be considered in all patients presenting with acute hemodynamic instability and new-onset back, chest, or abdominal pain.
   b. The classic triad of abdominal pain, hypotension, and a pulsatile abdominal mass is present in less than one third of patients and supports the diagnosis of ruptured AAA.
   c. Ruptured TAA can present with acute hemothorax or hemorrhagic pericardial effusion and tamponade. The most common site of rupture is in the descending thoracic aorta.
2. Diagnostic testing
   a. Imaging studies (CT or abdominal ultrasound) should be obtained only in the stable patient. If there is clinical concern of ruptured TAA or AAA in an unstable patient, immediate surgical exploration should be pursued.

D. Treatment

1. Ruptured TAA or AAA is a surgical emergency. Immediate surgical consultation is critical for patients with symptomatic or aneurysms with suspected rupture. Endovascular repair is less morbid and is increasingly used in patients with favorable anatomy.

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EVALUATION AND MANAGEMENT OF HYPERTENSION IN THE INTENSIVE CARE UNIT

31

Benjamin M. Scirica

I. DEFINITIONS

A. *Hypertensive crisis* is defined as a severe elevation in blood pressure (BP).

1. *Hypertensive emergencies* and *urgencies* are categories of hypertensive crises that are potentially life threatening and may occur with chronic essential hypertension, secondary forms of hypertension, or *de novo* (Table 31-1).

2. Usually associated with systolic BPs >180 mm Hg and diastolic BPs >120 mm Hg.

B. *Hypertensive emergencies* and *urgencies* can be considered a continuum of disease, but are differentiated by the presence or absence of acute and progressive target organ damage (TOD).

1. In *hypertensive emergencies,* BP elevation is associated with ongoing central nervous system (e.g., encephalopathy or hemorrhage), myocardial (e.g., ischemia, pulmonary edema), hematologic (e.g., hemolysis), or renal (e.g., acute renal failure) TOD.

2. In *hypertensive urgencies,* the potential for TOD damage is great and likely if BP is not soon controlled. These may be associated with symptoms such as headache, shortness of breath, or anxiety.

C. *Accelerated hypertension* and *malignant hypertension* are traditionally referred to as *hypertensive crises* with either early retinopathy (accelerated) or encephalopathy or nephropathy (malignant). These terms should not be used in current practice, but rather referred to as *hypertensive urgencies or emergencies*.

II. APPROACH TO THE PATIENT

A. Immediate identification of both hypertension and potential TOD is critical to properly triage patients. This should occur in the clinic, ambulance, or emergency department. Patients with hypertensive emergencies should be admitted to an intensive care unit (ICU) setting for continuous monitoring and treatment.

B. In the ICU, therapy must often begin before a comprehensive patient evaluation is completed. A systematic approach offers the opportunity to be both expeditious and inclusive (Table 31-2).

C. A brief history and physical examination should be initiated to assess the degree of TOD and to rule out obvious secondary causes of hypertension. The following should be assessed:

1. History

a. History of hypertension or other significant medical disease

b. Medication use and compliance

c. Drugs of abuse or withdrawal

d. Symptoms attributable to TOD:

i. Neurologic (headache, nausea, and vomiting; visual changes; seizures; focal deficits; mental status changes)

ii. Cardiac (chest pain, shortness of breath)

iii. Renal (hematuria, decreased urine output)

TABLE 31-1 Examples of Hypertensive Crises

Generalized	Cardiovascular	Neurologic	Renal
Accelerated and malignant hypertension	Acute left ventricular failure	Hypertensive encephalopathy	Acute renal failure
Microangiopathic hemolytic anemia/disseminated intravascular coagulation	Unstable angina pectoris	Subarachnoid hemorrhage	Acute glomerulonephritis
Eclampsia	Myocardial infarction	Intracerebral hemorrhage	Scleroderma crisis
Catecholamine excess (drugs, rebound syndrome, pheochromocytoma)	Aortic dissection	Cerebrovascular accident	
Vasculitis	Suture integrity after surgery		

(From Vidt DG, Gifford RW. A compendium for the treatment of hypertensive emergencies. *Cleve Clin Q* 1984;51:421, with permission.)

2. Physical examination
- **a.** BP readings in both arm and legs
- **b.** Signs of neurologic ischemia, such as altered mental status or focal neurologic deficits
- **c.** Direct ophthalmologic examination
- **d.** Auscultation of the lungs and heart
- **e.** Evaluation of the abdomen and peripheral pulses for bruits, masses, or deficits

D. Ancillary and laboratory evaluation

1. Electrolytes, blood urea nitrogen and creatinine, cardiac enzmyes, liver function test complete blood count with differential, coagulation studies, urinalysis, electrocardiogram and chest radiography

TABLE 31-2 Initial Evaluation of Hypertensive Crisis in the Intensive Care Unit

1. Continuous blood pressure monitoring
   a. Direct (intra-arterial) preferred
   b. Indirect (cuff)
2. Brief initial evaluation — history and physical examination with attention to:
   a. Neurologic including funduscopic examination, cardiac, and pulmonary system
   b. Assessment organ perfusion and function (e.g., mental status, heart failure, urine output)
3. Blood and urine studies: electrolytes, BUN, creatinine, CBC with differential, urinalysis with sediment; if indicated, serum catecholamines, cardiac enzymes
4. ECG (examine for LV strain or ischemia)
5. Chest radiograph (assess for size of aorta, cardiomegaly, pulmonary edema)
6. Initiation of therapy (within 1 h of presentation for *hypertensive emergencies*)
7. Further evaluation of etiology once stabilized

BUN, blood urea nitrogen; CBC, complete blood count; ECG, electrocardiogram; LV, left ventricular
(From Vidt DG, Gifford RW. A compendium for the treatment of hypertensive emergencies. *Cleve Clin Q* 1984;51:421, with permission.)

III. TREATMENT

- **A.** The intensity of intervention is determined by the clinical situation.
- **B.** Goal of initial therapy is to terminate ongoing TOD, *not* to return BP to normal levels because cerebral autoregulation determines the initial blood pressure goal.
- **C.** Goal is approximately 25% lower than the initial *mean arterial pressure* within the first minutes to hour after initiation of treatment.
- **D.** After initial stabilization, the goal should be to reduce BP to 160/100–110 mm Hg over the next several hours.
  1. Patients with acute left ventricular failure, myocardial ischemia, or aortic dissection may require more aggressive treatment.
  2. Interventions such as intubation, control of seizures, treating withdrawal, hemodynamic monitoring, and maintenance of urine output can be as important as prompt control of BP.
  3. Care should be given to avoid aggressive BP reduction because it may lead to ischemia of the kidneys, brain, or myocardium because of arterial autoregulation. Also, patients with ischemic strokes are often managed with a higher BP range.
- **E.** After 24 hours of maintaining BP in the 160/100 mm Hg range, further BP therapy can be initiated to achieve the final goal BP.
- **F.** Oral versus parenteral therapy:
  1. In the ICU, parenteral therapy with close hemodynamic monitoring is preferred as it is the most rapid and reliable method to reduce the BP.
  2. Treatment needs to be individualized, but generally use different agents in an orderly and logical manner to assess the effect of a new dose or drug and avoid immediate reductions in BP >25% as it may exacerbate TOD if there is evidence of cardiac, cerebrovascular, or renovascular disease.

IV. SPECIAL SCENARIOS OF HYPERTENSIVE EMERGENCIES

- **A.** New onset of severe hypertension in patients without prior history
  1. Secondary causes, such as pain, anxiety, new onset of angina, hypercarbia or hypoxia, hypothermia, rigors, excessive arousal after sedation, withdrawal, or fluid mobilization with volume overload, can all lead to short-term elevations in BP.
  2. If antihypertensive agents are necessary, low doses of short-acting, intravenous agents should be used to avoid sharp drops in BP in this usually self-limited situation.
- **B.** Perioperative hypertension
  1. Preoperative. Moderate chronic hypertension is not a major risk factor for surgery, but is a marker for potential coronary artery disease which may require further risk stratification.
  2. Perioperative. BP >160/100 mm Hg or an increase of >30 mm Hg (systolic or diastolic) above preoperative are worrisome and require evaluation.
  3. Postoperative. BPs can vary widely due to an increase in pressor reflexes and central nervous system activity due to pain, hypothermia with shivering, hypercarbia and hypoxia, volume resuscitation, or reflex excitement after anesthesia.
- **C.** Hypertension in the obstetric patient (see chapter 112).

V. PHARMACOLOGIC AGENTS (Table 31-3)

- **A.** Direct vasodilators
  1. Sodium nitroprusside: the most predictable and effective agent for the treatment of severe hypertension. It dilates both arterioles and venules (reducing both afterload and preload) and lowers myocardial oxygen demands.
  2. Nitroglycerin: predominantly dilates the venous system. Useful in patients with cardiac ischemia or congestive heart failure.

TABLE 31-3 Proper Dosing for Agents to Treat Hypertensive Crisis

Agent	Administration	Onset	Duration
Direct vasodilators			
Nitroprusside	IV infusion: 0.25–10.0 μg/kg/min	Immediate	1–2 min
Nitroglycerin	IV infusion: 5–200 μg/min	2–5 min	5–10 min
Fenoldopam	IV infusion: 0.1 μg/kg/min; ↑ by 0.05–0.2 μg/kg/min at 20-min intervals to maximum 1.6 μg/kg/min	5 min	15–30 min
Hydralazine	IV bolus: 10–20 mg	10–20 min	1–4 h
Adrenergic blockers			
Phentolamine	IV 5–15 mg	1–2 min	10–20 min
Esmolol	IV bolus: 250–500 μg/kg/min; IV bolus: repeat after 5 min IV infusion: 50–100 mg/kg/min/; give new bolus when increasing infusion	5–10 min	10–30 min
Labetalol	IV bolus: 20–80 mg q 10 min IV infusion: 0.5–2 mg/min	5–10 min	3–6 h
Calcium antagonists			
Nicardipine	IV infusion: 5–15 mg/h	5–10 min	1–2 h
Nimodipine	PO: 60 mg, q 4 hrs	15–30 min	3–6 h
Angiotensin-converting enzyme inhibitors			
Captopril	PO: 6.25–25 mg, repeat q 30 min, if necessary	1 h	1–4 h
Enalaprilat	IV bolus: 1.25–5.0 mg (over 5 min) q6 h	15–30 min	6–8 h
Central agonists			
Clonidine	PO: 0.2 mg initially; 0.2 mg/h (total 0.7 mg)		3 h
Miscellaneous			
Trimethaphan	IV infusion: 0.5–5 mg/min	1–5 min	5–15 min

↑, increase.
IV, intravenous; PO, oral.

3. Hydralazine: a direct parenteral arterial vasodilator that will increase cardiac output, but may cause a reflex increase in heart rate.

B. β-Adrenergic receptor blockers

1. Parenteral agents include labetalol (nonselective), propranolol (nonselective), metoprolol (selective), and the short-acting esmolol (selective).
   a. Labetalol, which has both β- and α-blocking properties, is particularly useful for hypertensive emergencies—to achieve immediate BP control with intravenous bolus and then use a continuous infusion for maintenance.
   b. Esmolol is a short-acting, β_1 selective agent that needs to be given as a continuous infusion.

C. Calcium channel antagonists

1. Dihydropyridines: principally direct vasodilatory effects
   a. Nicardipine: a rapid-acting systemic and coronary artery vasodilator with minimal effects on cardiac conductivity or inotropy.

   b. Nimodipine: recommended only for patients with subarachnoid hemorrhage.
   c. Nifedipine: decreases peripheral vascular resistance and increases collateral coronary blood flow in an uncontrolled and unpredictable manner and may result in serious complications. Do not use short acting or sublingual formulations, but the long-acting formulation is good chronic therapy.
  2. Non-dihydropyridines:
   a. Verapamil: an arterial vasodilator that delays atrioventricular conduction and has a negative inotropic effect. Avoid in patients with left ventricular dysfunction.
   b. Diltiazem: effective arterial vasodilator, slows electrical conduction but with less negative chronotropic effect compared to verapamil.

D. Angiotensin-converting enzyme inhibitors
  1. Captopril: rapid onset of effect after oral administration (30 minutes) with little change in cardiac output or reflex tachycardia.
  2. Enalaprilat: the only parenteral angiotensin-converting enzyme inhibitor. Use with caution because of reflex tachycardia. Avoid in acute myocardial infarction (MI).

E. Other agents
  1. Clonidine: an oral or transdermal centrally acting α_2 adrenergic receptor agonist that decreases peripheral vascular resistance. Takes several days to achieve a steady state.
  2. Fenoldopam: peripheral dopamine D_1, and α_2 adrenergic receptor agonist that reduces BP through vasodilation of renal, splanchnic, coronary, and peripheral vascular beds. Indicated for short-term, in-hospital management of hypertensive emergencies.

F. Diuretics: not considered primary agents in managing hypertensive crises because many patients are hypovolemic. In patients who are volume overloaded, loop diuretics, such as furosemide or bumetanide, can help control intravascular volume and maintain urine output.

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32 SYNCOPE

Karen E. Thomas and William H. Maisel

I. GENERAL PRINCIPLES

A. Definition: Sudden, transient loss of consciousness with loss of postural tone.

II. PATHOPHYSIOLOGY

A. Caused by hypoxia and/or hypoperfusion of the cerebral cortices and reticular activating system.

B. Systolic blood pressure <70 mm Hg or interruption of cerebral blood flow for 8 to 10 seconds usually results in syncope.

C. Syncope is one of numerous causes of loss of consciousness. Seizures, which cause loss of consciousness through global interruption of cerebral electrical activity without necessarily impairing blood flow, are another. See Table 32-1A, B for causes of loss of consciousness.

III. ETIOLOGY

A. Differential diagnosis

1. A number of different disease processes can cause syncope. See Table 32-1A.
2. Neurocardiogenic syncope and orthostatic intolerance are most common. Neurologic, cardiovascular, and psychogenic causes occur with decreasing frequency.
3. Up to 45% of patients will be labeled as having "syncope of unknown cause" despite a thorough evaluation.
4. Etiology of syncope has important prognostic significance.
5. Syncope of cardiac etiology, in the absence of implantable defibrillator, has a 1-year mortality of 20% to 30% compared to 0% to 12% for patients with noncardiovascular causes of syncope, and 6% for those with syncope of unknown etiology.
6. Younger patients more frequently have syncope due to noncardiovascular cause or syncope of unknown origin and overall have a more favorable prognosis.
7. Older patients more often have a cardiac etiology or syncope due to polypharmacy.

IV. DIAGNOSIS

A. Initial diagnostic evaluation

1. Algorithm for the approach to the patient with syncope (Fig. 32-1).
2. Goal is to differentiate between benign and potentially life-threatening causes.
3. Presence of cardiovascular disease identifies patients at increased risk of sudden death.
4. History and physical examination alone can identify the etiology of syncope in 45% of patients and suggest a diagnosis in another 40%.

B. History

1. Obtain patient's and eyewitnesses' report of event.
2. Ask specifically about situational or provocative factors, postural or exertional symptoms, and symptoms of cardiac or neurologic origin.

   a. Tongue biting, aching muscles, or disorientation following loss of consciousness suggest a seizure.
   b. Sweating, nausea, vertigo, incontinence, injury, headache, family history of epilepsy, and history of prior concussion are not predictive of seizures.
3. Take a careful medication history.
4. Past medical history should focus on prior syncopal events, as well as prior cardiac and neurologic history.
5. Family history for familial cardiomyopathy, sudden cardiac death, or syncope should be sought.

TABLE 32-1A Causes of Syncope

Cardiovascular
Arrhythmia
Bradyarrhythmia
Sinus node disease
AV node disease
Drug induced
Pacemaker malfunction
Tachyarrhythmia
Supraventricular arrhythmias
Ventricular arrhythmias
Low cardiac output
Obstruction to flow
Aortic stenosis
Mitral stenosis
Tricuspid stenosis
Hypertrophic cardiomyopathy
Atrial myxoma
Pulmonary stenosis
Pulmonary embolism
Pulmonary hypertension
Cardiac tamponade
Aortic dissection
Pump failure (cardiomyopathy, myocardial infarction)
Disorders of autonomic control
Autonomic insufficiency
Diabetes mellitus
Parkinson's disease
Primary
Reflex mediated
Neurocardiogenic (vasovagal/vasodepressor)
Carotid sinus hypersensitivity
Situational (cough, defecation, micturition, swallow)
Neuralgia (trigeminal, glossopharyngeal)
Orthostatic hypotension
Volume depletion
Medication related

AV, atrioventricular.

TABLE 32-1B Causes of Nonsyncopal Attacks (Often Confused with Syncope)

Neurologic event
- Cerebrovascular disease (cerebrovascular accident, transient ischemic attack)
- Seizure
- Hyperventilation
- Migraine
- Narcolepsy
- Subclavian steal

Psychiatric illness
- Anxiety or panic disorder
- Major depression
- Somatization
- Munchausen's
- Substance abuse

Metabolic
- Hypoadrenalism
- Hypoglycemia
- Hypothyroidism
- Hypoxia

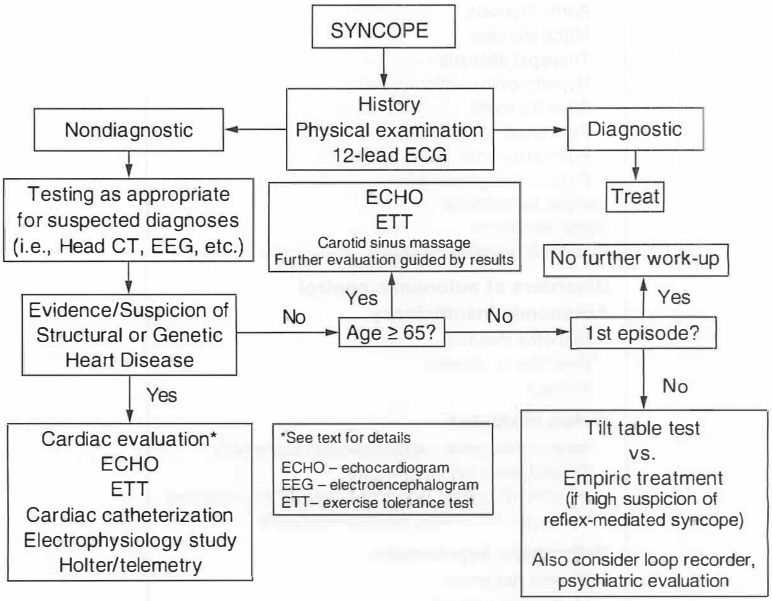

Figure 32-1. Algorithm for the approach to the patient with syncope. ECG, electrocardiogram; CT, computed tomography.

C. Physical examination
  1. Should focus on identifying potential clues as to the etiology of the syncopal episode.
    a. Murmurs, bruits, and signs of heart failure might suggest cardiovascular etiology.
    b. Neurologic abnormalities such as diplopia, headache, or other focal signs may suggest a neurologic etiology.
  2. Orthostatic blood pressure measurements should be taken. Although, orthostatic hypotension as etiology of syncope should only be diagnosed when the history and examination are consistent and other potential etiologies of syncope have been excluded.

D. A 12-lead electrocardiogram (ECG)
  1. Half the patients presenting with syncope have significant baseline ECG abnormalities. However, the ECG alone is diagnostic of the cause of syncope in fewer than 10% of cases.
  2. An abnormal ECG that suggests the presence of underlying heart disease warrants further cardiac evaluation.
  3. The ECG is the only way to diagnose some genetic disorders which can cause syncope including long QT syndrome and Brugada syndrome.

E. Laboratory tests
  1. The ordering of blood chemistries, hematologic studies, and cardiac biomarkers such as troponin and brain naturetic peptide should not be routinely performed, but should be guided by the history and physical examination.

F. Cardiac evaluation (Table 32-2)
  1. Echocardiography
    a. Part of the initial evaluation for patients with known or suspected cardiac disease.
    b. Unselected patients have unanticipated findings 5% to 10% of the time.
  2. Exercise tolerance test
    a. Part of the initial evaluation of patients with suspected ischemia or exercise induced arrhythmias.
    b. Rarely reveals the precise cause of syncope; fewer than 1% have an arrhythmia during exercise testing.
  3. Telemetry/24-hour Holter monitoring
    a. Diagnostic in up to 20% of selected patients (symptoms during monitoring either with or without arrhythmia).
    b. The majority of patients have no symptoms and no diagnostic arrhythmia during monitoring.
  4. Electrophysiology study
    a. Well established for detecting ventricular and supraventricular arrhythmias; less sensitive for detecting bradyarrhythmias.
    b. Diagnostic yield is approximately 30% to 50% in patients with syncope.
    c. A "positive" electrophysiologic (EP) study predicts an increased 3-year sudden death and total mortality rate compared to patients with a negative EP study.
    d. EP studies are low yield in patients without structural heart disease; patients with normal hearts and normal ECGs rarely require EP testing.
  5. Implantable loop recorder
    a. May be useful for patients with infrequent but recurrent episodes of syncope.
    b. Can diagnose arrhythmic causes of syncope in up to 50% of patients.

G. Evaluation for disorders of autonomic control/reflex-mediated syncope
  1. A number of syncope syndromes are related to abnormal control of autonomic function (Table 32-1A, B). More than 50% of patients with syncope of undetermined etiology may have neurally mediated syncope.

TABLE 32-2 Indications for Cardiac Tests in Patients with Syncope

Electrocardiogram (ECG)
All patients at initial presentation

Echocardiogram
Patients with known or suspected cardiac disease (including patients with chest pain, heart murmur, abnormal ECG, etc.)

Exercise tolerance test
Patients with chest pain, ischemic changes on ECG, or exercise induced or postexertional syncope (who do not undergo cardiac catheterization)

Holter or in-patient ECG telemetry
Patients with symptoms suggestive of arrhythmic syncope (brief loss of consciousness, no prodrome, presence of palpitations), unexplained cause of syncope, underlying heart disease, or an abnormal ECG

Electrophysiologic studies
Patients with known or suspected structural heart disease and unexplained syncope or in patients with no organic heart disease but recurrent syncope and a negative tilt table test

Tilt table test
Patients with recurrent syncope or patients with a single episode of syncope accompanied by physical injury, motor vehicle accident, or high-risk setting (pilot, surgeon, window-washer, etc.) thought to be vasovagal. Indicated in patients with unexplained syncope after other appropriate workup

2. Tilt table test
   a. May be used to support the diagnosis of neurocardiogenic (also known as *vasodepressor* or *vasovagal*) syncope.
   b. Among patients with syncope of unknown origin, 25% to 50% will have positive tilt table tests with passive tilt alone.
   c. False positive (10% to 30%) and false negative (30% to 35%) test results are common.
3. Carotid sinus massage
   a. Performed by firm massage of the carotid artery for 5 to 10 seconds in an attempt to elicit a baroreflex-mediated vagal response that can cause bradycardia and/or hypotension.
   b. A positive test is ≥3 seconds of asystole, a ≥50 mm Hg systolic blood pressure decrease, or a ≥40 beats per minute decrease in heart rate.
   c. Contraindicated in patients with a carotid bruit, recent myocardial infarction (MI), recent stroke, or a history of ventricular tachycardia (VT).

H. Neurologic evaluation
1. Patients with focal neurologic signs or symptoms should undergo further evaluation, but additional neurologic testing is rarely indicated in the absence of specific clinical abnormalities or suspicion.
2. Electroencephalography (EEG)
   a. Yields a diagnosis of seizure disorder in fewer than 2% of unselected patients with syncope referred for EEG.
   b. Not recommended as part of the routine evaluation of patients with syncope, but should be considered when seizure is strongly suspected.

3. Head computed tomography (CT)
   a. Yields a positive finding in fewer than 5% of patients with syncope.
   b. Unsuspected central nervous system (CNS) abnormalities are found in fewer than 1% of patients without neurologic abnormality on history or physical examination.
   c. Should be reserved for patients with neurologic abnormality and those who have suffered head trauma.

I. Psychiatric evaluation
   1. Up to 25% of patients with syncope of unknown etiology have a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) psychiatric diagnosis of panic disorder, generalized anxiety disorder, or major depression.
   2. Screening for psychiatric disorders is recommended for patients with recurrent syncope of unclear etiology.

V. TREATMENT

A. Admission criteria

1. Hospital admission is suggested for patients with syncope who have:
   a. A history or suspicion of coronary artery disease (CAD), congestive heart failure (CHF), or ventricular arrhythmia
   b. Physical signs of significant valve disease, CHF, stroke or focal neurologic disorder
   c. ECG findings of ischemia, arrhythmia, increased QT interval, or bundle branch block
   d. Syncope with injury, rapid heart action, chest pain, or exertion
   e. Frequent episodes of syncope
   f. Moderate to severe orthostatic hypotension
   g. Age older than 70
2. Intensive care unit (ICU) admission should be strongly considered in syncope patients with:
   a. Sustained VT
   b. Symptomatic nonsustained VT
   c. Second- or third-degree heart block
   d. Pauses >3 seconds
   e. Symptomatic bradycardia
   f. Severe aortic stenosis
   g. Severe CHF
   h. Evidence of acute ischemia
   i. Ongoing hemodynamic instability

B. Specific treatment

1. Arrhythmias—guidelines for implantation of permanent pacemakers and implantable cardioverter defibrillators (ICDs) for patients with syncope are summarized in Table 32-3.
2. Neurally mediated syndromes
   a. Patients should be counseled to sit or lie down and/or perform isometric contractions at the onset of prodromal symptoms.
   b. Primary treatment is hydration and salt repletion.
   c. β-Adrenergic blockers, selective serotonin reuptake inhibitors (e.g., fluoxetine), and α-adrenergic agonists (midodrine) have demonstrated efficacy in randomized trials.
   d. Other agents, including volume expanders (e.g., fludrocortisone) and disopyramide, appear useful in some patients.
   e. Patients with recurrent, medically refractory vasovagal syncope associated with marked bradycardia may benefit from implantation of a permanent pacemaker.

TABLE 32-3 Current ACC/AHA Guidelines for Implantation of Permanent Pacemakers and Implantable Cardioverter Defibrillators in Patients with Syncope

Indication for implantation of pacemakers in patients with syncope

- Symptomatic sinus pauses or sinus bradycardia ([a]Class I)
- Bradycardia and second- or third-degree AV block (Class I)
- Recurrent syncope caused by carotid sinus stimulation; minimal carotid sinus pressure induces ventricular asystole of >3 s duration in the absence of any medication that depresses sinus node or AV conduction (Class I)
- Recurrent syncope without clear provocative events and with a hypersensitive cardioinhibitory response (Class IIa)
- Major abnormalities of sinus node function or AV conduction discovered or provoked at electrophysiology study (Class IIa)
- Chronic bifascicular or trifascicular block and syncope not proved to be due to AV block when other likely causes have been excluded, specifically VT (Class IIa)
- Neurally mediated syncope with significant bradycardia reproduced by a head-up tilt (Class IIb)

Indication for implantation of ICD in patients with syncope

- Clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiology study (Class I)
- Significant left ventricular dysfunction, nonischemic dilated cardiomyopathy, and unexplained syncope (Class IIa)
- Patients with long QT syndrome or catecholaminergic polymorphic VT with recurrent syncope on β-blocker therapy (Class IIa)
- Patients with Brugada syndrome (Class IIa)
- Advanced structural heart disease and unexplained syncope despite noninvasive and invasive evaluation (Class IIb)

Class I: Evidence and/or general agreement that treatment is beneficial.
Class IIa: Conflicting evidence and/or divergence of opinion but weight of evidence/opinion is in favor of treatment.
Class IIb: Conflicting evidence and/or divergence of opinion with treatment efficacy less well established.
[a] Indication Class in parentheses.
ACC, American College of Cardiology; AHA, American Heart Association; AV, atrioventricular; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia; VF, ventricular fibrillation.

   f. Can consider pacemaker implantation in patients with severe bradycardic response to carotid sinus massage after other potential causes of syncope are excluded.
3. Psychiatric causes—treatment of the underlying psychiatric disorder abolishes recurrent episodes in most patients.

C. Special considerations

1. Patients suspected of having arrhythmic syncope should not drive pending diagnosis and treatment.
2. Many states require a 3- to 12-month driving restriction following a syncopal episode.
3. State laws vary with respect to the patient's and physician's responsibility to report individuals with syncope to their respective Department of Motor Vehicles. Physicians should become familiar with their local requirements.

Suggested Reading

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Comprehensive overview of neurocardiogenic syncope.

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A review of how to approach the challenge of the patient with unexplained syncope.

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Guidelines for the evaluation of patients with syncope.

33 PENETRATING AND BLUNT CARDIAC AND THORACIC AORTIC TRAUMA

James P. Greelish, Jared Antevil, William P. Riordan Jr., and John G. Byrne

I. PENETRATING CARDIAC INJURY

A. General principles

1. Despite advanced prehospital care, only a minority of patients reach the hospital alive.
2. Usually these injuries are the result of violent conflicts involving knives and guns and are less frequently caused by traffic, and occupational or recreational accidents.
3. Stab wounds usually lead to single-chamber injury, whereas gunshot wounds frequently lead to multiple-chamber injury, as well as concomitant injuries to other organ systems. As such, these injuries result in a higher mortality.
4. The right ventricle and right atrium are the most common sites of penetrating injury due to their anterior location.

B. Presentation

1. Any penetrating injury to the chest, neck, or upper abdomen should prompt a thorough evaluation for intrathoracic injury, including cardiac injury.
2. Hypotension—present in almost all patients.
3. Hemopericardium and pericardial tamponade present acutely with a dramatic increase in intrapericardial pressures, impairment of cardiac venous return and subsequent reduced cardiac output. The classic Beck's triad (distant heart sounds, distended jugular veins, and decreased arterial pressure) is not common in hypovolemic patients, thereby making the diagnosis of tamponade difficult.
4. Hemorrhage due to free wall or coronary vessel laceration, or great vessel injury usually manifests with hemothorax and hypovolemia. Chest tubes will exhibit significant drainage, heralding the immediate need for exploration in the emergency room or operating room.

C. Diagnosis

1. Typically made by physical examination, and clinical scenario.
2. Chest radiograph (CXR), although a useful diagnostic tool in trauma, is of little value in diagnosing penetrating cardiac trauma.
3. *Echocardiography* is the study of choice because it can be performed in the trauma resuscitation room and offers accurate, rapid identification of pericardial tamponade or bleeding.
4. The definitive diagnosis of cardiac trauma is confirmed in the operating room on direct inspection of the heart.
5. When echocardiography is either unavailable or equivocal, subxiphoid pericardial window remains a highly sensitive diagnostic test. It should be performed in the operating room with preparations in place for immediate sternotomy if grossly bloody pericardial fluid is encountered.

D. Treatment

1. Emergency department management

a. All penetrating wounds between the right midclavicular and left midaxillary lines should be assumed to involve the heart (Fig. 33-1).

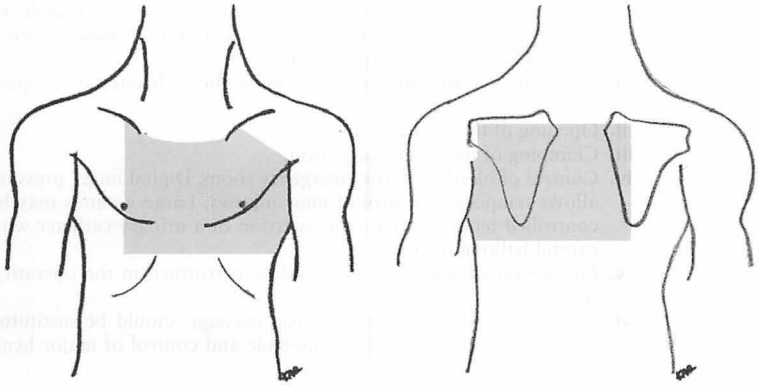

Figure 33-1. Extended anterior and posterior box. Chest injuries involve the *gray* zones.

Impaled objects should be left *in situ*, if possible, until operative exploration.

b. Treatment always begins with the "A, B, C, D, E" of the primary survey including airway, breathing, circulation, assessment of disability, and exposure.

c. Large-caliber upper extremity intravenous access is established, and volume resuscitation is initiated with crystalloid, colloid, and/or O negative blood.

d. *Hemodynamically stable patients* (either initially or after fluid resuscitation) should undergo diagnostic evaluation including a thorough physical examination, CXR, and echocardiogram as part of the secondary and tertiary surveys.

e. *Hemodynamically unstable patients* (systolic blood pressure [SBP] <80 to 90 mm Hg or in cardiopulmonary arrest) are intubated and a large-bore chest tube is inserted (for absent or decreased breath sounds) to evacuate pneumothorax or hemothorax. The amount of hemothorax dictates the need for operative exploration (Table 33-1).

f. When appropriate, **emergency department thoracotomy** is best applied to patients with penetrating cardiac injuries who arrive with a short transport time and witnessed signs of life (i.e., pupillary response,

TABLE 33-1 Indications for Urgent Surgical Exploration

1	Hemodynamic instability despite volume resuscitation
2	Excessive chest tube drainage (1.5–2.0 L or more total, or >300 mL/h for 3 or more h)
3	Significant hemothorax on chest radiograph
4	Suspected penetrating cardiac trauma
5	Gunshot wound to the abdomen
6	Penetrating torso trauma, particularly if associated with peritoneal perforation
7	Positive diagnostic peritoneal lavage (particularly with evidence of ongoing hemorrhage)
8	Significant solid-organ or bowel injury

spontaneous ventilation, presence of carotid pulse, measurable or palpable blood pressure, extremity movement, and cardiac electrical activity). These patients should undergo:

i. Emergent left anterior thoracotomy in the fifth intercostal space (ICS).
ii. Opening of the pericardium.
iii. Clamping of the descending aorta.
iv. Control of bleeding in the emergency room. Digital finger pressure allows temporary control of most injuries. Large wounds may be controlled temporarily by the insertion of a urinary catheter with careful balloon inflation.
v. Further repair and closure should be performed in the operating room.
vi. In cases of arrest, internal cardiac massage should be instituted immediately after relief of tamponade and control of major hemorrhage.

2. Operative management

a. Median sternotomy (stable patients) and left anterior thoracotomy (unstable patients) are the most common approaches. Other incisions depend on the presumptive diagnosis and should be used only when the diagnostic results dictate such action.

b. Atrial injuries are controlled with Satinsky vascular clamps and the defect is repaired with continuous prolene sutures. Ventricular injuries should be controlled initially by digital compression, and the defect repaired with interrupted nonabsorbable sutures, with or without the use of Teflon pledgets. Larger defects may require cardiopulmonary bypass, aortic cross clamping, and the use of autologous or prosthetic material for patching. With wounds in close proximity to major coronary vessels, mattress sutures may be used to avoid obstructing coronary flow (Table 33-2).

c. Missiles should be removed surgically because of the risk of embolization, endocarditis, and the erosion into adjacent vessels.

d. Coronary artery injuries are uncommon but carry a high mortality. Small branches may be ligated, but larger vessels should be either repaired or bypassed.

e. Only life-threatening injuries should be repaired at the time of surgery; all others should be approached in a future session.

II. PENETRATING THORACIC AORTIC INJURY

A. Background

Injury to the thoracic aorta occurs in 1.4% of gunshot and 0.6% of stab injuries to the chest and carries a mortality rate as high as 93%. Coexistent major injuries are common.

TABLE 33-2 Cardiac Injuries and Repair Techniques

Myocardial free wall	Primary repair buttressed with felt or pledgets
Ventricular septal defect (VSD), papillary muscles	Delayed repair preferred
Coronary arteries: Small or distal vessels	Ligate
Coronary arteries: proximal vessels, especially left anterior descending	Coronary artery bypass grafting (CABG)
VSD	Patch repair

B. Presentation

Most patients arrive at the hospital with minimal or no sign of life and emergent thoracotomy in the emergency room is the only chance for survival. Patients who arrive hemodynamically stable usually have contained ruptures or fistulous communications with adjacent veins.

C. Diagnosis

1. Hemodynamically stable patients should undergo CXR, and a chest tube should be placed for absent or diminished breath sounds or for signs of hemothorax.
2. Hemodynamically unstable patients should undergo emergent left anterior thoracotomy.
3. Helical chest computed tomography (CT)/CT angiogram is very sensitive and has negative predictive values that approach 100%. This modality is replacing aortography as the gold standard for detecting aortic injury, but like aortography is appropriate only in hemodynamically stable patients.
4. Transesophageal echocardiography should be used only if esophagogram has excluded esophageal injury and is not routinely used.

D. Treatment

1. The operative approach includes primary control of the bleeding during the emergency thoracotomy.
2. Small lacerations may be repaired through tangential clamping (side biting clamp) and direct suture. For large defects, replacement of the aorta is performed with a synthetic tube graft or homograft.

III. BLUNT CARDIAC INJURY

A. Background

1. The diagnosis of myocardial contusion is made with high clinical suspicion in patients with direct blows to the chest wall. Clinical signs and symptoms are typically either missing or nonspecific and hemodynamic instability may be due to other causes (Table 33-3).
2. For prognostic and treatment purposes it is helpful to classify patients into two categories:
   a. *Subacute injury*—those who are stable or whose hemodynamic instability is not due to their cardiac injury

TABLE 33-3 Causes of Cardiopulmonary Deterioration Associated with Blunt Trauma

1	Severe central neurologic injury with secondary cardiovascular collapse
2	Hypoxia secondary to respiratory arrest resulting from neurologic injury, airway obstruction, large open pneumothorax, or severe tracheobronchial laceration or crush
3	Direct and severe injury to vital structures, such as the heart, aorta, or pulmonary arteries
4	Underlying medical problems or other conditions that led to the injury, such as sudden ventricular fibrillation in the driver of a motor vehicle or the victim of an electric shock
5	Severely diminished cardiac output from tension pneumothorax or pericardial tamponade
6	Exsanguination leading to hypovolemia and severely diminished oxygen delivery
7	Injuries (e.g., fractured leg) in a cold environment complicated by secondary severe hypothermia

b. *Life-threatening injury*—those with major life-threatening cardiac injuries who require emergent intervention

B. Presentation

1. *Subacute blunt cardiac injury*
   a. Many patients are asymptomatic, but common presentations include chest pain, arrhythmias (premature atrial or ventricular contractions, tachycardia, and bradycardia), and pericardial tamponade.
   b. Chest pain is usually an early symptom but may also manifest several hours or even days after injury and has two forms: an angina-like pain and the usual thoracic pain associated with chest injury.
   c. Mortality in patients with subacute injury is mainly dependent on extracardiac comorbidities.
2. *Life-threatening blunt cardiac injury*
   a. Present with hemodynamic instability or cardiogenic shock
   b. Myocardial lacerations or great vessel injury present with hemopericardium and/or hemothorax
   c. Malignant arrhythmias or severe left ventricular dysfunction may also result in cardiogenic shock.
   d. Myocardial rupture from blunt injury generally occurs due to:
      i. Deceleration-type injuries and the most common sites involved include the venae cavae attachment to the right atrium and the pulmonary vein attachment to the left atrium, or the left atrial appendage or
      ii. Direct precordial blows and involve the pulmonary artery origin from the right ventricular these patients almost universally present with tamponade.
      iii. Specific presentations
         (a) *Pericardial tamponade* may develop because of hemorrhage after rupture of the myocardium or great vessels, or because of exudation of fluid through the injured pericardium or epicardium.
         (b) *Chest pain* is rather nonspecific.
         (c) *Arrhythmias* occur, which may be fatal, even in cases of blunt trauma with no histologic evidence of myocardial contusion.
         (d) Injury to the aortic, mitral, and tricuspid valves and the atrioventricular septae may occur and often appears as combined injuries.
         (e) Injury to the coronary vessels—including laceration, dissection, thrombosis, or spasm—may occur with a low incidence and presents as tamponade, hemorrhage, or ischemia.

C. Diagnosis

1. The first step in diagnosing blunt myocardial injury is an awareness that such an injury might have occurred.
2. Evaluation for possible preexisting heart disease is mandatory, so that differentiation between old and new findings can be appreciated.
3. *A 12-lead electrocardiogram (ECG)* should be obtained and this, combined with the clinical presentation, will determine whether further diagnostic evaluation or treatment is necessary. However, misinterpretation of preexisting conditions is common. *ECG findings include* sinus tachycardia, ST and T-wave abnormalities, conduction abnormalities, atrial or ventricular arrhythmias, or ischemic changes.
4. While some advocate the use of serum creatine-kinase-myocardial band (MB) isoenzyme and troponin I levels for the diagnosis or characterization of blunt myocardial injury, their relatively low sensitivity, specificity, and predictive value do not support routine use in this clinical setting.

5. A CXR is obtained to assess for signs of injury, including mediastinal widening, sternal or rib fractures, tracheal or nasogastric tube displacement, pneumothorax, hemothorax, diaphragmatic rupture, and apical capping or indistinct aortic knob. Further evaluation may be performed by CT, according to patient stability and the index of suspicion.
6. *Transthoracic echocardiography* can be performed in the emergency or operating room, while other procedures are taking place, and should be performed early in patients with hemodynamic instability or ECG changes.
7. *Coronary angiography* is indicated in patients who present acutely with the suspicion of coronary trauma and require immediate diagnosis and intervention or in patients with persistent symptoms or ECG findings over several days.

D. Treatment

1. ECG and echocardiography are used to establish diagnosis and guide further management (Fig. 33-2).
2. *Hemodynamically stable patients* who are younger than 55 years, have a normal ECG and no history of heart disease, and do not require surgical or neurologic observation do not require specific cardiac evaluation and can be discharged from the hospital.

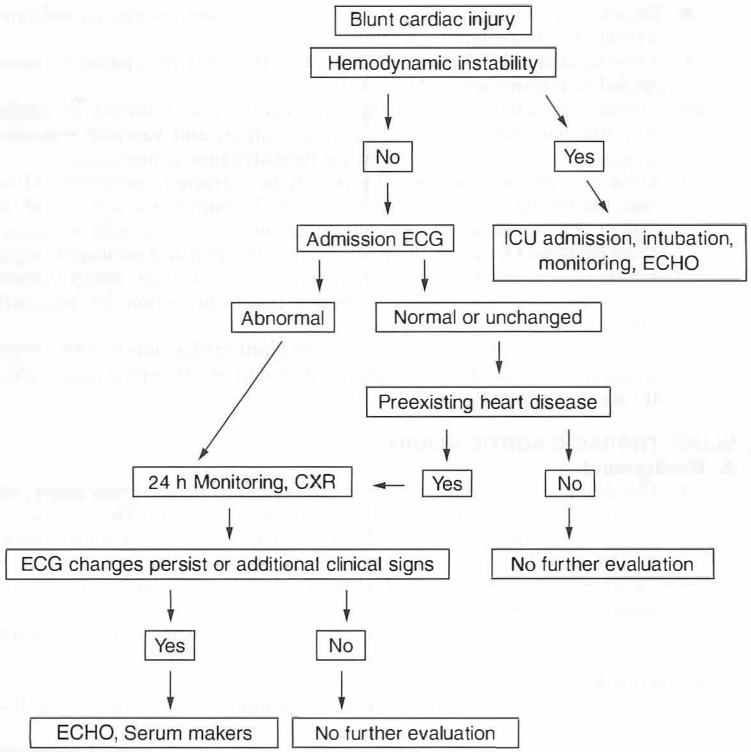

Figure 33-2. Blunt cardiac injury. ECG, electrocardiogram; ICU, Intensive care unit; ECHO, echocardiogram; CXR, chest radiograph.

3. *An abnormal ECG or history of cardiac disease dictates ECG monitoring and observation for 24 hours.* In the absence of arrhythmia, ECG changes, or complications, no further evaluation is needed.
4. *If ECG changes progress or persist, then echocardiography should be performed.*
5. *Hemodynamically unstable patients* should undergo cardiac evaluation to identify injury. They are admitted to the intensive care unit (ICU), intubated, and undergo ECG monitoring and continuous measurement of arterial and central venous pressures. Echocardiography is performed to estimate the degree of cardiac involvement and identify the specific anatomic injuries.
6. Patients with blunt cardiac injury are treated similarly to those with acute myocardial infarction. Bed rest, oxygen, drug therapy, and electrocardiographic or hemodynamic monitoring are the mainstays of treatment. Analgesics or narcotics should be administered as needed.
7. Drugs that may potentiate arrhythmias should be avoided; however, antiarrhythmic agents may be indicated in rare cases. Digitalis may be used for rate control of atrial fibrillation but should be avoided for sinus tachycardia because it increases electrical instability in contused myocardium. β-Blockers have not been sufficiently studied, but their use appears reasonable for clinically significant myocardial damage or tachyarrhythmias.
8. Diuretics or inotropic agents, or intra-aortic balloon pumps are indicated if congestive heart failure develops.
9. Anticoagulants should be avoided because they may precipitate intrapericardial or intramyocardial hemorrhage.
10. Volume resuscitation should be done carefully and should be guided by pulmonary wedge pressure, cardiac output, and vascular resistance measurements in patients with major hemoclynamic compromise.
11. Valve or septal injuries should generally be corrected operatively. However, the timing of surgery depends on the hemodynamic stability of the patient. Treatment of all non–life-threatening injuries should be delayed when possible. Occasionally small ventricular septal and most atrial septal defects (ASDs) are treated conservatively but followed up closely. Interval transcatheter device closure is often a treatment option for traumatic ASDs.
12. Emergent thoracotomy for patients with blunt cardiac injury who present *in extremis* is almost always futile and should be attempted only if there are no signs of associated brain injury.

IV. BLUNT THORACIC AORTIC INJURY

A. Background

1. The thoracic aorta is particularly susceptible to deceleration injury, the most frequent cause of which is a motor vehicle accident. The incidence in blunt chest trauma victims is 4% among patients who reach the hospital alive and 15% to 17% at autopsy.
2. Aortic injury is often associated with other organ injuries that are not limited to the chest.
3. Unlike patients with penetrating injury, most patients with blunt aortic injury are stable enough to undergo diagnostic evaluation.

B. Presentation

1. Seventy-five percent to 90% of blunt aortic injuries will result in immediate death.
2. Clinical presentation in survivors varies widely, from hemoclynamically stable with radiographic abnormalities to profound hemodynamic instability.

3. The spectrum of aortic injuries includes hemorrhage, dissection, partial or full transection, pseudoaneurysm, and thrombosis. Aortic wall disruption ranges from a small intimal tear to full transection, held together only by the adventitia or the mediastinal reflection of the pleura.
4. Intrapericardial aortic injuries may manifest as acute pericardial tamponade.

C. Diagnosis

1. Physical examination is neither sensitive nor specific. Up to 50% of patients with blunt aortic injury will have no associated external injuries.
2. A CXR is the first diagnostic step. The most common abnormality is a widened mediastinum (sensitivity approximately 75%), but the CXR may be normal in up to 40% of cases. Less common findings include indistinct aortic knob, widening of the paratracheal stripe, and pleural effusion (Table 33-4).
3. Helical chest CT with appropriate contrast timing is the modality of choice to evaluate for blunt aortic injury, and has replaced traditional aortography in the evaluation of the multiply injured patient.
4. Prompt diagnosis is of the utmost importance as 30% of patients will die from untreated blunt aortic injury in the first 24 hours.

D. Treatment

1. The first priority is to control aortic wall stress by maintaining SBPs at or below 100 mm Hg, avoiding tachycardia, providing adequate analgesia and sedation and minimizing movement of the thoracic vertebral column.
2. Vasodilators and short-acting β-blockers may be used for blood pressure control, just as would be the case for acute dissection. β-Blockers are particularly suitable because they reduce the blood pressure, the force of arterial upstroke, and the heart rate.
3. Operative correction should be performed as soon as possible. Delay may be acceptable in patients who require operative correction of other, more urgent injuries and sometimes in stable patients with small intimal tears who have major comorbidities that place them in a prohibitive operative risk category. In these cases, aortic repair utilizing endoluminal stent-grafts may represent a better option in the future.
4. Signs of free perforation, such as rapid evolving mediastinal hematoma or pleural effusion, should be indications for emergent surgery.
5. Injuries to the aorta distal to the left carotid artery should be approached through a left posterolateral thoracotomy and left heart bypass.
6. Defects located between the intrapericardial aorta and aortic arch are best approached through median sternotomy with cardiopulmonary bypass and/or circulatory arrest.

TABLE 33-4 Chest Radiographic Findings Associated with Blunt Aortic Injury

Widened mediastinum (transverse dimension >8 cm)
Left apical pleural cap
Fractures of first and second ribs or scapula
Widening of paratracheal stripe
Blurring of the aortic contour and AP window
Right tracheal deviation
Pleural effusion
Depressed left mainstem bronchus
NG tube deviation

7. Multiple tears may require a combination of these approaches.
8. The use of endovascular repair techniques is currently limited by a lack of appropriate devices available for immediate implantation and minimal data on long-term outcome. However, there is growing evidence that endovascular repair may be a safe treatment alternative in a significant percentage of trauma patients, and may be particularly useful in bridging a multiply injured patient to a more stable chronic pseudoaneurysm.

Suggested Reading

Asensio JA, Berne JD, Demetriades D, et al. One hundred five penetrating cardiac injuries: a 2-year prospective evaluation. *J Trauma* 1998;44:1073–1082.
This study validated physiologic variables and injury severity scoring systems as predictors of outcome in penetrating cardiac injury.

Bertinchant JP, Polge A, Mohty D, et al. Evaluation of incidence, clinical significance, and prognostic value of circulating cardiac troponin I and T elevation in hemodynamically stable patients with suspected myocardial contusion after blunt chest trauma. *J Trauma* 2000;48:924–931.
This study demonstrated that elevations of circulating troponin I and T had a low sensitivity in hemodynamically stable patients with suspected blunt cardiac injury and did not correlate with outcome.

Campbell NC, Thomson SR, Muckart DJ, et al. Review of 1198 cases of penetrating cardiac trauma. *Br J Surg* 1997;84:1737–1740.
Classic description of the prevalence and outcome of traumatic cardiac injuries.

Fabian TC, Richardson JD, Croce MA, et al. Prospective study of blunt aortic injury: multicenter trial of the American Association for the Surgery of Trauma. *J Trauma* 1997;42:374–380;discussion 380–383.
Large, multicenter trial of 274 cases of blunt aortic injury that compared the clamp and sew technique with bypass techniques with respect to mortality and paraplegia rates. Mortality was not affected by the type of repair. Clamp and sew as well as bypass times greater than 30 minutes were associated with a higher rate of postoperative paraplegia.

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This comparison study of transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) demonstrated that of those patients who sustained a myocardial contusion, echocardiography benefited only those who developed a cardiac complication. Additionally, TEE was useful when aortic injury was suspected and the results of TTE were suboptimal.

Minard G, Schurr MJ, Croce MA, et al. A prospective analysis of transesophageal echocardiography in the diagnosis of traumatic disruption of the aorta. *J Trauma* 1996;40:225–230.
Direct comparison of transesophageal echocardiography (TEE) with aortography in the diagnosis of traumatic aortic disruption. The sensitivity and specificity of TEE were 57% and 91%, respectively, and the sensitivity and specificity of aortography were 89% and 100%, respectively. The authors concluded that aortography remains the gold standard diagnostic method for diagnosing traumatic aortic disruption.

Nagy K, Fabian T, Rodman G, et al. Guidelines for the diagnosis and management of blunt aortic injury: An EAST Practice Management Guidelines Work Group. *J Trauma* 2000;48(6):1128–1143.
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Pasquale M, Nagy K, Clarke J. Eastern Association for the Surgery of Trauma. *Practice management guidelines for screening of blunt cardiac injury.* 1998.

Practice guidelines based on meta-analysis for screening patients for suspected blunt cardiac injury by the EAST organization. The guidelines assess the role of ECG, enzyme analysis, echocardiography, radionuclide imaging, and pulmonary arterial monitoring in the diagnosis of blunt cardiac imaging.

Pretre R, Chilcott M. Blunt trauma to the heart and great vessels. *N Engl J Med* 1997;336:626–632.

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Pretre R, LaHarpe R, Cheretakis A, et al. Blunt injury to the ascending aorta: three patterns of presentation. *Surgery* 1996;119:603–610.

Excellent description of the injury patterns observed in blunt aortic injury.

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Working Group, Ad Hoc Subcommittee on Outcomes, American College of Surgeons-Committee on Trauma. Practice management guidelines for emergency department thoracotomy. *J Am Coll Surg* 2001;193(3):303–309.

Excellent evidence-based review of the literature with analysis of published studies and recommendation.

34 MANAGEMENT OF UNSTABLE ANGINA AND NON–ST-ELEVATION MYOCARDIAL INFARCTION

Eli V. Gelfand and Christopher P. Cannon

I. GENERAL PRINCIPLES AND DEFINITIONS

A. A total of 1.6 million patients are admitted to the hospital each year in the United States with an acute coronary syndrome (ACS).

B. Eighty percent of ACS patients do not have ST-segment elevations on an initial electrocardiogram (ECG) and are said to have unstable angina (UA) or non–ST-segment elevation myocardial infarction (NSTEMI).

II. PATHOPHYSIOLOGY

A. UA/NSTEMI is caused by erosion or rupture of a vulnerable atherosclerotic plaque and formation of an overlying thrombus.

B. In contrast to ST-segment elevation myocardial infarction (STEMI), in UA/NSTEMI the intracoronary thrombus is typically only partially occlusive, although brief periods of total occlusion and subsequent reperfusion are common.

C. There is embolization of the thrombus fragments downstream, causing obstruction of coronary microcirculation and additional myocardial ischemia and necrosis.

D. The sequence of events in UA/NSTEMI is:

1. Rupture of a vulnerable atherosclerotic plaque
2. Platelet activation, aggregation, and adhesion
3. Secondary activation of plasma coagulation system
4. Coronary vasoconstriction
5. Imbalance in myocardial oxygen and demand

III. GENERAL ASPECTS OF DIAGNOSIS

A. On the basis of new or accelerating symptoms of coronary ischemia, with or without ECG changes.

B. Elevation of cardiac troponin beyond 99th percentile of normal distinguishes NSTEMI from UA.

C. ECG changes in UA/NSTEMI may include:

1. ST-segment depressions
2. Transient ST-segment elevations
3. New T-wave inversions

IV. INITIAL EVALUATION AND RISK STRATIFICATION OF SUSPECTED UA/NSTEMI

A. Focused **history** should concentrate on the nature of anginal symptoms, prior history of coronary artery disease (CAD), and traditional cardiovascular (CV) risk factors.

B. **Physical examination** is directed toward assessment of:

1. Possible precipitants of UA/NSTEMI, such as hypertension, thyroid disease, or anemia
2. Hemodynamic effects of UA/NSTEMI, such as congestive heart failure and arrhythmia
3. Important alternate diagnoses, for example, acute pericarditis, pulmonary embolism, or aortic dissection

C. A **12-lead ECG** should be interpreted within 10 minutes of the patient's arrival to the emergency department (ED).
  1. If initial ECG is not diagnostic of ACS, follow-up ECG should be performed every 15 to 30 minutes to evaluate for evolving ST elevations or depressions.
  2. Posterior leads V_7-V_9 should be utilized to enhance detection of posterior myocardial infarction (MI).

D. Cardiac biomarkers, preferably, **cardiac-specific troponin,** should be measured.
  1. For patients presenting <6 hours from symptom onset, considerations are to:
    a. Measure myoglobin (an early marker of myocardial damage) along with troponin.
    b. Repeat troponin levels in 6 to 8 hours, or as guided by timing of symptom onset.
  2. Additional biomarkers, such as total creatinine kinase-myocardial band (CK-MB) mass, B-type natriuretic peptide (BNP), or N-terminus pro-BNP (Nt-proBNP) may have additional prognostic information in UA/NSTEMI.

E. Focused evaluation for **other causes of chest discomfort** should be undertaken (Table 34-1).

F. On the basis of clinical history, ECG and initial laboratory and imaging tests, patients are assigned the probability of having ACS. Further triage and management decisions are made accordingly.
  1. In patients with **noncardiac chest pain,** a search is undertaken in the ED for the underlying cause.
  2. Patients with **stable angina** benefit from uptitration of antianginal therapy with or without observation in a dedicated chest pain unit.
  3. Patients with **possible UA/NSTEMI** who have a nondiagnostic ECG and normal initial cardiac biomarkers are observed for at least 6 to 12 hours from symptom onset.
    a. If recurrent ischemic pain is present or follow-up studies are positive, treatment for definite ACS is initiated.
    b. If there is no further pain and ECG/biomarkers remain within the range of normal, stress testing should be considered.

TABLE 34-1 Differential Diagnosis of Chest Discomfort

Conditions with immediate life-threatening potential
- Acute coronary syndrome
- Acute aortic dissection
- Pulmonary embolism
- Esophageal rupture
- Tension pneumothorax

Common other conditions
- Acute pericarditis
- Gastroesophageal reflux disease
- Costochondritis and related musculoskeletal conditions
- Acute myocarditis
- Transient apical ballooning syndrome ("takotsubo-type" cardiomyopathy)
- Esophageal spasm
- Pleurisy
- Referred pain from abdominal organs, particularly spleen and gallbladder

TABLE 34-2 Thrombolysis in Myocardial Infarction (TIMI) Risk Score for Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI)

Age ≥65 yr	1 pt
Prior coronary stenoses >50%	1 pt
≥3 Risk factors for CAD	1 pt
Use of aspirin in the preceding 24 h	1 pt
≥2 Anginal events in the preceding 24 h	1 pt
ST segment changes	1 pt
Elevated cardiac biomarkers	1 pt
Total possible score	**0–7 points**

CAD, coronary artery disease.
(Adapted from Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non–ST-elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284(7):835–842.)

   i. If stress test shows provokable ischemia or new regional left ventricular (LV) dysfunction, therapy for ACS is started.
   ii. If stress test is negative, a diagnosis of noncardiac chest pain is likely and arrangements should be made for outpatient follow-up.
4. Patients with **probable/definite UA/NSTEMI** are admitted to a coronary care or telemetry unit for continuous cardiac monitoring, risk stratification, antithrombotic and antianginal therapy, and consideration of revascularization.

G. Patients with UA/NSTEMI must be **risk stratified,** as certain therapies have been shown to benefit only high-risk patients.

H. Thrombolysis in myocardial infarction (TIMI) risk score (Table 34-2) provides a rapid way of assessing the patient's risk.
1. Has been prospectively validated in UA/NSTEMI.
2. Useful in predicting short (14- to 30-day) CV event rate (death, MI, or recurrent ischemia) and long-term (1-year) mortality.
3. Higher risk score identifies patients who progressively benefit from aggressive therapy with low molecular weight heparin (LMWH), glycoprotein (GP) IIb/IIIa inhibitors, and early invasive strategy.

V. MANAGEMENT OF UA/NSTEMI

A. General aspects of care

1. Dual goals in management of UA/NSTEMI must be taken into account at all times.
   a. Immediate **relief of myocardial ischemia**
   b. **Prevention of adverse outcomes**, specifically: (re)infarction, death, and future heart failure
2. The overall management plan is described in Figure 34-1.
3. The general plan of management of patients with UA/NSTEMI should develop as follows:
   a. Establish **basic care and monitoring**: oxygen, continuous ECG monitoring, resuscitation equipment.
   b. Administer **analgesic and anti-ischemic therapy**: β-blockers, nitrates, and morphine.
   c. **Define risk** using a standardized scoring system (see preceding text).
   d. Determine the appropriate overall treatment strategy:
      i. **Early invasive strategy**: planned cardiac catheterization within 4 to 48 hours with revascularization where feasible.

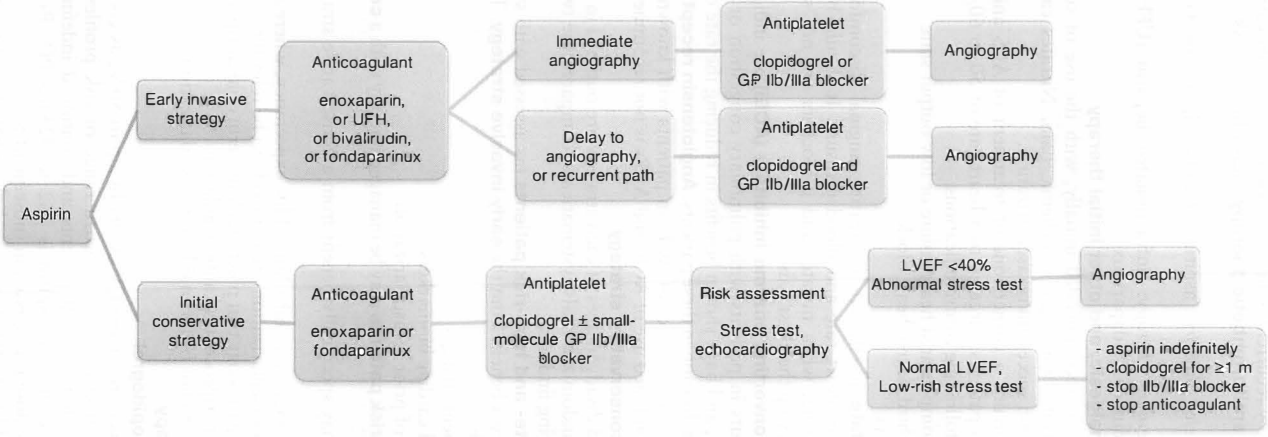

Figure 34-1. Overall contemporary treatment strategy for unstable angina and non–ST-elevation myocardial infarction (UA/NSTEMI). UFH, unfractionated heparin; GP, glycoprotein; LVEF, left ventricular ejection fraction. (Data from Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association. *J Am Coll Cardiol* 2007;50(7):e1–e157.)

ii. **Conservative strategy:** medical management with revascularization dictated by recurrent ischemia at rest or upon provocative testing.

e. Administer **antithrombotic therapy**, according to risk and planned strategy.

i. *Antiplatelet therapy:* aspirin, clopidogrel, and/or GPIIb/IIIa inhibitors

ii. *Anticoagulant therapy*: unfractionated heparin (UFH), LMWH, bivalirudin, or fondaparinux

B. Anti-ischemic, analgesic, and other initial therapy

1. **Nitrate** therapy is recommended initially, with the use of sublingual or intravenous nitrates for ongoing ischemic pain. Nitrates can be safely discontinued upon successful revascularization.
2. **β-Blockade** remains a cornerstone of treatment of ACS and should be administered to patients, targeted to a heart rate of 50 to 60 bpm, in the absence of the following contraindications:
   a. Signs of decompensated heart failure or low-output state
   b. Second- or third-degree heart block
   c. Active asthma
3. **Morphine sulfate** is effective in treating anginal discomfort and also modestly reduces heart rate and blood pressure. It should be used with careful monitoring, when nitrates and β-blockers are not successful in completely relieving the chest pain.
4. **Angiotensin converting enzyme inhibitors (ACEi)** are indicated within the first 24 hours in patients with pulmonary congestion or LV ejection fraction <40%, and have shown benefits in reducing the rate of death and recurrent hospitalization in these patients. **Angiotensin receptor blockers** (ARBs) may be used in place of ACEi in patients with known intolerance to ACEi, but combined use of ACEi and ARBs is not recommended.

C. Invasive versus conservative strategy

1. Advantages and disadvantages of each strategy are outlined in Table 34-3.
2. Several large randomized trials systematically compared the two strategies with the following findings:
   a. **Intermediate- and high-risk patients** (as assessed with standard risk scores) derive a benefit from the **early invasive strategy**. This includes patients with:
      i. ST-segment changes
      ii. Elevated cardiac biomarkers
      iii. History of prior revascularization
   b. Stable, **low-risk patients** may be managed initially with a **conservative strategy**.
3. Patients who may specifically benefit from a conservative strategy include those with:
   a. Advanced malignancy and a limited life expectancy, where accumulated benefits of revascularization are not likely to be relevant
   b. Intracranial pathology that precludes long-term dual-antiplatelet therapy or intensive periprocedural anticoagulation
   c. CAD known to not be amenable to revascularization

D. Antiplatelet therapy

1. **Aspirin and clopidogrel**
   a. **Aspirin** reduces recurrent CV events by up to 50%, as compared with placebo, is effective across a broad range of risk profiles, should be started immediately in all patients and continued indefinitely. Initial recommended dose of aspirin is 162 to 325 mg PO. Recommended maintenance dose is discussed in subsequent text.
   b. **Clopidogrel** blocks the adenosine diphosphate pathway and decreases platelet activation and aggregation. In the clopidogrel in unstable angina

TABLE 34-3 Comparison of Early Invasive And Conservative Strategies for Unstable Angina/ Non-ST-Elevation Myocardial Infarction (UA/NSTEMI)

Early invasive	Conservative
Advantages	
■ Identifies patients with severe CAD who derive survival benefit from CABG ■ Identifies patients without significant CAD ■ PCI and CABG can reduce subsequent hospitalization and complicated antianginal therapy	■ Avoids routine early use of invasive procedures ■ More widely available
Limitations	
■ Potential vascular and bleeding complications ■ Significant upfront costs ■ Not available in all facilities	■ Coronary revascularization not routinely achieved ■ Patients with "surgical" CAD or without CAD are not identified

CAD, coronary artery disease; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

to prevent recurrent events (CURE) trial, clopidogrel in combination with aspirin and on top of other standard therapies led to a 20% relative risk reduction in CV death, MI, or stroke compared with aspirin alone. Clopidogrel should be added to aspirin in the following patients with UA/NSTEMI:

- **i.** As monotherapy in those who cannot tolerate aspirin
- **ii.** In addition to aspirin, if either an initial conservative strategy or early invasive strategy is selected
- **iii.** **Dual-antiplatelet therapy** with aspirin and clopidogrel increases the risks of bleeding, especially in the setting of cardiac surgery. It is recommended that clopidogrel be stopped 5 to 7 days before elective coronary artery bypass graft (CABG). Therefore:
  - **(a)** Some centers accept a delay in clopidogrel administration until angiography demonstrates that CABG is *unlikely* to be required, provided that the angiography itself is done expeditiously.
- **iv.** A loading dose of 300 mg has been typically administered, but 600 mg is now generally recommended for patients undergoing percutaneous coronary intervention (PCI).

c. The maintenance dose of aspirin and duration of clopidogrel therapy both depend on the management of ACS as follows:

- **i. Medical management without stent:** aspirin 75 to 162 mg indefinitely; clopidogrel 75 mg/day for at least 1 month, and ideally for 1 year.
- **ii. Bare-metal stent:** aspirin 162 to 325 mg for 1 month, then 75 to 162 mg indefinitely; clopidogrel 75 mg/day for at least 1 month, and ideally for 1 year.
- **iii. Drug-eluting stent:** aspirin 162 to 325 mg for 3 to 6 months, then 75 to 162 mg indefinitely; clopidogrel 75 mg/day for at least 1 year.

2. **Glycoprotein IIb/IIIa inhibitors**
   a. Intravenous GP IIb/IIIa inhibitors prevent fibrin from binding to platelets and thereby inhibit platelet aggregation. **Abciximab** is a monoclonal antibody, **tirofiban** and **eptifibatide** are small-molecule GP IIb/IIIa inhibitors. They are used in the following situations:
      i. During PCI, where **abciximab** reduces the rate of death, MI, and recurrent revascularization.
      ii. For upstream therapy of patients managed with the **early invasive strategy**, already treated with aspirin and an anticoagulant:
         (a) *High-risk patients*: consider adding GP IIb/IIIa inhibitor in *addition* to clopidogrel.
         (b) *Low-risk patients*: GPIIb/IIIa inhibitor *or* clopidogrel may be used.
      iii. In high-risk patients treated with **initial conservative** strategy, eptifibatide or tirofiban may be added, but evidence for their use is less robust.
   b. GP IIb/IIIa inhibitors increase the risk of vascular and mucocutaneous bleeding, although excess intracranial bleeding has not been seen in trials.
   c. Patients on GP IIb/IIIa inhibitors must be monitored for thrombocytopenia, which is generally reversible upon discontinuation of the drug.

E. Anticoagulant therapy

1. It is recommended that all patients with non–ST-segment elevation acute coronary syndromes (NSTEACS) receive an anticoagulant, with one of four choices, as outlined. If PCI is required, a consistent antithrombotic strategy can be maintained.
   a. **Unfractionated heparin** (UFH):
      i. Reduces the rate of death or MI by 33% versus placebo in a meta-analysis of six trials
      ii. Typically titrated to an activated partial thromboplastin (aPTT) time of 50 to 70 seconds
      iii. Caution must be exercised to avoid excess anticoagulation by careful aPTT monitoring
   b. LMWH **enoxaparin** should be added to the medical regimen for all patients with UA/NSTEMI
      i. Most of the trials comparing enoxaparin with UFH favored enoxaparin, with lower rates of CV death or nonfatal MI.
      ii. Benefits of enoxaparin over UFH are substantial with conservative strategy, and less so, with early invasive management.
   c. A direct thrombin inhibitor, **bivalirudin**, may be used in place of a heparin in patients treated with an early invasive strategy.
      i. Associated with lower rates of bleeding versus GP IIb/IIIa inhibitor *plus* heparin.
      ii. If bivalirudin is chosen over a heparin-based strategy, patients should also be treated with concomitant clopidogrel.
   d. Factor Xa inhibitor **fondaparinux** results in a more sustained and predictable anticoagulation than heparin, is administered once daily subcutaneously, and does not require anticoagulation, but does not act against preformed thrombi, especially important during PCI, where intracoronary hardware may be prone to thrombosis.
      i. Fondaparinux-based therapy is suggested for conservatively treated patients at a high risk for bleeding.

ii. If patients go on to PCI, use of UFH or bivalirudin for procedural anticoagulation is recommended.

F. Fibrinolysis

1. Fibrinolytic therapy is not recommended as treatment for UA/NSTEMI.
   a. Fibrinolytics have been shown to result in worse outcomes in UA/NSTEMI, possibly because they activate platelets, and could also lead to hemorrhage into a nonocclusive plaque with subsequent coronary occlusion.

G. Strategies for coronary revascularization

1. Revascularization is most beneficial when performed in high-risk patients, early in the hospital course.
2. Introduction of drug-eluting stents has reduced the rates of in-stent restenosis, at the expense of a modest increase in late stent thrombosis.
3. Decision regarding the choice of revascularization technique, for example, PCI versus CABG is largely dependent on:
   a. Coronary anatomy
   b. LV systolic function
   c. Medical comorbidities, for example, diabetes, peripheral vascular disease, stroke, and coagulopathy
   d. Patient's compliance
      i. Especially important when considering placement of a drug-eluting stent, where uninterrupted, long-term, dual-antiplatelet therapy is required
4. A treatment strategy based on the coronary anatomy and medical comorbidities is given in Figure 34-2.

H. Long-term secondary prevention

1. Patients with UA/NSTEMI are at a high risk for recurrence. Validated risk scores exist to estimate an individual's risk of recurrent vascular event and mortality (Fig. 34-3).
2. Five classes of drugs receive a strong recommendation from American College of Cardiology/American Heart Association (ACC/AHA) for long-term medical therapy:
   a. Aspirin
   b. Clopidogrel
   c. β-Blockers
   d. ACEi
   e. Statins
3. For plaque stabilization, statins and ACEi are recommended in the long term.
   a. High-dose statins should be used, and a target low-density lipoprotein (LDL) should be <70 mg/dL.
   b. Secondary goal of high-density lipoprotein (HDL) >40 mg/dL is reasonable.
4. β-Blockers may help decrease "triggers" for MI during follow-up.
5. Dual-antiplatelet therapy is started at the time of the acute event, and continued as discussed earlier.
6. Other goals that should be emphasized before discharge include:
   a. Complete smoking cessation
   b. Achievement of ideal body weight
   c. Regular physical activity
   d. Glycemic control in diabetic patients
   e. Eliminating or minimizing the use of nonsteroidal anti-inflammatory drugs and cyclo-oxygenase–2 (COX-2) inhibitors
   f. Education on medication adherence, especially dual-antiplatelet therapy

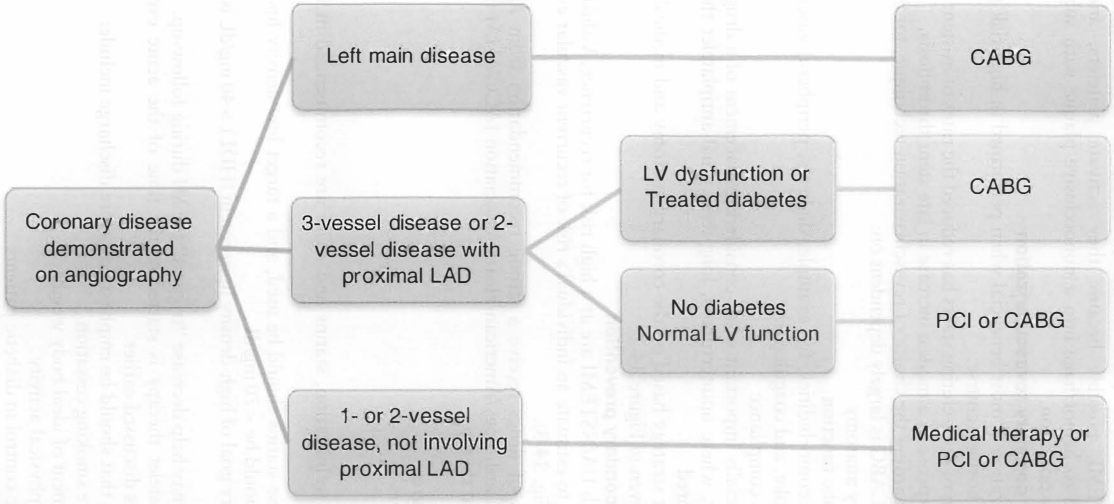

Figure 34-2. Revascularization strategy for unstable angina and non–ST-elevation myocardial infarction UA/NSTEMI. LAD, left anterior descending artery; LV, left ventricular; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention. (Adapted from Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association. *J Am Coll Cardiol* 2007;50(7):e1–e157.)

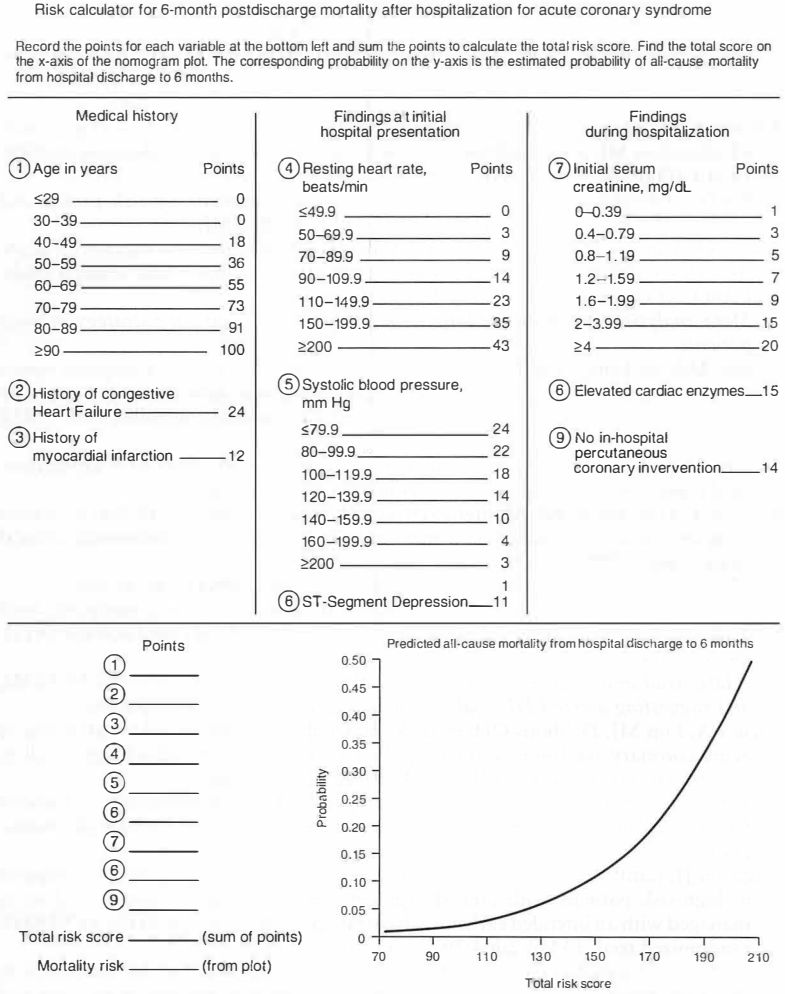

Figure 34-3. Global Registry of Acute Coronary Events (GRACE) prediction scorecard for all-cause mortality from discharge to 6 months. (Reproduced from Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004;291(22):2727–2733.)

Suggested Reading

ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. *Circulation* 1998;97(22):2202–2212.

Analysis showing a reduction in mortality with ACE inhibitors in patients with acute MI, or those who recently had an MI and have a depressed LVEF.

Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association. *J Am Coll Cardiol* 2007;50(7):e1–e157.
The most recent definitive guidelines for management of UA/NSTEMI.

Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284(7):835–842.
Study establishing the TIMI score, which stratifies patients by risk profile and likelihood of benefit from certain therapies of UA/NSTEMI.

Bavry AA, Kumbhani DJ, Rassi AN, et al. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol* 2006;48(7):1319–1325.
Meta-analysis supporting the long-term benefit of early invasive strategy in most patients.

Blazing MA, de Lemos JA, White HD, et al. Safety and efficacy of enoxaparin versus unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes who receive tirofiban and aspirin: a randomized controlled trial. *JAMA* 2004;292(1):55–64.
One of the trials showing an advantage of low molecular weight over unfractionated heparin—in this case, in patients managed conservatively.

Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 2002;359(9302):189–198.
Meta-analysis of all intravenous GP IIb/IIIa trials in UA/NSTEMI to date.

Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350(15):1495–1504.
A large trial showing benefits of intensive LDL lowering shortly after UA/NSTEMI, and suggesting a new LDL goal of <70 mg/dl for all post-ACS patients.

Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004;291(22):2727–2733.
Large registry study which developed a model for risk stratification of patients based on admission and in-hospital characteristics. See Figure 34-3 for the nomogram.

Ferguson JJ, Califf RM, Antman EM, et al. Enoxaparin versus unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. *JAMA* 2004;292(1):45–54.
A randomized trial of enoxaparin versus unfractionated heparin. An analysis from this trial showed that bleeding rates were increased if patients were switched between the two anticoagulation strategies.

Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110(2):227–239.
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Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med* 2001;344(15):1117–1124.
The ARTS trial found similar rates of survival free of MI or stroke in patients with multivessel disease randomized to either multivessel PCI or CABG.

Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update

endorsed by the National Heart, Lung, and Blood Institute. *J Am Coll Cardiol* 2006;47(10):2130–2139.
A recent summary of recommendations for long-term post-ACS management.

Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;355(21):2203–2216.
A study establishing bivalirudin as an anticoagulation option for patients with UA/NSTEMI treated with the early invasive therapy.

Yusuf S, Mehta SR, Chrolavicius S, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006;354(14):1464–1476.
The OASIS-5 trial showed that fondaparinux was noninferior to enoxaparin in UA/NSTEMI, with lower rates of bleeding.

Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345(7):494–502.
The CURE trial showed a substantial reduction in ischemic events with clopidogrel versus placebo in unstable angina patients at the expense of an increase in bleeding.

35 ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Frances O. Wood and James A. de Lemos

I. GENERAL PRINCIPLES

A. Rapid reperfusion of the infarct-related artery (IRA), with either primary percutaneous coronary intervention (PCI) or fibrinolytic therapy is the cornerstone of management for patients with ST-segment elevation myocardial infarction (STEMI).

B. Adjunctive therapy with aspirin (ASA), clopidogrel, β-blockers (BB), angiotensin-converting enzyme inhibitors (ACEi), and statins further prevents death and major cardiovascular events after reperfusion.

II. PATHOPHYSIOLOGY

A. Rupture of lipid-rich, inflammatory atherosclerotic plaque causes collagen exposure, platelet adhesion, and activation.

B. Fibrinogen binds to platelet glycoprotein IIb/IIIa (GP IIb/IIIa) receptors on adjacent platelets causing platelet aggregation.

C. A fibrin-platelet clot develops as thrombin converts fibrinogen to fibrin.

D. Platelet-fibrin clot completely occludes the IRA causing transmural myocardial injury, manifested by ST-segment elevation on the electrocardiogram (ECG).

III. DIAGNOSIS

A. Differential diagnosis: rapidly consider/rule out pneumothorax, aortic dissection, pericarditis, tamponade, pulmonary embolism, cholecystitis, apical ballooning (Takotsubo's) syndrome.

B. History

1. Angina is classically described as severe, pressure-type pain in midsternum, often with radiation to left neck, arm, or jaw. (Note onset of symptoms.)
2. Associated symptoms: dyspnea, nausea, vomiting, diaphoresis, weakness.
3. Silent infarction in 25% of cases, especially in elderly and diabetic patients.

C. Physical examination

1. Not helpful in confirming the diagnosis of STEMI.
2. Examination should focus on eliminating other potential diagnoses and assessing for complications of STEMI (Table 35-4).

D. ECG

1. ST elevations are found in regional distributions with concurrent ST depression in reciprocal leads.
2. Consider pericarditis with global ST elevations and PR depressions, early repolarization, old left ventricular (LV) aneurysm, and Prinzmetal angina.
3. *New* left bundle branch block (LBBB) represents large anterior infarction; indication for reperfusion therapy.

E. Cardiac biomarkers

1. Biomarkers of limited use for diagnosis of STEMI.
2. Myoglobin is earliest detector of myocardial damage.
3. B-type natriuretic peptide (BNP) useful in prognostic assessment.

IV. REPERFUSION THERAPY

A. Goal of reperfusion therapy is rapid and complete restoration of epicardial coronary artery and microvascular blood flow using pharmacologic, mechanical, and combined reperfusion modalities.

1. Reperfusion method depends on availability of PCI within 90 minutes of medical contact (Fig. 35-1).
2. Resolution of ST-segment elevation is the best indicator of successful reperfusion.
3. If thrombosis in myocardial infarction (TIMI)-3 flow achieved within 1 hour, mortality decreases by 50%.
4. After 12 hours, no mortality benefit with fibrinolytic therapy but modest benefit with PCI.

B. Guidelines for reperfusion therapy in non-PCI centers

1. If symptom onset is >3 hours and there is no delay to an invasive strategy, there is no preference for either strategy.
2. Transfer for primary PCI if patient has access to high-volume PCI center within 90 minutes of medical contact.
3. Transfer to PCI facility if patient has contraindication to fibrinolytic therapy (Table 35-1).
4. If (2) and (3) are not met, then administer fibrinolytics within 12 hours of onset of symptoms (Table 35-2).

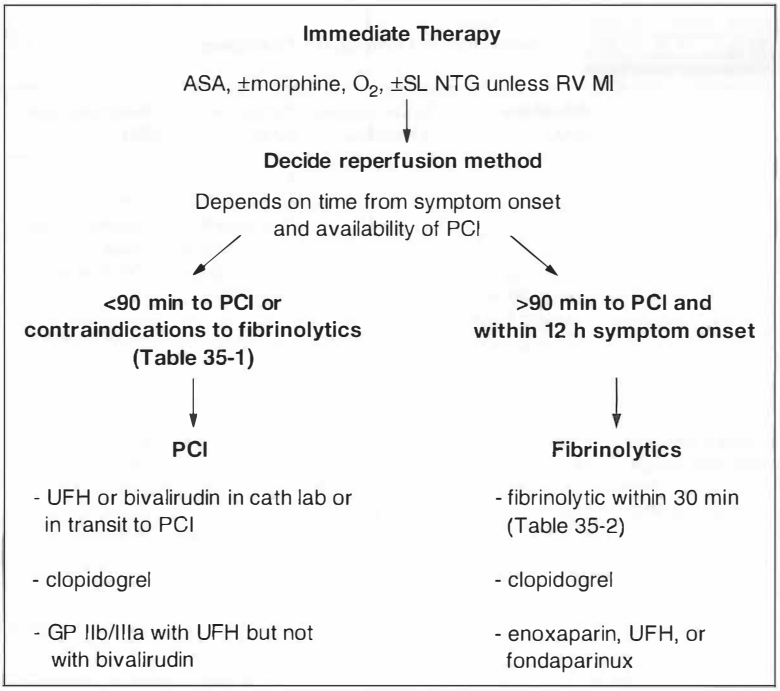


Figure 35-1. Immediate therapy overview. ASA, aspirin; O_2, oxygen; SL NTG, sublingual nitroglycerine; RV MI, right ventricular myocardial infarction; PCI, percutaneous coronary intervention; UFH, unfractionated heparin; GP, glycoprotein.

TABLE 35-1 Contraindications to Fibrinolytic Therapy

Absolute contraindications	Relative contraindications
Active internal bleeding	Blood pressure consistently >180/110 mm Hg
Any history of CNS hemorrhage	History of ischemic stroke, dementia, AVM >3 mo
Ischemic stroke within 3 mo	Recent (2–4 wk) internal bleeding
Significant head trauma within 3 mo	Prolonged CPR (>10 min)
Known cerebrovascular lesion (e.g., AVM)	For SK/anistreplase: prior exposure (5 d to 2 yr) or prior allergic reaction
CNS neoplasm	Pregnancy
Suspected aortic dissection	Major surgery or trauma within 3 wk
	Active peptic ulcer
	Anticoagulation use
	Puncture of a noncompressible vessel

CNS, central nervous system; AVM, arteriovenous malformation; CPR, cardiopulmonary resuscitation; SK, streptokinase.

TABLE 35-2 Comparison of Fibrinolytic Therapies

	Alteplase (tPA)	Tenecteplase (TNK-tPA)	Reteplase (rPA)	Streptokinase (SK)
Fibrin-selective	+++	++++	++	–
Half-life	5 min	17 min	14 min	20 min
Dose	15-mg bolus; then 0.75 mg/kg over 30 min; then 0.5 mg/kg over 60 min (maximum 100-mg total dose)	0.53 mg/kg as a single bolus	Two 10-unit bolus doses given 30 min apart	1.5 million units over 30–60 min
Weight adjusted	Partial	Yes	No	No
Possible allergy	No	No	No	Yes
TIMI 3 flow (90 min)	55%–60%	55%–65%	60%	32%
Efficacy vs. tPA	NA	Equivalent	Similar	1% ↑ Mortality
Safety vs. tPA	NA	Similar ICH ↓ Non-ICH bleeding	Similar	↓ ICH ↓ Overall bleeding
Cost	+++	+++	+++	+

↑, increase; ↓, decrease.
ICH, intracranial hemorrhage; tPA, tissue plasminogen activator (alteplase); TIMI, thrombosis in myocardial infarction; NA, not available; TIMI flow, angiographic measure of epicardial flow.
The pluses and minuses represent the relative degree of fibrin selectivity or relative expense of the medication.

5. Less clear guidelines include patients older than age 75, symptoms between 12 and 24 hours, hypertensive and high-risk patients.
6. No indication for fibrinolytic therapy if symptoms >24 hours or non-STEMI.
7. Primary PCI preferred if symptom onset >3 hours or patient is in cardiogenic shock.

C. Limitations to fibrinolytic therapy
1. Intracranial hemorrhage in approximately 1%; higher in elderly, women, low body weight, hypertension.
2. TIMI-3 flow remains 50% to 60%. PCI achieves TIMI-3 in 80% to 90% of cases.

D. Combination therapy with GP IIb/IIIa inhibitors and reduced-dose fibrinolytics not recommended. No mortality benefit; increases bleeding risk.

E. Rescue PCI after failed fibrinolytic therapy
1. Noninvasive criteria to define successful fibrinolytic therapy include ST-segment resolution >50% to 70%, chest pain resolution, and early peaking of cardiac biomarkers; accuracy of these tools is modest.
2. Persistent ST-segment elevations (even without symptoms) in elderly, diabetic patients, previous coronary artery disease, or anterior infarction identify high-risk patients who should be considered for rescue PCI.

F. Primary PCI
1. Percutaneous transmural coronary angioplasty (PTCA)
   a. Demonstrates mortality benefit when compared with fibrinolytics.
   b. Increases TIMI-3 flow, decreases stroke risk, and decreases reocclusion and recurrent myocardial infarction (MI).
   c. Requires skilled technicians in high-volume PCI centers.
2. Intracoronary stenting
   a. No survival benefit but decreases reocclusion and restenosis when compared to PTCA.
   b. Choice of bare metal stent (BMS) versus drug-eluting stent (DES) depends on ability to take clopidogrel consistently for 12 months. Consider medical compliance, bleeding risk, and future surgeries. If in doubt, choose BMS.
   c. Adjunctive GP IIb/IIIa inhibitors improve outcomes with primary PCI.

G. Facilitated PCI
1. Pharmacologic reperfusion therapy before PCI is designed to open the IRA early, followed immediately by definitive therapy with coronary stenting.
2. Trials to date are negative for the routine use of GP IIb/IIIa inhibitors alone, fibrinolytics alone, and several combinations of fibrinolytics and GP IIb/IIIa inhibitors.

V. ADJUNCTIVE ANTITHROMBOTIC THERAPY

A. ASA and clopidogrel (antiplatelet activity)
1. ASA reduces mortality, reocclusion, and reinfarction.
2. Administer ASA 325 mg chewed at presentation; continue daily at 81 mg if no stent; 325 mg for 3 to 6 months followed by 81 mg indefinitely if DES; 325 mg for 1 month followed by 81 mg if BMS.
3. Clopidogrel is indicated in all STEMI patients for 1 year regardless of reperfusion method.

B. Unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux
1. Adjunctive therapy for all intravenous fibrinolytics.
2. UFH administered intravenously 60 units/kg bolus, then 12 units/kg/hour.

3. Enoxparin 30 mg SQ bolus + 1 mg/kg SQ every 12 hours subQ decreases nonfatal ischemic events when combined with fibrinolysis. For patients 75 years or older omit bolus, reduce dose to 0.75 mg/kg every 12 hours.
4. Fondaparinux 2.5 mg subcutaneous every 24 hours. Additional anticoagulant with anti-IIa activity (UFH or bivalirudin) required if undergoing PCI to reduce catheter thrombosis.

C. Warfarin indicated for LV aneurysm, atrial fibrillation.

VI. ANTIISCHEMIC THERAPY

A. β-Blockers (BB)
1. Limit size of infarction, decrease recurrent MI, improve survival, and prevent arrhythmias and cardiac rupture.
2. Administer BB **orally** on days 0 to 1 only if no signs of heart failure, low output state (systolic blood pressure [sBP] <120 mm HG, heart rate [HR] >110 or <60), PR interval >0.24 seconds, second- or third-degree heart block, or active asthma.
3. IV BB increase cardiogenic shock on days 0 to 1 and are rarely indicated except for control of hypertension and arrhythmias.
4. Once patient is hemodynamically stable, continue oral BB indefinitely.

B. Angiotensin-converting enzyme inhibitors (ACEi)
1. Prevent congestive heart failure (CHF) and death by halting adverse remodeling of LV chamber.
2. Decrease recurrent ischemic events through direct vascular effects.
3. Not necessary in first hours of STEMI, particularly if blood pressure is low.

C. Nitrates
1. Decrease myocardial demand by decreasing preload and afterload.
2. Increase oxygen supply by dilating coronary resistance vessels.
3. No mortality benefit demonstrated.
4. Sublingual or intravenous nitrates beneficial for angina, CHF, hypertension.
5. Contraindicated in right ventricular infarction.

TABLE 35-3 Electrical Complications of Acute MI

Complication	Prognosis	Treatment
Ventricular tachycardia/fibrillation		
Within first 24 to 48 h	Good	Immediate cardioversion; lidocaine; β-blockers
After 48 h	Poor	Immediate cardioversion; electrophysiology study/implantable defibrillator; amiodarone
Sinus bradycardia	Excellent	Atropine for hypotension or symptoms
Second-degree heart block		
Mobitz type I (Wenkebach)	Excellent	Atropine for hypotension or symptoms
Mobitz type II	Guarded	Temporary pacemaker
Complete heart block		
Inferior MI	Good	Temporary pacemaker
Anterior MI	Poor	Temporary pacemaker followed by permanent pacemaker
Atrial fibrillation	Good	β-Blocker and/or amiodarone

MI, myocardial infarction.

TABLE 35-4 Mechanical Complications of Acute Myocardial Infarction

		Pathophysiology	Physical examination	Intervention
VSD	Acute—subacute	Myocardial necrosis of ventricular septum causing left to right flow during systole	Early, soft, high-frequency systolic murmur at mid to LLSB; elevated JVP; RV heave ± thrill; pulmonary congestion	Emergent echo; right heart catheterization: O_2 step-up in RV; IABP; surgery
Acute MR	Early	Myocardial necrosis of papillary muscles that tether mitral valves	CHF symptoms; early systolic, decrescendo, or holosystolic murmur; thrill radiating to apex ± S3.	Emergent echo; right heart catheterization: large v waves. IABP; surgery
LV aneurysm	Late (weeks to months)	Regional dilatation and dyskinesis of LV. Risk of thrombus formation, arrhythmias, CHF	ECG shows persistent ST-segment elevation.	Echo; oral anticoagulation
RV MI	Acute	Hypokinesis or akinesis of right ventricle; may involve SA node and/or AV node	Hypotension, bradycardia (Bezold-Jarish reflex); elevated JVP; congested liver; ST elevations in V1, (± V2, V3), V3 R, V4 R	IV fluids; temporary pacemaker; emergent catheterization
LV rupture	Acute—subacute	Myocardial necrosis of LV causing free wall rupture and flow into pericardial chamber	Usually presents as sudden death; hypotension, muffled heart sounds, elevated JVP	Emergent echo; pericardiocentesis[a] emergent surgery

[a] Pericardiocentesis should be avoided if patient has stable blood pressure, because this may precipitate hemodynamic collapse.

VSD, ventricular septal defect; MR, mitral regurgitation; LV, left ventricle; TTE, transthoracic echocardiogram; TEE, transesophageal echocardiogram; IVF, intravenous fluids. IABP, intra-aortic balloon pump; RV, right ventricle; TR, tricuspid regurgitation; MI, myocardial infarction; SA, sinoatrial; AV, atrioventricular; CHF, congestive heart failure; LLSB, left lower sternal border; JVP, jugular venous pressure; ECG, electrocardiograph.

D. Calcium channel blockers (CCB)
1. No mortality benefit.
2. Nifedipine and other dihydropyridines may cause reflex tachycardia and should not be administered without concurrent BB.
3. Diltiazem and verapamil may be effective in patients with BB contraindications, but they should be avoided in patients with CHF.

E. Aldosterone antagonists
1. Mortality benefit in STEMI complicated by heart failure or LV dysfunction.
2. Avoid with renal insufficiency and hyperkalemia.

VII. COMPLICATIONS. See Tables 35-3 and 35-4.

Suggested Reading

ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. *Circulation* 1998;97:2202–2212.
Early administration of ACE inhibitors reduces 30-day mortality by 7%, and most of the benefit is gained in the first week of use. Hypotension and renal dysfunction are significant complications.

Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *Br Med J* 2002;324:71–86.
Aspirin, in doses of 75 to 150 mg, is effective in lowering the absolute risks of fatal and nonfatal myocardial infarction or stroke.

Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol* 2004;44:671–719.

Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction. *J Am Coll Cardiol* 2007;51:210–247.

Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 2006;354:1477–1488.
In the ExTRACT-TIMI 25 trial, 20506 STEMI patients with planned fibrinolytic therapy were randomized to enoxaparin or UFH. Patients receiving enoxaparin had lower rates of death and recurrent MI but slightly higher bleeding risk.

Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA* 2000;283:2941–2947.
Prospective, observational study of 27,000 patients demonstrates that a door-to-balloon time greater than 120 minutes increases inpatient mortality by 40% to 60%. Furthermore, primary angioplasty at high-volume primary PCI centers has less inpatient mortality than low-volume centers.

Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial. *Lancet* 2005;366:1607–1621.
Patients with suspected MI who did or did not receive fibrinolytics benefited from clopidogrel 75 mg daily; A reduction in composite primary endpoint of death, stroke or reinfarction was seen.

Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial. *Lancet* 2005;366:1622–1632.

In this large randomized controlled trial, COMMIT-CCS 2, early beta blocker use reduced reinfarction and ventricular fibrillation but increased the risk of cardiogenic shock.

de Lemos JA, Braunwald E. ST segment resolution as a tool for assessing the efficacy of reperfusion therapy. *J Am Coll Cardiol* 2001;38:1283–1294.
ST-segment resolution during acute myocardial infarction is a simple, inexpensive, and universally available tool to predict patent IRA, enhanced microvascular flow, morbidity, and mortality. This tool should be utilized in clinical trials comparing different reperfusion regimens and as indication for rescue PCI.

Ellis S, da Silva ER, Heyndrickx G, et al. Randomized comparison of rescue angioplasty with conservative management of patients with early failure of thrombolysis for acute anterior myocardial infarction. *Circulation* 1994;90:2280–2284.
A small, randomized trial demonstrating that rescue angioplasty after failed fibrinolytic therapy is beneficial in patients with anterior infarction.

Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;343:311–322.
Meta-analysis of nine large-scale trials comparing fibrinolytic therapy with control in AMI or unstable angina patients. With 58,000 patients evaluated, mortality at 30 days was reduced by 1.9% with fibrinolytic therapy. Mortality reduction greater in younger patients, ST elevations, new bundle branch block, lower blood pressure, and earlier intervention. Increased mortality observed in ST depressions.

Grines CL, Cox DA, Stone GW, et al. Stent Primary Angioplasty in Myocardial Infarction Study Group. Coronary angioplasty with or without stent implantation for acute myocardial infarction. *N Engl J Med* 1999;341:1949–1956.
In acute MI patients, stent placement demonstrated less need for target-vessel revascularization compared to PTCA. No mortality benefit demonstrated.

The GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. *Lancet* 2001;357:1905–1914.
No 30-day mortality benefit is achieved when comparing standard-dose reteplase with half-dose reteplase and full-dose abciximab in acute myocardial infarction patients. Combined therapy significantly greater nonintracranial bleeding complications.

Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;361:13–20.
A thorough review concluding that primary PCI is superior to thrombolytic therapy at high-volume catheterization centers with door-to-balloon time of 90 minutes or less.

Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 2001;344:1895–1903.
With a combined end point of death, reinfarction, or urgent revascularization of the IRA, abciximab with stent placement is superior to stent placement alone at 30 days and 6 months.

Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation. *Circulation* 2000;102:2031–2037.
A simple arithmetic sum of ten baseline variables provides a clinical risk score (30-day mortality from presentation) that is useful in triage and management of fibrinolytic-eligible STEMI patients.

Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;352:1179–1189.

STEMI patients less than 75years old receiving fibrinolytic therapy may receive a loading dose of 300 mg clopidogrel followed by 75 mg daily. CLARITY-TIMI 28 showed a reduction in the primary endpoint of an occluded infarct artery on angiograiophy, death or recurrent MI; the reduction was primary driven by the reduction of occluded infarct artery.

Yusuf S, Mehta SR, Chrolavicius S, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006;295:1519–1530.

STEMI patients were randomized to either fondaparinux or control and stratified based on the need for UFH. Fondaparinux was superior to placebo with regard to MI or death at 30 day, but was not superior to UFH.

COMPLICATED MYOCARDIAL INFARCTION

Abelardo A. Martinez-Rumayor and James L. Januzzi Jr.

36

I. BACKGROUND

A. Most complications and the highest mortality occur in the first few months after the acute event (Fig. 36-1); therefore, prompt identification and treatment of any established or potential complications are necessary.

II. PATHOPHYSIOLOGY. It has been well established that the proximate cause of acute myocardial infarction (MI) in most patients is acute coronary occlusion resulting from plaque rupture and platelet initiated thrombosis. The sequelae of coronary occlusion are depicted in Figure 36-2.

III. PROGNOSIS AFTER MYOCARDIAL INFARCTION

A. Incidence of complications has decreased in the reperfusion era, recent registries show in-hospital mortality following MI is 6% with reperfusion therapy (thrombolytics or percutaneous revascularization) and approximately 20% without it (Table 36-1).

B. The Thrombolysis in Myocardial Infarction (TIMI) study group recognized predictors of mortality: age, time to treatment, anterior MI, MI with new left bundle branch block, and development of heart failure (HF).

IV. RECURRENT ISCHEMIA OR INFARCTION

A. Incidence and clinical consequences. Recurrent ischemic events after acute MI are a major cause of subsequent mortality. Recurrent infarction may occur in patients whose initial MI was treated with thrombolytic agents and in those whose MI evolved without such therapy. Reinfarction occurs in 4% to 10% of patients after thrombolytic therapy.

B. The consequences of reinfarction with regard to short- and long-term mortality are great. In the Multicenter Investigation of Limitation of Infarct Size (MILIS) study, patients who had infarct extension had an in-hospital mortality more than fourfold higher than patients without extension (30% vs. 7%, $p < 0.01$). In the TIMI trials, patients who had reinfarction had an approximately 2.5 times higher mortality at 1- to 3-year follow-up, compared with those who did not have reinfarction.

C. Prevention

1. Antithrombotic therapy

a. The first component of antithrombotic therapy is aspirin, which has been shown to be of benefit across a wide spectrum of patients with ischemic heart disease. The thienopyridine, clopidogrel, provides further benefit when added to aspirin in patients with acute coronary syndrome (ACS), and in any patient after stent deployment. Glycoprotein (GP) IIB/IIIA receptor antagonists are useful for high-risk patients undergoing percutaneous coronary intervention (PCI). Usual clopidogrel dosing is a 300 to 600 mg loading dose, then a transition to a daily dose of 75 mg.

b. The second component of antithrombotic therapy for prevention of recurrent infarction is unfractionated heparin (UFH). After

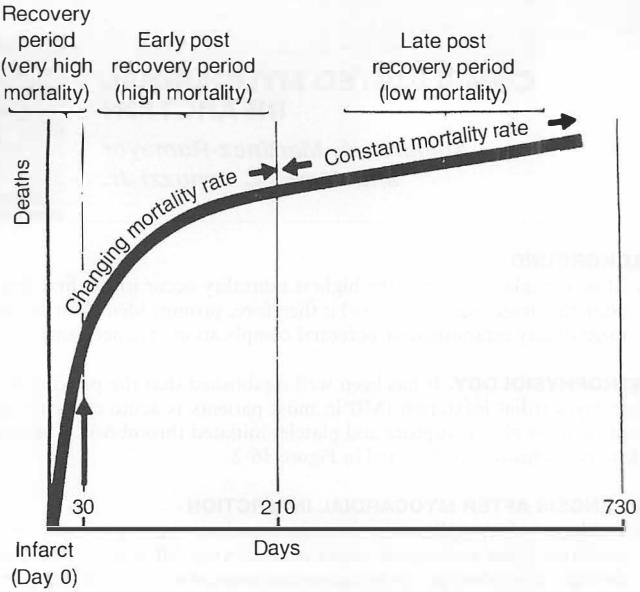


Figure 36-1. Cumulative mortality after an acute myocardial infarction (From Sherry S. The anturane reinfarction trial. *Circulation* 1980;62(Suppl 5):73, with permission. Copyright 1980, American Heart Association.)

thrombolytic therapy with tissue-type plasminogen activator (tPA), intravenous UFH is necessary to maintain infarct-related artery patency. Low molecular weight heparin (LMWH) given subcutaneously has recently been shown to reduce mortality in acute MI and can be an acceptable alternative to UFH if age, weight, and renal function allow.

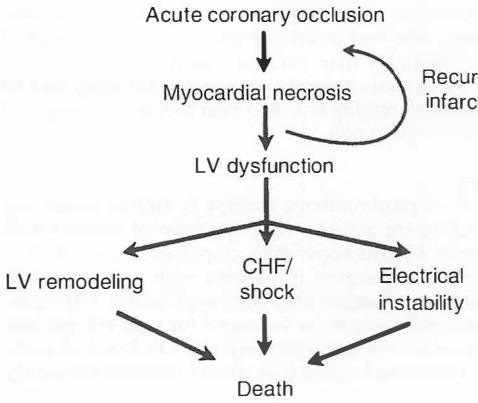


Figure 36-2. Sequelae of coronary artery occlusion. LV, left ventricle; CHF, congestive heart failure.

TABLE 36-1 Complications Following Acute Myocardial Infarction (MI)

Recurrent infarction or ischemia	Infarct expansion: Thinning and dilation of infarct segment without pain or CK leak Infarct extension: Recurrent pain, ECG changes and CK-MB leak
Left ventricular dysfunction	Acute: Diastolic dysfunction may lead to pulmonary edema and LV thrombus on hypokinetic wall Systolic dysfunction may lead to cardiogenic shock Chronic: LV dilation and remodeling LV aneurysm and pseudoaneurysm LV thrombus
Inferior MI complications	RV infarct physiology: Preload-dependent hypotension, increased JVP and clear lungs; Kussmaul's sign often present Heart block: High-degree AV block originating abruptly
Mechanical complications	Free wall rupture VSD Papillary muscle rupture causing acute MR
Electrical disturbances and conduction disorders	Ventricular tachycardia and ventricular fibrillation Atrial fibrillation (10%–17% incidence) Conduction disorders and bradyarrhythmias
Miscellaneous	Complications of angiography and PCI such as aortic or LAD dissection and cholesterol emboli syndrome. Thromboembolism Pericarditis

LV, left ventricle; CK, creatinine kinase; MB, MB fraction of creatinine kinase; ECG, electrocardiogram; RV, right ventricle; JVP, jugular venous pressure; AV block, atrioventricular block; VSD, ventricular septal defect; MR, mitral regurgitation; PCI, percutaenous coronary intervention; LAD, left anterior descending coronary artery.

c. A third antithrombotic class of agents are the GP IIb/IIIa inhibitors, which are useful when used in conjunction with PCI (60% decrease in death/recurrent MI and urgent revascularization rate); in contrast, GP IIb/IIIa agents do not provide benefit when used with thrombolysis, and in certain groups worsen bleeding risk.

2. β-Blockade has been studied extensively and has been found to be beneficial, especially among patients at highest risk, such as those with HF or ventricular arrhythmias after MI.

D. Treatment: An approach to the acute evaluation and treatment of recurrent ischemic events is outlined in Figure 36-3.

V. RIGHT VENTRICULAR INFARCTION

A. Background. Right ventricular (RV) infarction occurs clinically in approximately 30% of patients with inferior MI (themselves accounting for more than half of all MIs) but only in half of those cases is it clinically relevant. It requires special diagnostic evaluation and therapy.

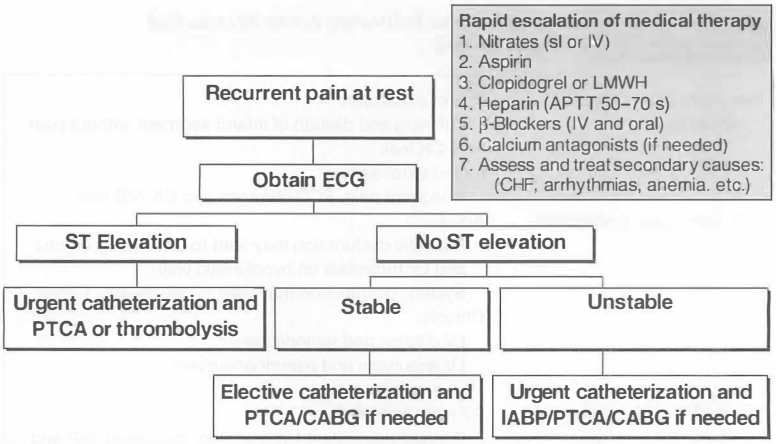


Figure 36-3. An approach to the acute evaluation and treatment of recurrent ischemic events. SI, sublingual; IV, intravenous; LMWH, low molecular weight heparin; APTT, automated partial thromboplastin time; CHF, congestive heart failure; ECG, electrocardiogram; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; IABP, intra-aortic balloon pump.

B. Pathophysiology
1. RV infarction is caused by very proximal occlusion of the right coronary artery.
2. A loss of contractile performance of the RV—a thin-walled chamber—results in reduced left ventricular (LV) preload and systemic hypotension. The associated diastolic abnormalities cause and systemic venous hypertension.
3. Atrioventricular (AV) or sinoatrial (SA) nodal block occurs in 10% to 15% of patients with inferior MI but is particularly prevalent in those with RV infarction; approximately 25% of patients with inferior MI with RV involvement develop conduction disease.

C. Clinical presentation
1. Jugular venous distension (JVD) and clear lungs distinguish RV infarction from combined right-and left-sided congestion resulting from LV dysfunction.
2. Systemic hypotension is a frequent complication of RV infarction, in which poor RV output leads to decreased LV filling.
3. Precordial ST-segment depressions can be seen on the electrocardiogram (ECG) of patients with RV infaction in 15% to 30% of cases and must be differentiated from anterior ischemia.
4. The differential diagnosis for RV infarction includes hypotension resulting from LV infarction, pericardial tamponade, constrictive pericarditis, and pulmonary embolism (PE).

D. Treatment
1. Initial treatment of RV infarction involves early reperfusion therapy directed at limiting infarct size.
2. Volume expansion is the mainstay of therapy in patients with hypotension, with the aim of a right atrial or central venous pressure as high as necessary to fill the LV adequately. A central venous pressure value up to 15 to 20 mm Hg is acceptable.

3. If volume expansion alone does not restore systemic blood pressure to >90 mm Hg, dobutamine or dopamine should be used to increase RV output.
4. In contrast to left-sided HF, for right-sided HF, venous vasodilators such as nitrates (and to a lesser extent morphine) should be avoided.
5. If hemodynamically significant sinus bradycardia or AV block develops, temporary ventricular pacing may be necessary.

VI. LEFT VENTRICULAR DYSFUNCTION (PUMP FAILURE)

A. Background
1. The most important determinant of prognosis after MI is the degree of LV dysfunction.
2. The following factors influence residual ventricular function:
   a. LV function before the acute MI
   b. Infarct size
   c. Infarct location

B. Pathophysiology
1. The clinical consequence of LV dysfunction is HF.
2. There may be systolic dysfunction, manifested by reduced systemic perfusion and evidence of pulmonary congestion, or diastolic dysfunction, manifested by increases in LV filling pressures and pulmonary congestion, but less evidence of reduced systemic perfusion.
3. Diastolic dysfunction occurs almost uniformly in patients with acute MI, although it becomes clinically significant in only one fourth to one third of such patients. It is the most common cause of early mild HF in the setting of acute MI and can be responsible for acute pulmonary edema.

C. Treatment
1. The treatment goals in patients with diastolic dysfunction include treatment of the pulmonary congestion, which involves diuresis, and treatment of the ischemia.
2. Intravenous nitroglycerin has been used widely because it can be rapidly titrated in response to blood pressure.
3. β-Blockers may be invaluable in patients whose pulmonary congestion is due to isolated diastolic dysfunction but this may be hard to assess clinically; therefore, β-blockers should be used with caution in those with HF of uncertain origin.
4. Inotropic agents and mechanical support may also be required in patients with systolic dysfunction.

VII. CARDIOGENIC SHOCK

A. Background
1. Occurs in approximately 7% of MI cases and is the most malignant end of the spectrum of HF, developing frank systemic hypotension and pulmonary congestion.
2. Hemodynamic parameters suggest it when mean arterial pressure (MAP) is <60 mm Hg, cardiac index (CI) <2 L/minute/m^2 and pulmonary capillary wedge pressure (PCWP) >18 mm Hg.
3. Patients with cardiogenic shock have the highest risk of cleath after MI.

B. Pathophysiology
1. Majority of patients with cardiogenic shock will have large infarctions causing a critical reduction in LV performance.
2. Patients with prior infarctions, multivessel coronary artery disease, or mechanical defects (ventricular septal defect [VSD], mitral regurgitation [MR], free wall rupture) should be included in the differential diagnosis.

C. Prognosis. Patients with cardiogenic shock following acute MI have an in-hospital mortality rate approaching 70%.

D. Diagnosis. The diagnostic hallmarks of cardiogenic shock are hypotension and hypoperfusion.

E. Treatment:

1. The initial goal of treatment for severe HF is to:

a. Ensure adequate oxygenation with supplemental oxygen (and endotracheal intubation, if necessary).

b. Maintain systolic blood pressure at 90 mm Hg or greater (MAP >65 mm Hg).

c. Provide adequate perfusion of vital organs.

2. Diuretics and nitrates diminish pulmonary congestion, but the patient will have no major improvement in CI if preload is compromised. Targeted preload reduction is recommended to achieve a goal PCWP 15 to 20 mm Hg.

3. A balanced vasodilator such as nitroprusside reduces both preload and afterload, thereby increasing cardiac output, reducing LV end-diastolic pressure, and alleviating pulmonary congestion. CI goal should be >2 L/minute/m^2. A short-acting angiotensin-converting enzyme inhibitors (ACEI) can also be used to decrease afterload.

4. Most effective is administration of both inotropic and vasodilator therapies, with nitroprusside to reduce afterload and dopamine, dobutamine or milrinone to act as inotropic cardiac stimulants.

5. High-risk patients with cardiogenic shock may require insertion of an intra-aortic balloon pump (IABP) or LV assist device to increase cardiac output as an adjunct in the treatment of severe systolic dysfunction.

6. More important in the treatment of patients with cardiogenic shock is reperfusion of the infarct-related artery. Therefore, early, emergent angiography and revascularization should be considered, particularly for patients younger than 75 years.

VIII. VENTRICULAR RUPTURE

A. Background

1. Rupture of the myocardial wall is one of the most serious complications of acute MI.

2. Rupture can occur in the free wall, the interventricular septum, or the papillary muscle. Papillary muscle rupture is more common with inferior-posterior MI. Table 36-2 summarizes the clinical profiles in ventricular rupture presentations.

3. Rupture usually occurs 3 to 5 days after MI but occurs earlier in patients treated with thrombolytic therapy.

B. Prognosis.Myocardial rupture, particularly of the LV free wall, is associated with a mortality rate exceeding 80%. Prompt surgical repair of myocardial rupture can improve outcome.

C. Diagnosis

1. A high index of suspicion is required for patients with hypotension, severe HF or cardiogenic shock, or an unexplained change in clinical states, especially if a new systolic murmur is present.

2. Transthoracic echocardiography is the diagnostic test of choice in patients with suspected ventricular rupture. VSD can be differentiated from MR on the basis of right heart oximetric data with a step-up in oxygen saturation between the right atrium and pulmonary artery. A new systolic murmur is a clinical feature of VSD and MR.

D. Treatment

1. Pericardiocentesis is potentially lifesaving in patients with free wall rupture but should not delay surgical repair.

TABLE 36-2 Clinical Profiles of Mechanical Complications in Acute Myocardial Infarction (MI)

Variable	VSD	Free wall rupture	Papillary muscle head transection
Risk factors	Age, female, no prior MI, total occlusion with minimal collaterals	Female, first MI, AS, HTN, steroids, NSAIDs	Common in small infarctions, less CAD, good LVEF
Days post MI	3–5 d post MI; 20% in 24 h; rare after 2 wk	90% occur within first wk	2–7 d post MI (20% in first day)
Anterior MI	66%	50%	25%
New murmur	90%	25%	50%
Palpable thrill	Yes	No	Rare
Previous MI	0%–25%	25%	30%
Echocardiographic findings 2-D	Location, size of VSD, L-R shunt	Visualizes defect, presence of hemoperi-cardium	Flail leaflet, severe mitral regurgitation
PA catheterization	O_2 step-up in RV	Equalization of diastolic pressures	Prominent V-wave in PCWP pressure tracing
Incidence	~1%–2% in prethrombolytic era; 0.2% in reperfusion era	3% of MI (<1% with reperfusion)	1%
Medical mortality	90%	90%	90%
Surgical mortality	42%–75%	Case reports of success	40%–90%

VSD, ventricular septal defect; AS, aortic stenosis; HTN, hypertension; NSAIDs, nonsteroidal anti-inflammatory drugs; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; PA, posteroanterior; RV, right ventricular; PCWP, pulmonary capillary wedge pressure
(Updated from Pasternak RC, Braunwald E, Sobel BE. Acute myocardial infarction. In: Braunwald E, ed. *Heart disease*, 4th ed. Philadelphia: WB Saunders, 1992:1257.)

2. Supportive measures, IABP placement, and prompt surgical intervention are mainstays of treatment in patients with MR or VSD.

IX. THROMBOEMBOLISM

A. Background. LV mural thrombus formation is a well-recognized complication of acute MI, occurring in approximately 30% of patients especially after a large anterior-apical MI. Both arterial and venous emboli can occur, with LV mural thrombi accounting for most arterial emboli and RV or deep venous thrombi leading to PE.

B. Treatment

1. Anticoagulation represents first-line therapy and is usually continued for 3 to 6 months. Echocardiography is routinely performed to evaluate resolution and stability.
2. Fibrinolytic therapy may be considered in patients with cardioembolic stroke but should be undertaken with great caution.

TABLE 36-3 Arrhythmias During Acute Myocardial Infarction

Category	Arrhythmia	Objective of therapy	Therapeutic options
Ventricular tachycardias (VT)	Ventricular fibrillation	Urgent reversion to perfusing rhythm	Defibrillation; amiodarone, lidocaine, bretylium
	VT	Restoration of normal sinus rhythm (NSR)	Cardioversion/defibrillation; amiodarone, lidocaine, procainamide
	Accelerated idioventricular rhythm (AIVR)	Observation unless hemodynamically unstable.	Atropine; atrial pacing
Supraventricular tachycardias (SVT)	Sinus tachycardia	When appropriate, reduction of rate to diminish O_2 demand	Identify and treat underlying cause
	Atrial fibrillation or atrial flutter (AF)	Reduction of ventricular rate, restoration of NSR	Cardioversion when unstable; β-blockers, calcium channel blockers, digoxin, consider amiodarone
	Paroxysmal SVT	Reduction of ventricular rate, restoration of NSR	Vagal maneuvers; adenosine Same as AF
	Nonparoxysmal junctional tachycardia	Reduction of ventricular rate, restoration of NSR	Search for precipitating cause (e.g., digitalis toxicity); observe, consider overdrive atrial pacing or antiarrhythmics if unstable
Bradyarrhythmias	Sinus bradycardia	Increase heart rate (HR) only if hemodynamically compromised	Atropine; temporary pacing
	Junctional escape	Increase HR only if hemodynamically compromised	Atropine; temporary pacing
	High-degree atrioventricular block	Increase HR	Atropine, aminophylline; temporary pacing

(From Ganz LI, Antman EM. Cardiac arrhythmias during acute myocardial infarction. In: Antman EM, Rutherford JD, eds. *Coronary care medicine: a practical approach*, 2nd ed. Boston: Martinus Nijhoff. Reprinted with permission by Kluwer Academic Publishers.)

X. PERICARDITIS

A. Background. Pericardial irritation occurs in approximately one fourth of patients with acute MI and usually begins 1 to 4 days after MI. It is far more common with ST-elevation MI.

B. Diagnosis. Pericarditis may present as an asymptomatic pericardial effusion, early symptomatic pericarditis with or without effusion, or late pericarditis. It is usually accompanied by a pericardial rub.

1. Aspirin is given to relieve pain and to decrease inflammation; up to 650 mg every 4 hours may be required.
2. Other nonsteroidal anti-inflammatory medications relieve pain but may lead to infarct thinning and coronary artery vasoconstriction.
3. Corticosteroids should be avoided.
4. Minimizing anticoagulation is recommended.

XI. ARRHYTHMIAS COMPLICATING MYOCARDIAL INFARCTION

A. Background

1. Cardiac arrhythmias are an important complication of MI.
2. In the prehospital phase, ventricular tachycardia and fibrillation probably account for the majority of sudden deaths.
3. Tachyarrhythmias and bradyarrhythmias are frequently seen in the in-hospital phase of acute MI.

B. Pathophysiology. Arrhythmias in the setting of acute MI may be due to reentry, abnormal automaticity, or conduction block; these mechanisms are modulated by ischemia, LV failure, and variations in autonomic tone. Arrhythmias and their treatment are outlined in Tables 36-3 and 36-4.

C. Indications for pacemaker placement during MI. (See Chapter 39.)

D. Prophylactic implantation of implantable cardioverter defibrillator (ICD) is recommended in convalescent phase post-MI if EF <30%.

TABLE 36-4 Intravenous Antiarrhythmic Drug Dosing During Acute Myocardial Infarction

Drug	Bolus	Infusion
Lidocaine	1.0–1.5 mg/kg initially; additional boluses (0.5–0.75 mg/kg every 5–10 min) as necessary to control VT/VF to maximum total load 3.0 mg/kg	1–4 mg/min
Procainamide	17 mg/kg (maximum 1,000 mg) over 15–30 min, monitoring blood pressure	1–4 mg/min
Amiodarone	150 mg over 10 min for SVT, 300 mg for VT/VF, monitoring blood pressure	1 mg/min for 6 h, then 0.5 mg/min for 18 h, then transition to oral dosing
Bretylium	5 mg/kg initially; additional boluses (10 mg/kg every 5–10 min) as necessary to control VT/VF to maximum total load 35 mg/kg)	1–2 mg/min

(From Ganz LI, Antman EM. Cardiac arrhythmias during acute myocardial infarction. In: Antman EM, Rutherford JD, eds. *Coronary care medicine: a practical approach*, 2nd ed. Boston: Martinus Nijhoff. Reprinted with permission by Kluwer Academic Publishers.)

Suggested Reading

Becker RC, Gore JM, Lambrew C, et al. A composite view of cardiac rupture in the United States National Registry of Myocardial Infarction. *J Am Coll Cardiol* 1996;27:1321.

Cardiac rupture, although relatively rare, is responsible for 10% to 15% of all deaths after MI. Thrombolytic therapy accelerates the occurrence of rupture, at times within 24 hours of treatment.

Cannon CP. Evidence-based risk stratifications to target therapies in acute coronary syndromes. *Circulation* 2002;106:1588–1591.

A brief overview of the approach to ACS.

Loh E, Sutton MS, Wun CC, et al. Ventricular dysfunction and the risk of stroke after myocardial infarction. *N Engl J Med* 1997;336:251.

The risk of thromboembolism following MI is influenced by ventricular performance. An LV ejection fraction of less than 35% increases the risk of stroke, and therefore long-term anticoagulant therapy should be considered.

Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation* 2000;102:2031–2037.

The Thrombolysis in Myocardial Infarction (TIMI) study group recognized predictors of mortality: age, time to treatment, anterior MI, MI with new left bundle branch block, and development of heart failure (HF).

Muller JE, Rude RE, Braunwald E, et al. Myocardial infarct extension: occurrence, outcome, and risk factors in the multi-center investigation of limitation of infarct size. *Ann Intern Med* 1988;108:1.

MILIS, a landmark study, provided pivotal insights that paved the way for trials of thrombolytic therapy.

TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction: results of the thrombolysis in myocardial infarction (TIMI) phase II trial. *N Engl J Med* 1989;320:618.

Treatment: an approach to the acute evaluation and treatment of recurrent ischemic events is outlined in Figure 36-3.

VENTRICULAR TACHYCARDIA

Bruce A. Koplan and William G. Stevenson

37

I. GENERAL PRINCIPLES

A. Definitions

1. **Ventricular tachycardia (VT)**
   - **a.** ≥3 beats at a rate ≥100 bpm
   - **b.** QRS width ≥0.12 seconds
   - **c.** Originates from the ventricle
2. **Nonsustained ventricular tachycardia (NSVT)**
   - **a.** Terminates spontaneously within 30 seconds without causing severe symptoms

B. Classification (Fig. 37-1)

1. **Monomorphic VT.** Same configuration from beat to beat
   - **a.** Usually due to a circuit through a region of old myocardial infarction (MI) scar
   - **b.** Idiopathic VT (less common): VT in the absence of an identifiable cause (e.g., structural heart disease/prior MI)
     - **i.** Right ventricular outflow tract (RVOT) tachycardia: most common idiopathic VT. Left bundle branch block morphology with inferior axis.
2. **Polymorphic VT.** Continually changing QRS morphology
   - **a. Etiologies**
     - **i.** Active cardiac ischemia (most common)
     - **ii.** Electrolyte disturbance
     - **iii.** Drug toxicity
     - **iv.** Familial
   - **b. *Torsade de pointes***
     - **i.** Unique form of polymorphic VT
     - **ii.** Waxing and waning QRS amplitude during tachycardia associated with prolonged QT interval
     - **iii.** Secondary to QT-prolonging drugs, electrolyte abnormalities, or familial ion channel disorders (long QT syndrome)
3. **Sinusoidal VT.** Sinusoidal appearance often associated with severe electrolyte disturbance (e.g., hyperkalemia).
4. ***Accelerated idioventricular rhythm* (AIVR)**
   - **a.** Wide complex, ventricular rhythm at 40 to 100 beats/minute
   - **b.** Usually hemodynamically stable
   - **c.** Can occur in the first 12 hours after reperfusion of an acute MI or during periods of elevated sympathetic tone
   - **d.** Onset typically preceded by sinus slowing
   - **e.** Usually resolves without specific therapy
   - **f.** Antiarrhythmic drug (AAD) treatment rarely necessary

II. DIAGNOSIS

A. Differentiating VT from supraventricular tachycardia (SVT) in a patient with a wide complex tachycardia (WCT)

1. **Differential diagnosis of WCT:**
   - **a.** VT

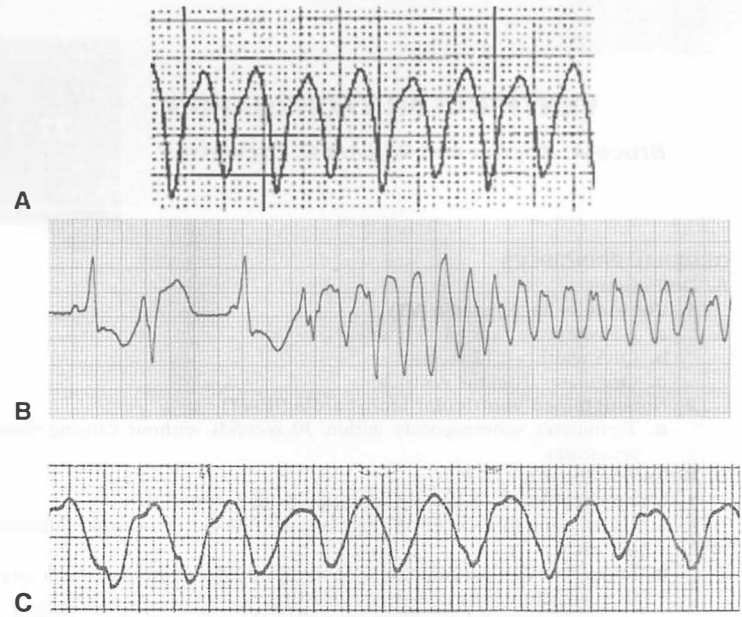


Figure 37-1. Three different wide QRS tachycardias are shown: monomorphic VT in **(A)**; polymorphic VT in **(B)**, and sinusoidal VT due to hyperkalemia in **(C)**.

   b. SVT with aberrancy (bundle branch block)
   c. SVT conducting of an accessory pathway (Fig. 37-2B)
2. Assume VT until proven otherwise.
3. WCT with a history of MI can be assumed to be VT with >95% certainty.
4. If the patient is hemodynamically stable, obtain a 12-lead electrocardiogram (ECG).
5. **ECG criteria** that favor VT over SVT (Figs. 37-3A and 37-3B):
   a. AV dissociation (Fig. 37-2A)
   b. QRS concordance. absence of an rS or Rs complex in any precordial lead (V_1-V_6)
   c. RS >100ms. an interval between the onset of the R and the nadir of the S wave >100ms in any precordial lead (V_1-V_6)
   d. Capture beats/fusion beats during tachycardia
      i. Occur when a supraventricular beat is able to conduct to the ventricles, depolarizing the ventricle (completely—capture beat, or partially—fusion beat) in advance of the next tachycardia beat
      ii. Morphologically identical (capture beat) or similar (fusion beat) to the QRS complex seen in sinus rhythm but occur in the midst of a wide QRS complex tachycardia
      iii. Capture beats during WCT are pathognomonic for VT
6. Additional principles:
   a. Hemodynamic instability is dependent on the rate and underlying ventricular function and does not differentiate VT from SVT.
   b. Electrocardiographic artifacts can mimic VT/ventricular fibrillation (VF) (Fig. 37-2D)

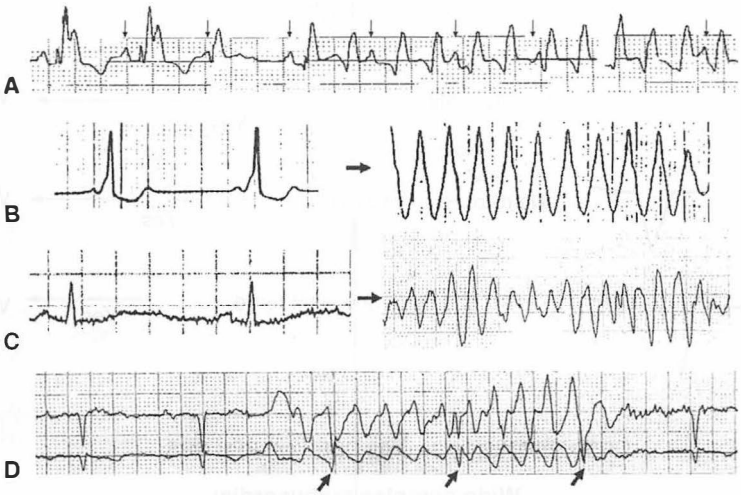


Figure 37-2. Wide complex tachycardias. **A:** Transition from sinus rhythm to ventricular tachycardia with AV dissociation (P waves identified by *small arrows*). **B:** Short PR and delta wave on left, and atrial fibrillation with rapid, irregular, wide complex ventricular response in a patient with the Wolff–Parkinson–White syndrome due to an accessory pathway. **C:** The polymorphic VT *torsade de pointes* (right side) in a patient with QT prolongation (left side). **D:** Motion artifact mimicking a wide complex tachycardia. Note that QRS complexes (*large arrows*) are present within the artifact that occurs at the same interval as before and after the onset of the irregular artifactual waveform. AV, atrioventricular; VT, ventricular tachycardia.

III. TREATMENT. First priority—determine whether the patient is hemodynamically stable.

A. Management of hemodynamically unstable VT/VF (see algorithm—Fig. 37-4)

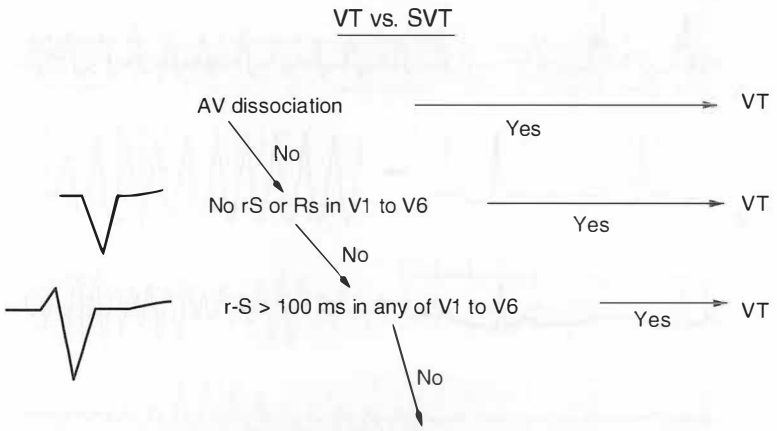
1. Rapid defibrillation (up to 3 shocks) is the most important measure to improve survival.
2. If VT/VF persists after defibrillation, *epinephrine* (1 mg IV every 3 minutes) should be given. *Vasopressin* (40 units IV, single bolus) is an acceptable alternative to epinephrine.
3. **Antiarrhythmic drugs (AAD)—see III.B.1 in subsequent text**
   a. Used when cardioversion fails or VT/VF recurs
   b. *Amiodarone* (often used as first-line therapy), *Procainamide* (alternative to amiodarone), *lidocaine* (most appropriate during suspected acute myocardial ischemia).

B. Management of hemodynamically stable WCT (see algorithm, Fig. 37-5).

1. **AADs**:
   a. Amiodarone
   b. Procainamide
   c. Lidocaine
2. **Electrical cardioversion** is also appropriate initial therapy.
3. If Wolff–Parkinson–White (WPW) syndrome (see Chapter 38) is suspected (Fig. 37-2B), intravenous procainamide or cardioversion are first-line therapies.

C. Management of polymorphic VT/sinusoidal VT

1. Correct reversible causes.
   a. Cardiac ischemia



A QRS morphology criteria for RBBB or LBBB QRS

Wide complex tachycardia:
Additional ECG/clinical findings supporting VT vs. SVT

Characteristic	Favors VT	Favors SVT
Capture beats	++	
Fusion beats	+	
Prior known MI or CMP	+	
Irregularly irregular		+
Prior delta wave		+
Onset with a PAC		+
Identical morphology during SR in a patient with IHD		+
QRS >140 ms with RBBB or >160 ms with LBBB	+	

B

Figure 37-3. A: Electrocardiographic features to differentiate VT versus SVT in patients presenting with wide QRS complex tachycardia. VT, ventricular tachycardia; SVT, supraventricular tachycardia; AV, atrioventricular; RBBB, right bundle branch block; LBBB, left bundle branch block.(Modified from Brugada P, Brugada J, Mont L, et al. A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. *Circulation* 1991;83:1649–1659.) See text for details. **B:** Additional clinical and ECG findings to assist with differentiation between ventricular tachycardia (VT) and supraventricular tachycardia (SVT) in patients with wide complex tachycardia. See text for details. ECG, electrocardiogram; MI, myocardial infarction; CMP, cardiomyopathy; PAC, premature atrial contraction; SR, sinus rhythm; IHD, ischemic heart disease; RBBB, right bundle branch block; LBBB, left bundle branch block.

   b. Metabolic abnormalities
   c. Drug toxicity including QT-prolonging drugs.
2. Lidocaine and amiodarone can be considered for recurrent episodes.
3. Treatment of *torsade de pointes* (polymorphic VT due to QT prolongation):
   a. Intravenous magnesium sulfate (1 to 2 g) (can be repeated).
   b. Correct electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia).
   c. Discontinue QT prolonging medications.

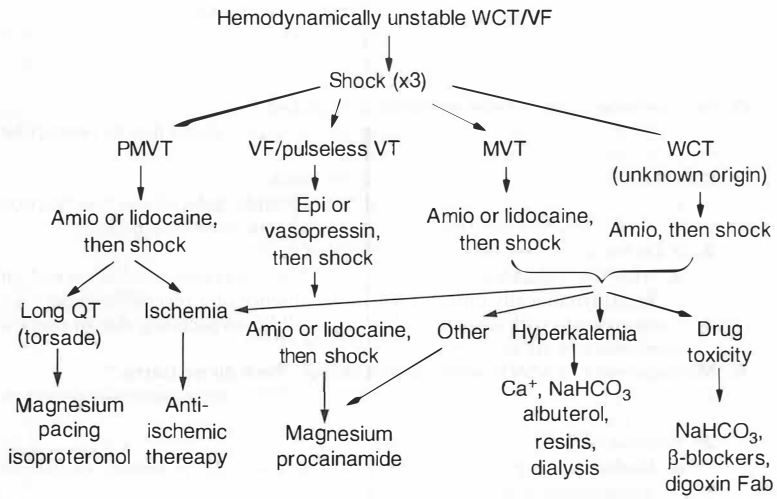


Figure 37-4. Approach to unstable wide complex tachycardia (WCT)/VF. This algorithm assumes that CPR is initiated after the three unsuccessful shocks and maintained until a pulse is achieved. VF, ventricular fibrillation; PMVT, polymorphic ventricular tachycardia; VT, ventricular tachycardia; Amio, amiodarone; Epi, epinephrine; MVT, monomorphic ventricular tachycardia; CPR, cardiopulmonary resuscitation.

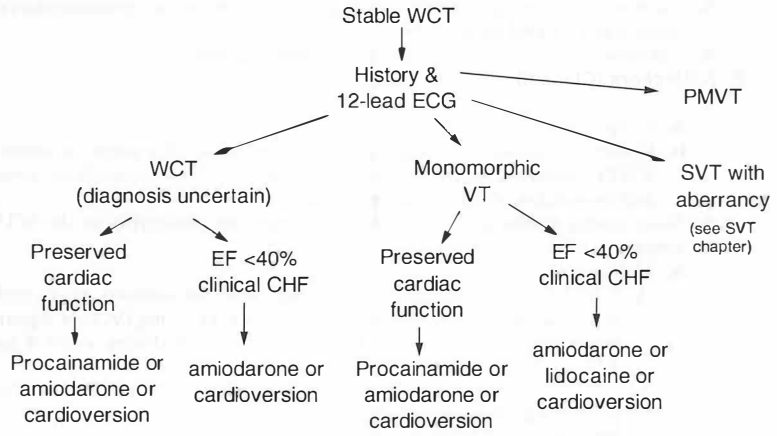


Figure 37-5. Approach to stable wide complex tachycardia. WCT, wide complex tachycardia; ECG, electrocardiogram; EF, ejection fraction; CHF, congestive heart failure; VT, ventricular tachycardia; PMVT, polymorphic ventricular tachycardia; SVT, supraventricular tachycardias. See text for details.

d. Increasing heart rate with **pacing** or **isoproterenol** can be highly effective. Transvenous temporary ventricular pacing is most reliable (target rate of 110 to 120 bpm). Isoproternol should not be used if congenital long QT syndrome is suspected.

D. Implantable cardioverter defibrillators (ICDs)

1. May be considered for long-term protection from death due to ventricular arrhythmias after acute issues resolve.

2. ICDs for primary prevention of sudden death:

a. May be indicated in patients with persistently reduced ejection fraction ≤35% due to either ischemic or nonischemic cardiomyopathy.

3. ICDs for secondary prevention of sudden death:

a. May be indicated in patients who have survived cardiac arrest or hemodynamically unstable VT in the absence of a reversible cause.

4. Some patients with severely reduced overall life expectancy due to chronic comorbidities are not candidates for an ICD.

E. Management of NSVT/ventricular ectopy: "first do no harm."

1. NSVT/premature ventricular contractions (PVCs) are common in the intensive care unit (ICU).

2. Treatment:

a. Evaluate for possible aggravating factors (e.g., ischemia, electrolyte disturbance, hypoxia, hypoventilation).

b. β-Blocking agents (if not contraindicated).

c. In the absence of symptoms, other antiarrhythmic agents should be avoided and may increase mortality.

IV. OVERVIEW OF DRUGS COMMONLY USED FOR MANAGEMENT OF VT/VF IN THE ICU

A. General principles

1. Narrow toxic-therapeutic relationship and potential for proarrhythmia necessitates careful monitoring.

2. Titration to achieve the desired effect is often required.

B. β-*Blockers* (Class II)

1. Indications

a. Symptomatic ventricular ectopy.

b. Recurrent sustained ventricular tachyarrhythmias. Frequent recurrent VT/VF (electrical storm) is often aggravated by high sympathetic tone and responds to β-adrenergic blockade.

2. Short-acting agents (e.g., metoprolol tartrate) are preferable in the ICU setting.

a. *Metoprolol*

i. Can be given orally or as a 5-mg slow intravenous push and repeated every 5 to 10 minutes up to a total of 20 mg IV. Can repeat intravenous boluses every 4 to 6 hours or oral dosing every 4 to 8 hours.

ii. *Esmolol* (useful when there is concern that a β-blocker may be poorly tolerated (short half-life 2 to 9 minutes).

(a) 500 μg/kg IV bolus over 1 minute followed by maintenance dose of 50 μg/kg/minute titrated for effect up to 300 μg/kg/minute.

3. Adverse effects of β-blockers

a. Negative inotropy (avoid with decompensated heart failure)

b. Bradycardia

c. Aggravation of bronchospasm

C. *Amiodarone*

1. Indications

a. First-line AAD in advanced cardiac life support (ACLS) VF/pulseless VT algorithm

b. Hemodynamically stable VT that recurs after cardioversion or fails IV procainamide

2. Dosing
   a. A 150 to 300 mg IV bolus over 10 minutes, followed by an infusion at 1 mg/minute for 6 hours, then 0.5 mg/minute.
   b. Additional 150 mg boluses can be given for breakthrough arrhythmia up to a total load of approximately 2 g/24 hours and 5 to 8 grams total
   c. Can also be loaded orally (800 to 1,600 mg daily for 2 to 3 weeks, with maintenance dose of 400 mg daily for ventricular arrhythmias).
3. Adverse effects
   a. Even though amiodarone causes QT prolongation, *torsade de pointes* and other proarrhythmic complications are rare.
   b. Hypotension during intravenous administration.
   c. Bradycardia.
   d. Exacerbation of congestive heart failure (negative inotropic effect).
   e. Phlebitis (when administered through a peripheral intravenous line). Continuous infusions should be administered through a central venous catheter.
   f. Other adverse effects include hepatitis, hyper- or hypothyroidism, pneumonitis, neuropathy, and tremor.

D. *Procainamide*

1. First-line agent for WCT (along with amiodarone) for treatment of hemodynamically stable WCT and WCT due to WPW syndrome.
2. Alternative agent for hemodynamically unstable WCT and VF.
3. Dosing: 20 to 30 mg/minute IV infusion loading dose up to a total initial dose of 17 mg/kg followed by a maintenance infusion of 1 to 4 mg/minute.
4. Adverse effects
   a. Vasodilatation and negative inotropy.
      i. Avoid with depressed ventricular function (ejection fraction <40%) in favor of amiodarone.
      ii. Blood pressure should be monitored carefully during IV administration.
   b. *N*-acetyl-procainamide (NAPA), a metabolite of the drug, can increase QTc and cause *torsade de pointes*.
      i. Monitor serum procainamide and NAPA levels if the drug is continued for >24 hours.
      ii. QTc interval and QRS complex width should be monitored.
         (a) Discontinue if the QRS widens by >50% from baseline.
   c. Avoid in patients with significant renal dysfunction.
      i. NAPA is excreted entirely by the kidney.

E. *Lidocaine* (IB)

1. Indications:
   a. Acute management of life-threatening ventricular arrhythmias, especially when associated with myocardial ischemia. Often ineffective for treatment of sustained VT that is not due to acute myocardial ischemia or infarction; Amiodarone, procainamide, and β-blockers are preferable.
2. Dosing: 1 to 1.5 mg/kg IV bolus. Can repeat to a maximum bolus of 3 mg/kg, followed by an infusion of 1 to 4 mg/minute.
3. Adverse effects:
   a. Minimal adverse hemodynamic side effects
   b. Neurologic toxicity (seizures, tremors)
4. Class IC AADs (***flecainide, propafenone***) are rarely used in the ICU for VT/VF and can increase long-term mortality in patients with coronary artery disease and depressed ventricular function.

Suggested Reading

Advanced Life Support Working Group of the International Liaison Committee on Resuscitation. ILCOR Advisory statements: early defibrillation. *Circulation* 1997;95:2183–2184.

This citation is from the current guidelines on acute management of patients with cardiac arrest.

Advanced Life Support Working Group of the International Liaison Committee on Resuscitation. International guidelines 2000 for CPR and ECC. *Circulation* 2000;102(I-1-370):8.

AVID investigators. Comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *New Engl J Med* 1997;337:1576–1583.

Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter—defibrillator for congestive heart failure. *N Engl J Med* 2005;352: 225–237.

Brugada P, Brugada J, Mont L, et al. A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. *Circulation* 1991;83: 1649–1659.

This article describes how to use electrocardiographic criteria to differentiate VT from SVT in patients with wide complex tachycardia.

The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992;327:227–233.

This study also demonstrates the increased mortality associated with class IC antiarrhythmics when used in patient with coronary artery disease.

Connoly SJ. Evidenced based analysis of amiodarone efficacy and safety. *Circulation* 1999;100:2025–2034.

This article reviews many important studies regarding the efficacy and safety of amiodarone.

Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide or placebo: the Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991;324:781–788.

This study demonstrates the increased mortality associated with class IC antiarrhythmics when used in patient with coronary artery disease.

Gorgels AP, Vos MA, Letsch IS, et al. Usefulness of AIVR as a marker for myocardial necrosis and reperfusion during thrombolysis in acute MI. *Am J Cardiol* 1988;61:231.

This article describes the association between AIVR and myocardial reperfusion.

Jawad-Kanber G, Sherrod TR. Effect of loading dose of procaine amide on left ventricular performance in man. *Chest* 1974;66:269–272.

This article describes the hemodynamic and electrophysiologic effects of procainamide.

MacMahon S, Collins R, Peto R, et al. Effects of prophylactic lidocaine in suspected acute myocardial infarction. An overview of results from the randomized, controlled trials. *JAMA* 1988;260:1910–1916.

This study describes the lack of benefit of prophylactic lidocaine in suspected acute myocardial infarction.

Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *New Engl J Med* 2002;346:877–883.

Nalos PC, Ismail Y, Pappas JM, et al. Intravenous amiodarone for short term treatment of refractory ventricular tachycardia or fibrillation. *Am Heart J* 1991;122: 1629–1632.

This study demonstrates the usefulness of amiodarone for management of ventricular arrhythmias.

Nasir N Jr, Taylor A, Doyle TK, et al. Evaluation of intravenous lidocaine for the termination of sustained monomorphic ventricular tachycardia in patients with coronary artery disease in patients with or without healed myocardial infarction. *Am J Cardiol* 1994;74:1183–1186.

This study demonstrates the usefulness of lidocaine for management of ventricular arrhythmias in patients with coronary disease.

Tchou P, Young P, Mahmud R, et al. Useful clinical criteria for the diagnosis of ventricular tachycardia. *Am J Med* 1988;84:53–56.

This article describes the ability to use clinical history to assist with the differentiation of VT from SVT with aberrancy in patients with wide complex tachycardia.

The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *New Engl J Med* 1989;321(6): 406–412.

This study describes the increased mortality risk associated with class IC antiarrhythmics used in the patients with coronary artery disease.

Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation* 2006;114:e385–e484.

38 SUPRAVENTRICULAR TACHYCARDIA

John L. Sapp, Jr. and Laurence M. Epstein

I. BACKGROUND

A. Definition: supraventricular tachycardias (SVTs) are those that require involvement of the atrioventricular (AV) node or atria for their perpetuation. They are usually described by mechanism or by their electrocardiographic appearance (Figs. 38-1 and 38-2).

II. MECHANISMS. There are three main mechanisms underlying SVTs:

A. Abnormal automaticity: inappropriate sinus tachycardia, ectopic atrial tachycardia

B. Abnormal repolarization/triggered activity: atrial premature contractions, multifocal atrial tachycardia (MAT)

C. Reentry: atrioventricular reentrant tachycardia (AVRT), atrioventricular nodal reentrant tachycardia (AVNRT), atrial flutter

III. RECOGNITION AND DIAGNOSIS (Figs. 38-1 and 38-2)

A. QRS duration <120 milliseconds in *all* surface leads: likely supraventricular SVT may result in a wide complex tachycardia when there is a bundle branch block or intraventricular conduction delay. Wide complex tachycardia in the presence of structural heart disease should be considered ventricular tachycardia until proven otherwise.

B. Irregularly irregular QRS complexes most commonly signify atrial fibrillation (MAT is distinguished by the presence of P waves).

C. Rapid irregularly irregular wide QRS tachycardia may represent atrial fibrillation with preexcitation over an accessory pathway (AP) (Wolff–Parkinson–White syndrome).

D. Atrial activity?

1. P wave may be buried in the QRS-T complex. If possible, compare to sinus rhythm tracings.

2. Organized continuous atrial activity faster than 240 beats per minute is classified as atrial flutter. Typical atrial flutter: down-sloping flutter waves in the inferior leads followed by a rapid upstroke, short positive P waves in V1, and an atrial rate of approximately 300 beats per minute. Atypical flutter circuit or ectopic atrial tachycardia may have a different morphology or cycle length.

3. Every P wave is not associated with a QRS (i.e., AV block is present), the tachycardia is unlikely to depend on the AV node. Differential diagnosis: ectopic atrial tachycardia, rarely be seen with AVNRT.

4. A 1:1 relationship between P and QRS deflections? (Fig. 38-2.) A long RP (RP > PR) tachycardia. Differential diagnosis: ectopic atrial tachycardia, less commonly AVRT utilizing a slowly conducting bypass tract or atypical AVNRT. A short RP tachycardia (RP < PR). Differential diagnosis: AVNRT, AVRT, or ectopic atrial tachycardia.

IV. GENERAL MANAGEMENT OF SVTs. A general approach to the evaluation and management of SVTs is outlined in Figure 38-3.

A. Assess patient stability

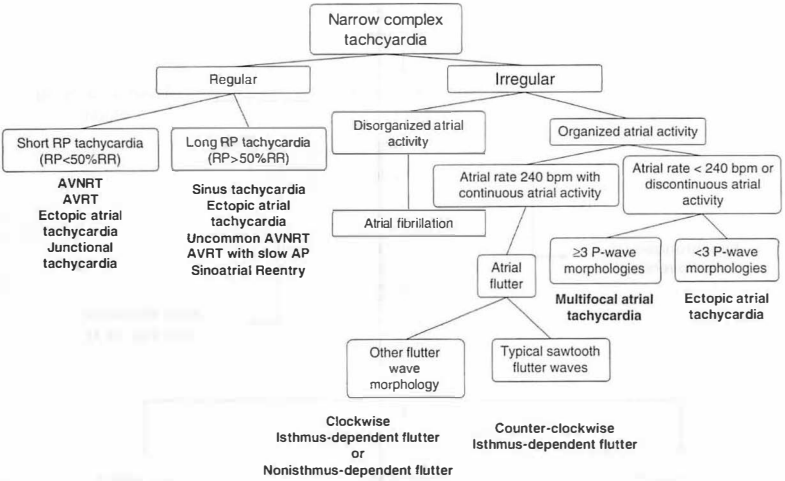


Figure 38-1. Electrocardiographic classification of supraventricular tachycardia; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; AP, accessory pathway.

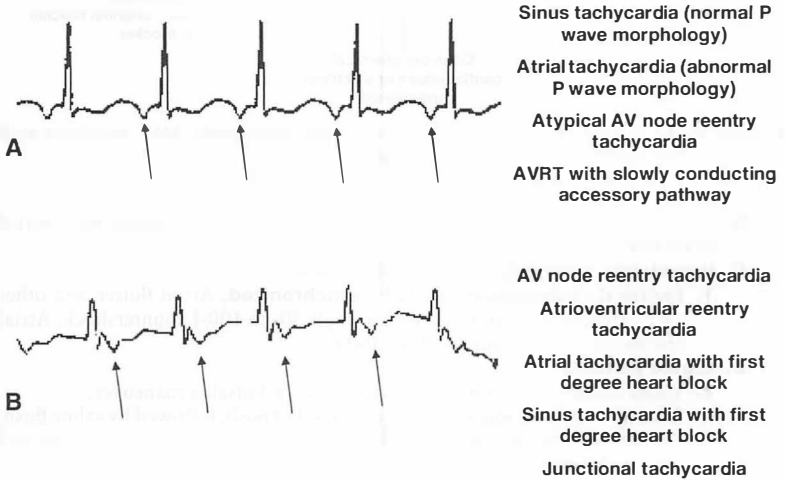


Figure 38-2. Diagnosis of regular narrow complex tachycardias. **A:** The RP interval (P waves indicated by *arrows*) is longer than the PR interval. The differential diagnosis is sinus tachycardia (which is associated with a normal or near normal P wave morphology), ectopic atrial tachycardia (which usually has an abnormal P wave morphology), atypical atrioventricular (AV) node reentry tachycardia (in which antegrade propagation is through the "fast pathway" and retrograde activation is through the "slow pathway"), or AV reentry tachycardia utilizing a slowly conducting accessory pathway. **B:** The RP interval (P waves indicated by *arrows*) is shorter than the PR interval. The differential diagnosis is typical AV nodal reentry tachycardia, atrioventricular reentry tachycardia, ectopic or sinus tachycardia with first-degree heart block (PR prolongation), or junctional tachycardia; AVRT, atrioventricular reentrant tachycardia.

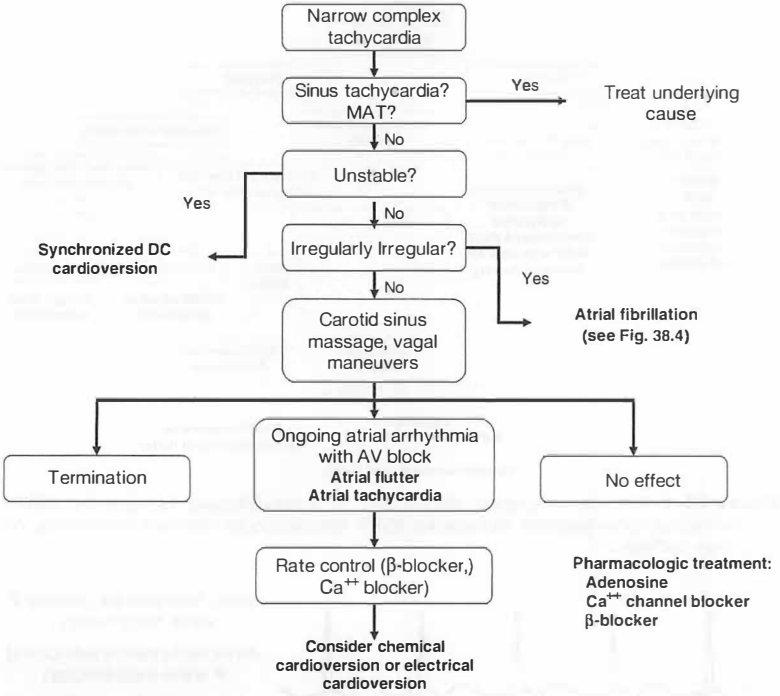


Figure 38-3. Therapeutic approach to narrow complex tachycardia; MAT, multifocal atrial tachycardia; DC, direct current; AV, atrioventricular.

B. Identify sinus tachycardia and MAT: treat the underlying causes and control heart rate

C. If unstable: prompt direct current (DC) cardioversion

1. Electrical cardioversion should be **synchronized**. Atrial flutter and other SVTs are usually terminable with a single 50- to 100-J countershock. Atrial fibrillation often requires 200 to 360 J.

D. Stable patients

1. Vagal maneuvers: carotid sinus massage or a Valsalva maneuver.
2. Adenosine: 6 to 12 mg, rapid intravenous (IV) push, followed by saline flush. Carbamazepine and dipyridamole potentiate the actions of adenosine and may prolong its action causing angina or bronchospasm. Methylxanthines (caffeine, theophyllines) antagonize the effects of adenosine and may render it ineffective.
3. IV verapamil, diltiazem, or β-blockers may be used (Table 38-1). Vagal maneuvers may be repeated in the presence of drug therapy and may act synergistically.
4. Atrial flutter and atrial fibrillation are unlikely to terminate with these measures, although flutter waves or ectopic P waves may be unmasked, facilitating diagnosis.
5. Type I or type III antiarrhythmic agents may be used for conversion alone or in combination with DC cardioversion.

TABLE 38-1 Drugs for Supraventricular Tachycardias

Drug	Class	Dosage	Potential adverse effects
Procainamide	**Ia**	IV 15 mg/kg not faster than 50 mg/min PO sustained release 250–1,000 mg q6 h	Hypotension Lupuslike syndrome, GI symptoms *Torsade de pointes*, QT prolongation May slow atrial arrhythmia with faster ventricular response
Quinidine	**Ia**	PO quinidine sulfate 200–400 mg q6 h	*Torsade de pointes*, QT prolongation GI symptoms May slow atrial arrhythmia with faster ventricular response
Disopyramide	**Ia**	PO 100–200 mg q6–8 h	*Torsade de pointes*, QT prolongation Anticholinergic effects Heart failure (negative inotrope)
Flecainide	**Ic**	PO 200–300 mg load, then 100–200 mg q12 h	Ventricular arrhythmia May slow atrial arrhythmia with faster ventricular response Hypotension
Propafenone	**Ic**	PO 450–600 mg load, 150–300 mg q8 h maintenance	Hypotension May slow atrial arrhythmia with faster ventricular response
Esmolol	**II**	IV 0.5 mg/kg over 1–2 min, then 0.05–0.2 mg/kg/min maintenance	Bronchoconstriction Bradycardia, heart block, hypotension
Metoprolol	**II**	IV load 2.5–5 mg q5 min up to 15 mg. May give IV maintenance 2.5–5 mg q6 h PO 25–100 mg bid	Bronchoconstriction Bradycardia, heart block, hypotension
Propranolol	**II**	IV load 0.15 mg/kg PO maintenance 20–80 mg q6 h	Bronchoconstriction Bradycardia, heart block, hypotension
Sotalol	**II/III**	PO maintenance 80–160 mg bid	Bronchoconstriction Bradycardia, heart block, hypotension QT prolongation, *torsade de pointes*
Amiodarone	**III**	IV load 5–7 mg/kg over 30–60 min, then 1.2–1.8 g/d IV or PO until 10 g administered, then 200–400 daily maintenance PO load 900–1,600 mg/d in 3–4 divided doses until 10 g administered, then 200–400 mg daily maintenance	Hypotension with rapid infusion, phlebitis if given peripherally Pulmonary toxicity, skin photosensitivity, and pigmentation Hypo-/hyperthyroidism, corneal deposits, hepatitis Optic/peripheral neuropathy, bradycardia, hypotension Interaction with multiple drugs including digoxin and warfarin

(continued)

TABLE 38-1 Continued

Drug	Class	Dosage	Potential adverse effects
Ibutilide	III	IV 1 mg over 10 min; repeat once if necessary	QT prolongation, *torsade de pointes*
Dofetilide	III	PO dose according to creatinine clearance: >60, 500 μg bid; 40–60, 250 μg bid; 20–40, 125 μg bid	QT prolongation, *torsade de pointes* Contraindicated for creatinine clearance <20 mL/min
Verapamil	IV	IV load 0.075–0.15 mg/kg over 5 min	Bradycardia, heart block, hypotension Edema, constipation
Diltiazem	IV	IV load 0.25 mg/kg over 2–5 min, then 5–15 mg/h maintenance PO 60–180 mg bid	Bradycardia, heart block, hypotension Edema, constipation
Digoxin	N/A	IV 0.25 load mg q2–4 h up to 1.5 mg PO maintenance 0.125–0.25 mg daily	Bradycardia, heart block, atrial/ventricular tachycardia Interaction with multiple drugs
Adenosine	N/A	IV 6–12 mg bolus followed by saline flush	Transient chest pain, bronchoconstriction, complete heart block Potentiated by dipyridamole, heart transplant and central administration route

GI, Gastrointestinal.

V. SPECIFIC ARRHYTHMIAS AND THERAPIES

A. Atrial fibrillation

1. Atrial fibrillation is the most common SVT, and involves chaotic atrial activation (Fig. 38-4F).

2. Acute treatment (Fig. 38-5).

a. Unstable: Synchronized DC cardioversion is the treatment of choice. Atrial fibrillation may be difficult to convert and requires higher energies than other arrhythmias.

b. Stable: pharmacologic rate control.

i. β_1-Selective adrenergic receptor antagonists in nonasthmatic patients.

ii. Nondihydropyridine calcium channel blockers (e.g., verapamil, diltiazem) may be used in absence of ventricular dysfunction.

iii. Digitalis may be used with relative safety in patients with poor ventricular function but provides only modest control of ventricular rate. It is ineffective in patients with high adrenergic tone or when rapid rate control is required.

iv. Amiodarone effectively controls ventricular rate response during atrial fibrillation when administered IV and is safe for use in patients with low ejection fraction. IV amiodarone should be administered through a central line to avoid phlebitis.

c. Treat underlying causes

i. Stop offending drugs (e.g., methylxanthine derivatives).

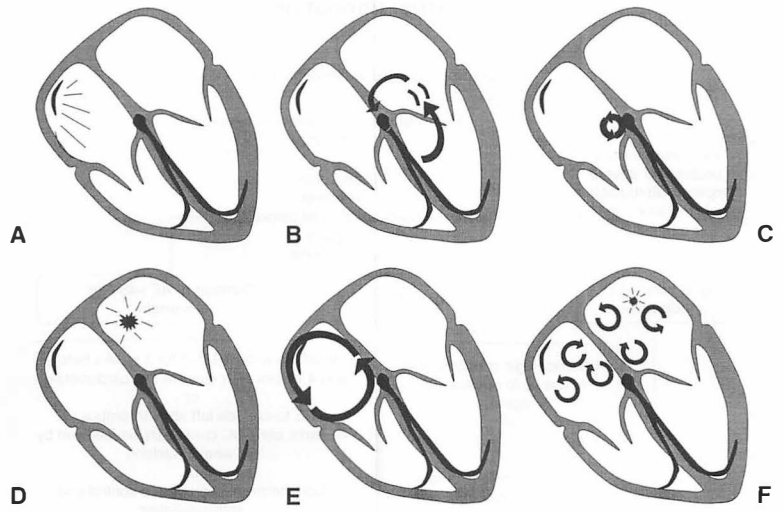


Figure 38-4. Mechanisms of supraventricular tachycardias. **A:** Inappropriate sinus tachycardia occurs when the sinus node or contiguous areas along the crista terminalis trigger heart rates that are inappropriately fast. **B:** Atrioventricular (AV) reentry tachycardia uses an accessory pathway for retrograde conduction. Accessory pathways may be manifest (Wolff–Parkinson–White syndrome, pathway can conduct antegrade or retrograde, associated with delta wave on electrocardiogram [ECG]) or concealed (incapable of antegrade conduction). Antegrade propagation through the His-Purkinje system leads to a narrow QRS, and reentry using the accessory pathway as the retrograde limb produces tachycardia. **C:** AV node reentry tachycardia utilizes two functional pathways within the AV node or approaches to the AV node, most commonly with antegrade conduction along the more slowly conducting pathway and retrograde conduction through the more rapidly conducting pathway. **D:** Ectopic atrial tachycardia requires the presence of a focus other than the sinus node, which usurps control of the atrial rate. The focus is often located on the crista terminalis, within a venous structure, or near an AV valve. **E:** Atrial flutter, in its most common (clockwise) form, consists of macroreentry within the right atrium. Activation proceeds up the interatrial septum, across the roof of the right atrium, anterolaterally anterior to the crista terminalis, and inferiorly to the Eustachian isthmus across which it conducts back to the interatrial septum. The atrial rate is usually approximately 300 beats per minute, with conduction to the ventricles limited by the AV node. **F:** Atrial fibrillation may be initiated by focal ectopy leading to multiple reentrant wavelets within the atria and a high-frequency barrage of impulses activating the AV node. Ventricular activation is limited by the AV node.

ii. Correct electrolyte abnormalities.
iii. Attend to other cardiac, endocrine (particularly thyroid), and pulmonary disease.
iv. Correct/treat severe metabolic stress, severe noncardiac disease, and other hyperadrenergic states.

d. Rate versus rhythm control

i. Rate control and anticoagulation are a reasonable approach in stable patients with limited symptoms.
ii. Patients in atrial fibrillation <48 hours or who have been anticoagulated (international normalized ratio [INR] >2 for at least 3 weeks) are candidates for early cardioversion.

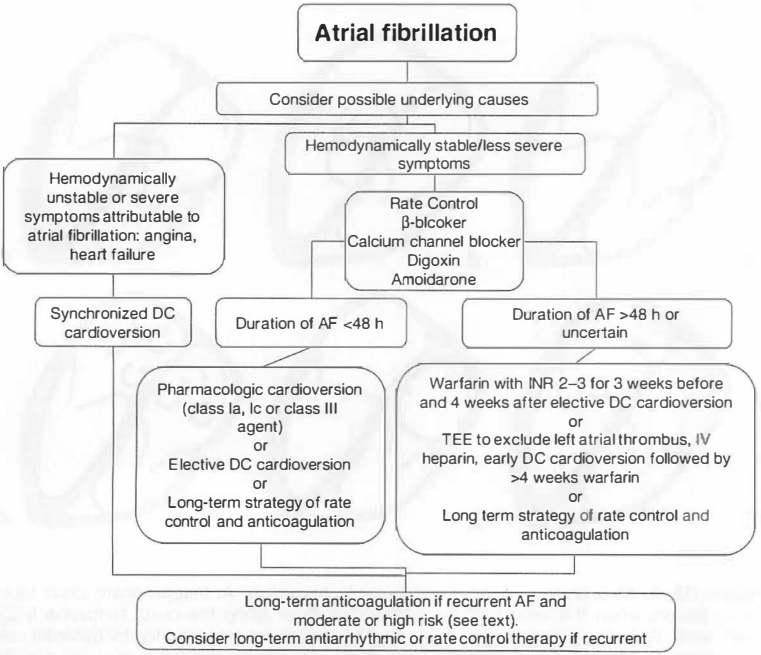


Figure 38-5. Therapeutic approach to atrial fibrillation; DC, direct current; AF, atrial fibrillation; INR international normalized ratio; IV, intravenous; TEE, transesophageal echocardiogram.

iii. Pharmacologic cardioversion: procainamide, flecainide, propafenone, dofetilide, ibutilide, and amiodarone. Class I drugs should always be preceded by rate control.

iv. Unanticoagulated patients in atrial fibrillation for >48 hours (or for an uncertain duration) are at elevated risk of thromboembolism. These patients require anticoagulation before conversion from atrial fibrillation. An alternative approach is to exclude left atrial thrombus with transesophageal echocardiography, initiate IV anticoagulation, and proceed to DC cardioversion, followed by oral anticoagulation for at least 4 weeks.

v. Drug therapy to maintain sinus rhythm includes class Ia, Ic, and III antiarrhythmic agents (Table 38-1). This approach may be warranted in patients who do not tolerate or are symptomatic in atrial fibrillation. Catheter ablation for maintenance of sinus rhythm may be helpful for selected patients.

vi. Catheter ablation of the AV node with permanent pacemaker implantation may be useful in patients in whom AV nodal blocking medications are not tolerated or in whom rate control is difficult with conventional agents.

vii. Patients with recurrent atrial fibrillation should be considered for anticoagulation. High risk patients (one of: prior stroke/TIA; mitral stenosis; prosthetic heart valve: or two of: age >75; history of hypertension; diabetes; moderate/severe ventricular dysfunction or heart failure) should be treated with warfarin, target INR 2.5 (range

2.0–3.0). Moderate risk patients (one of: age >75; history of hypertension; diabetes; moderate/severe ventricular dysfunction and/or heart failure) should be treated with warfarin in most cases, although aspirin may be appropriate in individual patients. Low risk patients (none of the above risk factors) may be treated with acetylsalicylic acid (ASA) 81 to 325 mg daily. Aspirin or no anticoagulation may be appropriate when the risk of bleeding is excessive.

e. Atrial fibrillation post-cardiac surgery. Atrial fibrillation is a common sequela to cardiac surgery, occurring in approximately 25% of patients.

i. Prophylactic treatment

(a) β-Blockade administered preoperatively is associated with a 77% reduction in relative risk of atrial fibrillation.

(b) Amiodarone administered orally preoperatively, or IV postoperatively, has been associated with reductions in the frequency of atrial fibrillation.

(c) Temporary atrial pacing post-cardiac surgery has also been associated with a decrease in the incidence of postoperative atrial fibrillation.

(d) In general, all patients undergoing cardiac surgery should receive prophylactic β-blockade, and those especially at high risk (older age, prior history of atrial fibrillation, mitral valve surgery) may be considered for prophylactic amiodarone therapy.

ii. Management of atrial fibrillation following cardiac surgery

(a) Unstable patients require urgent cardioversion.

(b) Stable patients usually require rate control.

(c) Rate control and anticoagulation are appropriate for most patients; a large proportion of patients will convert spontaneously.

B. Atrial flutter

1. Usually macroreentry with a single wave-front propagating around the tricuspid annulus, most commonly up the interatrial septum and down the right atrial free wall, anterior to the crista terminalis, and back across the isthmus between the inferior vena cava and tricuspid annulus (Fig. 38-4E).

2. Electrocardiogram (ECG) demonstrates typical flutter wave morphology, a slowly down-sloping initial portion followed by a sharp upward deflection toward the baseline.

3. The clinical presentation and management of atrial flutter are very similar to those of atrial fibrillation. However, rate control can be more difficult to achieve and radiofrequency catheter ablation is more effective for atrial flutter.

4. Acute treatment

a. Rate control, especially before attempting chemical cardioversion.

b. Typical atrial flutter is amenable to cure by catheter ablation. The narrow isthmus of atrium between the tricuspid annulus and inferior vena cava can be interrupted by a line of ablation with a high success rate and rare complications.

c. The risk of thromboembolism from atrial flutter is significant. Atrial flutter warrants anticoagulation in the same manner as for atrial fibrillation (see the preceding text).

C. AV nodal reentry tachycardia

1. AVNRT is the most common cause of rapid regular SVT, accounting for up to 60% of cases.

2. Paroxysmal rapid regular narrow complex tachycardia with heart rate often 150 to 250 beats per minute and P waves either buried within the QRS complex or visible at its termination (r′ or S wave). A "Short RP" tachycardia.

3. Symptoms: palpitations, pounding in the neck, lightheadedness, shortness of breath, chest pressure, weakness, and fatigue.
4. Presents in third to fifth decade, with a 70% female preponderance.
5. Initiated by a critically timed premature complex that blocks in the antegrade "fast" AV nodal pathway, conducts down the "slow" AV nodal pathway, and then reenters retrogradely up the fast pathway (Fig. 38-4C).
6. Atypical AVNRT is caused by reentry antegrade down the fast pathway and retrograde through the slow pathway. A form of long RP tachycardia.
7. **Acute treatment**: see Section IV.
8. **Chronic treatment**
   a. Pharmacologic therapy: β-blockers, calcium blockers, class I and III agents.
   b. Catheter ablation is curative with low risk and no need for long-term drug therapy.

D. Atrioventricular reentry tachycardia

1. AVRT is a common form of regular SVT, accounting for up to 30% of patients.
2. During tachycardia, the QRS usually appears normal, and P waves, if visible, will be seen at the end of the QRS complex, within the ST segment, or within the T wave.
3. The mechanism of tachycardia is reentry; an atrioventricular AP is the retrograde limb and the AV node is the antegrade limb (Fig. 38-4B).
4. APs are congenital anomalies of the heart that allow conduction of excitatory impulses across the AV groove, bypassing the AV node.
5. **Acute treatment**: see Section IV.
6. **Chronic treatment:** same as for AVNRT.

E. Wolff–Parkinson–White syndrome

1. The Wolff–Parkinson–White syndrome (WPW) consists of a short PR interval and ventricular preexcitation (delta wave) due to an AP, with symptoms of palpitations.
2. The most common arrhythmia associated with WPW is AVRT.
3. The accessory tract may also participate in arrhythmogenesis by allowing rapid ventricular rates during atrial fibrillation. The AP may permit very rapid ventricular activation during atrial arrhythmias, rarely resulting in ventricular fibrillation.
4. Patients with WPW may be at risk for sudden cardiac death, although the overall risk is rather low, on the order of 0.15% per patient-year.
5. **Acute management**
   a. Fast preexcited ventricular response to atrial fibrillation (irregular rhythm with varying QRS complexes) should undergo electrical cardioversion.
   b. Stable preexcited atrial fibrillation may be treated with class Ia, Ic, or III drugs. IV ibutilide (1 to 2 mg IV) or procainamide (10 to 15 mg/kg IV) may be effective.
   c. During rapid preexcited atrial fibrillation, AV nodal blocking drugs are contraindicated (digoxin, adenosine, calcium channel blockers, and β-blockers) due to the potential for more rapid ventricular rates.
   d. Treatment of AVRT in patients with WPW: as above.
   e. **Chronic therapy**
      i. Patients with symptoms or those in high-risk professions (e.g., airline pilots) should undergo curative catheter ablation.
      ii. Patients with a history of atrial fibrillation with rapid ventricular response or ventricular fibrillation should undergo catheter ablation.
      iii. Patients who are at low risk (intermittent preexcitation or sudden failure of preexcitation during increased atrial rates), yet who experience recurrent AVRT may be treated similarly to patients

with concealed APs or AV node reentry tachycardia. Catheter ablation of the AP causing WPW offers a high-success rate and a low-complication rate.

F. Ectopic atrial tachycardia

1. Ectopic atrial tachycardia most likely occurs as a result of abnormal automaticity or triggered activity within the atrium and may be more likely to be associated with structural heart disease than is AVNRT or AVRT.
2. Narrow complex tachycardia with an RP interval that is usually, but not always, longer than the PR interval, depending on AV nodal conduction properties.
3. The P wave morphology may or may not be visibly different from sinus.
4. Ectopic atrial tachycardia may occur in short runs, may be sustained, or even may be incessant.
5. May be associated with underlying disease (coronary artery disease, myocardial infarction, ethanol ingestion, hypoxia, theophylline toxicity, digitalis toxicity, or electrolyte abnormalities).
6. **Acute treatment**
   - **a.** β-Blockade
   - **b.** Calcium channel blockade (nondihydropyridine calcium channel blockers)
   - **c.** Class Ia and Ic antiarrhythmic drugs (with AV nodal blockade), amiodarone.
7. **Chronic treatment**
   - **a.** AV nodal blocking agents and antiarrhythmic agents, as above.
   - **b.** Catheter ablation is a viable option for treatment of ectopic atrial tachycardia.

G. MAT

1. MAT is thought to be caused by abnormal automaticity or triggered activity and may be triggered by hypoxia, elevated sympathetic tone, hypokalemia, hypomagnesemia, or theophylline.
2. It is recognized by a rapid atrial rhythm with at least three P wave morphologies and variable ventricular response.
3. **Acute treatment**
   - **a.** β-blockade: caution is required in patients with reactive airways disease.
   - **b.** Calcium channel blockers may be effective and are the treatment of choice in patients with known reactive airways disease.
   - **c.** Underlying triggers must be addressed, including oxygenation, CO_2 clearance, magnesium and potassium repletion, and avoidance of methylxanthine derivatives (e.g., theophylline).

VI. CONCLUSIONS

SVTs frequently complicate acute medical illness and uncommonly cause severe illness. An organized approach to patients presenting with narrow complex tachycardias facilitates accurate diagnosis and thereby guides therapy. Most SVTs can be medically managed, although DC cardioversion is a highly effective means of restoring sinus rhythm in the unusual circumstance that more conservative measures fail to implement or that time does not permit. Atrial fibrillation is the most common SVT and can usually be managed with a combination of pharmacologic therapy, including anticoagulation and treatment aimed at contributing causes.

Suggested Reading

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TEMPORARY CARDIAC PACING

David D. Spragg, Glenn R. Meininger, and Hugh G. Calkins

39

I. GENERAL PRINCIPLES

A. Background

1. Pacing options
   - a. Transcutaneous
     - i. Primarily used for protection in patients at risk for high-grade atrioventricular (AV) block
     - ii. Currently with multifunctional capabilities including sensing; can be used for overdrive pacing
     - iii. Limitations
       - (a) Patient discomfort
       - (b) Poor capture (particularly with obese patients)
       - (c) Large stimulus artifacts
   - b. Transvenous
     - i. Supplanted transcutaneous pacing given ease of use and less patient discomfort
2. Algorithm for managing patients with bradycardia (Fig. 39-1)

II. INDICATIONS

A. Overview

1. The indications for temporary pacing in the setting of an acute myocardial infarction (MI) have been well defined and are outlined in a recent consensus guideline from the American Heart Association and the American College of Cardiology (AHA/ACC).
2. No similar guidelines are available for temporary cardiac pacing for other conditions causing bradycardia (i.e., infection, electrolyte abnormalities, drug reactions).
3. Decision to initiate temporary pacing involves three considerations (Tables 39-1 and 39-2):
   - a. Is temporary pacing indicated?
   - b. Method of pacing (transvenous vs. transcutaneous)?
   - c. What is the end point? Should permanent pacing be considered?
     - i. Of patients needing temporary pacing, 50% require permanent pacing before discharge.
     - ii. Transient indications commonly include MI, infection, or overmedication.

B. Scope of therapy

1. Bradyarrhythmias
   - a. Most common indication is symptomatic bradycardia that is unresponsive to pharmacologic therapy
   - b. Classifications
     - i. Disordered impulse formation (i.e., sinus node dysfunction)
     - ii. Disordered impulse propagation (i.e., conduction block)
2. Tachyarrhythmias
   - a. Prevention or termination of supraventricular tachycardia (SVT) or ventricular tachycardia (VT)

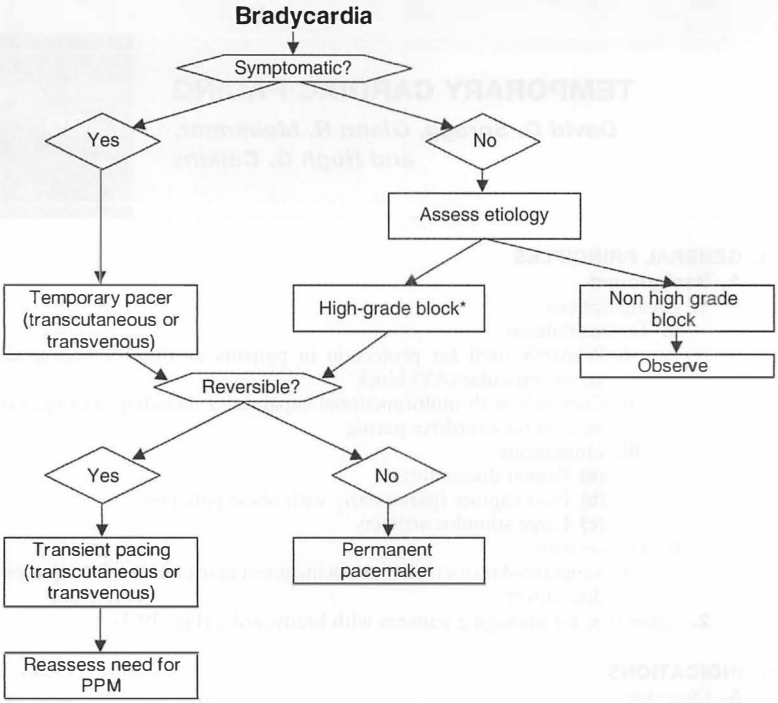

Figure 39-1. Algorithm for management of bradycardia unresponsive to pharmacologic therapy. *High-grade block includes those listed in Table 39-1 — Class I indications. PPM, permanent pacemaker.

- **b.** Rarely used in clinical practice due to efficacy of medications and increased prevalence of implantable cardioverter defibrillators (ICDs)
- **c.** Many reentrant rhythms are susceptible to pace termination
  - **i.** SVT (AVNRT, accessory pathway mediated tachycardia)
  - **ii.** VT (scar mediated)
- **d.** No role in management of ventricular fibrillation (VF) or triggered VT
- **e.** Prevention of triggered arrhythmias (i.e., *torsade de pointes*)
  - **i.** Shortening of QT interval with pacing to reduce risk of polymorphic VT.

3. MI (Table 39-1)

- **a.** Ischemia/infarction of the conduction system
  - **i.** Revascularization is primary management, particularly when AV nodal or fascicular blood supply is compromised
    - **(a)** Inferior ischemia (AV nodal blood supply)
    - **(b)** Anterior ischemia (disruption of fascicular blood supply)
  - **ii.** Prognosis
    - **(a)** Depends on the extent of underlying ischemia and left ventricular (LV) function.
    - **(b)** Death is rare from complete heart block (CHB).

TABLE 39-1 ACC/AHA Guidelines for Transcutaneous and Transvenous Pacing in Acute Myocardial Infarction*

Placement of transcutaneous patches and active (demand) transcutaneous pacing	
Class I	Sinus bradycardia (<50 bpm) with systolic BP <80 mm Hg unresponsive to drug therapy
	Mobitz type II second-degree AV block
	Third-degree heart block
	BBBB (alternating RLBB and LBBB)
	Newly acquired or age-indeterminate LBBB, RBBB and LAFB, or RBBB and LPFB
	RBBB or LBBB and first-degree AV block
Class II	Stable bradycardia with systolic BP >90 mm Hg or hemodynamic compromise responsive to drug therapy
	Newly acquired or age-indeterminate RBBB
Class III	Uncomplicated acute MI without evidence of conduction system disease
Temporary transvenous pacing in setting of acute myocardial infarction	
Class I	Asystole
	Symptomatic bradycardia (sinus bradycardia with hypotension, or type I second-degree AV block with hypotension unresponsive to atropine)
	BBBB (alternating BBB or RBBB with alternating LAFB/LPFB) any age
	New or indeterminate-age bifascicular block (RBBB with LAFB or LPFB, or LBBB) with first-degree AV block
	Mobitz type II second-degree AV block
Class IIa	RBBB and LAFB or LPFB (new or indeterminate)
	RBBB with first-degree AV block
	LBBB, new or indeterminate
	Incessant VT, for atrial or ventricular overdrive pacing
	Recurrent sinus pauses (>3 s) not responsive to atropine
Class IIb	Bifascicular block of indeterminate age
	New or age indeterminate isolated RBBB
Class III	First-degree heart block
	Type I second-degree AV block (Wenkebach) with normal hemodynamics
	Accelerated idioventricular rhythm
	BBB or fascicular block known to exist before acute myocardial infarction

BP, blood pressure; LBBB, left bundle branch block; RBBB, right bundle branch block; AV, atrioventricular; BBBB, bilateral bundle branch block; LAFB, left anterior fascicular block; LPFB, left posterior fascicular block; ventricular tachycardia.

*(Adapted from Ryan TJ, Antman EM, Brooks NH, et al. Update of ACC/AHA guidelines for the management of patients with acute myocardial infarction: executive summary and recommendations. *J Am Coll Cardiol* 1999;34:890–911.)

- **b.** Predicting risk of conduction block
  - **i.** Lamas scoring system based on simple electrocardiographic (ECG) variables
  - **ii.** One point each
    - **(a)** First-degree AV block
    - **(b)** Second-degree AV block
    - **(c)** Left anterior fascicular block (LAFB) or left posterior fascicular block (LPFB)
    - **(d)** Right bundle branch block (RBBB)
    - **(e)** Left bundle branch block (LBBB)

TABLE 39-2 Indications for Transvenous Pacing in the Absence of Myocardial Ischemia

Bradyarrhythmias
Asystole
Second- or third-degree AV block with hemodynamic compromise or syncope at rest
Complete heart block secondary to structural heart disease
Symptomatic sinus bradycardia
Prolonged sinus pauses (>3 s)
Tachyarrhythmias
Ventricular tachycardia secondary to bradycardia *torsade de pointes* associated with structural heart disease, metabolic abnormalities, or drug effects
Ventricular tachycardia unresponsive to medical therapy
Supraventricular tachycardia unresponsive to medical therapy
Prophylaxis for procedures or conditions which may promote bradycardia
General anesthesia with concomitant conduction block
Second- or third-degree AV block
Intermittent second- or third-degree AV block
First-degree AV block with bifascicular block
First-degree AV block with LBBB
Cardiac surgery
Tricuspid valve surgery
Ventricular septal defect closure
Ostium primum repair
Surgical procedures requiring permanent pacemaker deactivation
Percutaneous coronary intervention with associated bradycardia
Right heart catheterization in a patient with associated LBBB
Cardioversion with sick sinus syndrome
New AV block with endocarditis before cardiac surgery
Lyme carditis with associated conduction block
Electrophysiology studies

Not recommended for temporary pacing. Sinus node disease without hemodynamic compromise or syncope at rest. AV, atrioventricular; LBBB, left bundle branch block.

- **iii.** Score
  - **(a)** 0: Less than 4% risk of developing CHB
  - **(b)** 1: 12%
  - **(c)** 2: 28%
  - **(d)** 3: 45%

III. PROCEDURE

A. Equipment

1. Transcutaneous
   - **a.** External electrode pads
   - **b.** External pulse generator
2. Transvenous
   - **a.** Balloon-tipped electrode catheter
     - **i.** Platinum or gold tipped catheters
   - **b.** External pulse generator, power source

B. Technique

1. Transcutaneous
   - **a.** Electrode placement (anteroposterior or anterolateral)

i. Malpositioning may create problems
(a) Excessive skeletal muscle contraction
(b) Increased output requirements
(c) Increased patient discomfort
ii. Output ranges 0 to 140 mA
iii. Output is increased until a pacer stimulus captures
iv. Programmed to either primary pacing or demand only
v. Threshold is determined (typically 40 to 70 mA)
vi. Higher outputs improve capture, but associated with pain and skin injury

b. Pacing rate is determined
i. Consideration of rate based on need for protection of symptomatic bradycardia

c. Length of pacing
i. Pacing and sensing should be assessed daily, including measurement of threshold
ii. Observe for signs of infection

2. Transvenous
a. Site (subclavian, internal jugular, brachial, or femoral veins)
b. Fluoroscopy is helpful in positioning, but not necessary
c. Electrode catheter placement (Table 39-3)
i. Ensure that catheters are functioning appropriately
ii. Test the balloon integrity by inflating to the recommended volume (3 cc in most balloons)
iii. Connect the V1 surface lead to the distal electrode to provide continuous intravenous and intracardiac recordings
iv. Advance the pacing catheter into the sheath (approximately 15 cm)
v. Inflate the balloon
vi. Observe the ECG while advancing the catheter
vii. Advance to the right ventricular (RV) apex
viii. Deflate the balloon
ix. Watch for "injury current"
x. Determine pacing threshold (Note: threshold can be affected by ischemia, hyperkalemia, hypoxia, and medications.)

d. Pacing mode
i. Synchronous or asynchronous (fixed)
ii. Ventricular demand pacemaker (VVI) most common mode to manage bradycardia
iii. Determining sensitivity
(a) Lower sensitivity risk of oversensing ECG artifact and inappropriate suppression of pacing
(b) Higher sensitivity risk of inappropriate pacer firing and possibility of pacing on a T wave precipitating polymorphic VT

C. Efficacy

1. Transcutaneous
a. Safe and effective
b. Primary limitation is patient discomfort, which may improve with sedation
c. Similar achievable hemodynamic response compared with transvenous pacing (both in measured cardiac output and blood pressure (BP) augmentation)

2. Transvenous
a. High procedural success
b. Offers a low output with minimal discomfort
i. No skeletal muscle capture with pacing

TABLE 39-3 Bedside Positioning of a Temporary Electrode Catheter

Setup
Sterile preparation (gowns, gloves, masks, drape, hat)
Equipment (pacing electrode catheter, pulse generator, surface electrodes, sheath)
Connections
V1 surface electrode connects to distal electrode
Proximal electrode catheter connects to positive pole of pulse generator

Testing components
Inflate balloon to test integrity
Document V1 recordings when inserting electrode catheter into the sheath

Procedure
Carefully advance electrode catheter 15 cm and inflate balloon
Observe V1 transition with advancement of catheter
Atrial (p wave) dominant
Ventricular (QRS) dominant
Injury current
Stop advancing once injury current is detected

Pacing preparation
Confirm proximal electrode is connected to positive pole of pulse generator
Disconnect distal electrode from V1 surface lead and connect to the negative pole of the pulse generator

Pacing
Attempt pacing at 10 mA with the highest sensitivity
Observe capture
Determine thresholds and set output 1–2 mA above threshold (generally 3 mA)

Postprocedure
Document distance electrode is within the sheath
Confirm position with a chest radiograph
Routine care of pacemaker and site, including
Pacing parameters (threshold, rate, sensitivity, output) skin site (observing for infection)

D. Complications
1. Transcutaneous
   a. Local discomfort
      i. Temporary erythema at the contact site of the electrodes
   b. Skin injury limited due to
      i. Improved electrode pads
2. Transvenous
   a. Low risk
   b. Complication rate 13% to 18% (includes VT, VF, infection, pericarditis, and cardiac perforation); rare: local thrombus
   c. Component malfunction is rare (Table 39-4)
   d. Benefit of prophylactic antibiotics with permanent pacing systems, but less well established with the temporary systems and only routinely used if sterile technique is broken or suspected infection

E. Contraindications
1. Asystolic arrest victims
   a. No survival benefit from either transcutaneous or transvenous pacing

TABLE 39-4 Troubleshooting

Capture
- Loss of capture
  - Loose connections
  - Electrode catheter malposition
  - Increased myocardial stimulation threshold
  - Cardiac penetration or perforation
  - Lead fracture
  - Pulse generator malfunction (including improperly charged)

Sensing
- Loss of sensing
  - Inadequate intracardiac signal
  - Lead malposition
  - Spontaneous complexes falling within refractory period of generator
  - Generator malfunction
  - Lead fracture
- Undersensing intracardiac signals
- Etiology
- Inadequate signal voltage
- Slow rate of change of voltage (slew)
- Prolonged signal duration
- Clinical circumstances
  - Acute myocardial infarction and/or ischemia
  - Poor electrode position
  - Impulse originating in ventricular tissue
  - Pacemaker component failure
- Oversensing
  - P waves
  - T waves
  - Electromagnetic interference
  - Myopotentials
  - False signals generated from extension cables

IV. POSTPROCEDURE CONSIDERATIONS

A. Complications. Low complication rate, generally limited to local discomfort with transcutaneous pacing.

B. Monitoring. The patient needs to be monitored in an intensive care setting while a temporary pacing system is in place.

Suggested Reading

Bing OH, McDowell JW, Hantman J, et al. Pacemaker placement by electrocardiographic monitoring. *N Engl J Med* 1972;287(13):651.
Intracardiac electrocardiogram recordings during positioning of a temporary pacing lead.

Donovan KD, Lee KY. Indications for and complications of temporary transvenous cardiac pacing. *Anaesth Intensive Care* 1985;13(1):63–70.
Prospective survey of 153 transvenous pacing lead insertions, with limited complications (7% serious complications, but no deaths), identifying transvenous pacing as a safe and effective treatment for bradyarrhythmias and certain tachyarrhythmias.

Gregoratos G, Cheitlin MD, Conill A, et al. ACC/AHA Guidelines for implantation of cardiac pacemakers and antiarrhythmia devices: executive summary—a report of the American College of Cardiology/American Heart Association Task Force Practice Guidelines (Committee on Pacemaker Implantation). *Circulation* 1998;97(13):1325–1335.
Extensive literature review and guidelines, including ACC/AHA class I, II, and III recommendations for pacing.

Hynes JK Jr, Holmes DR, Harrison CE. Five-year experience with temporary pacemaker therapy in the coronary care unit. *Mayo Clin Proc* 1983;58(2):122–126.
Clinical course of 1,022 patients receiving temporary transvenous pacing with the right internal jugular approach, associated with the lowest complication rate.

Lamas GA, Muller JE, Turi ZG, et al. A simplified method to predict occurrence of complete heart block during acute myocardial infarction. *Am J Cardiol* 1986;57(15):1213–1219.
Report of 698 patients, status-post myocardial infarction, who were analyzed, and predictors for the development of complete heart block were reported, namely referring to first-degree atrioventricular block, Mobitz I and II, atrioventricular block, left anterior fascicular block, left posterior fascicular block, right bundle branch block, and left bundle branch block.

Silver MD, Goldschlager N. Temporary transvenous cardiac pacing in the critical care setting. *Chest* 1988;93(3):607–613.
Description of indications and complications associated with placement of transvenous pacing leads.

PERMANENT PACEMAKERS AND ANTIARRHYTHMIC DEVICES

40

Carl R. Reynolds and Michael R. Gold

I. PERMANENT PACEMAKERS (PPMs)

- **A.** General principles
  - **1.** Pacemaker nomenclature (Table 40-1)
  - **2.** Current pacemaker designs
    - **a.** Most current devices have both right atrial (RA) and right ventricular (RV) leads (dual chamber, or DC)
      - **i.** Allows sensing and tracking capabilities
      - **ii.** Able to mimic normal cardiac physiology with sequential atrial to ventricular (A–V) pacing and less atrial fibrillation (AF) versus RV-only devices
    - **b.** Biventricular (Bi-V) devices place an additional lead for left ventricle (LV) pacing
- **B.** Indications
  - **1.** DC
    - **a.** Multiple randomized, controlled trials (RCTs) show a reduction of AF and better quality of life (QOL)
      - **i.** Conduction system disease with high risk of progression to life-threatening bradycardia
      - **ii.** Bradycardia with symptoms
      - **iii.** Profound bradycardia without symptoms
      - **iv.** Sarcoidosis and high-grade second degree atrioventricular block (AVB)
      - **v.** Cardiac transplant, usually for sinus node dysfunction
      - **vi.** Pause-dependent ventricular tachycardia (VT), especially with congenital long-QT syndrome
      - **vii.** AF with sinus node dysfunction
    - **b.** May be useful in some cases, but prospective data weak
      - **i.** Hypertrophic obstructive cardiomyopathy (HOCM)
      - **ii.** Vasovagal syncope
  - **2.** Cardiac resynchronization therapy (CRT): Bi-V pacing
    - **a.** Reduces mortality/hospitalization (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure [COMPANION], Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure [CARE-HF]) if
      - **i.** New York Heart Association (NYHA) class III–IV heart failure
      - **ii.** Ejection fraction (EF) <35%
      - **iii.** QRS duration >120 ms
    - **b.** Other trials, including Multicenter InSync Randomized Clinical Evaluation (MIRACLE), showed improved QOL, exercise tolerance, and reverse remodeling with CRT
- **C.** Procedure
  - **1.** Placed percutaneously through the left subclavian/axillary vein, with pulse generator implanted in subcutaneous pocket over left pectoralis muscle
  - **2.** Strict sterile technique observed to prevent infection
  - **3.** Leads placed in RA appendage and RV apex/interventricular septum
  - **4.** CRT: third lead in coronary sinus (over LV lateral wall).

TABLE 40-1 Pacemaker Nomenclature Codes

First letter = chamber(s) sensed: A or V
Second letter = chamber(s) paced: A or V
Third letter = what the device does with the sensed information: O, I, or D
Fourth = rate responsiveness: O or R
Examples
- VOO
- VVI
- AAI
- DDD
- DDDR

CRT
Pacing in both ventricles, aka BiV pacing
CRT-P: device with pacing only function
CRT-D: device with BiV pacing and ICD capabilities

V, ventricle; A, atrial; D, dual (A and V/pace and inhibit); I, inhibit; R, rate responsiveness; O, does nothing; VOO, ventricular asynchronous; VVI, ventricular inhibited; AAI, atrial inhibited; DDD, dual chamber pacing and sensing, both triggered and inhibited mode; DDDR, AV concordance with physiologic response; CRT, cardiac resynchronization therapy; BiV, Biventricular; ICD, implantable cardioverter-defibrillator.

D. Postprocedure considerations
- **1.** Complications
  - **a.** Immediate
    - **i.** Pneumothorax/hemothorax
    - **ii.** Pocket hematoma (increased risk if anticoagulation, heparin > coumadin)
    - **iii.** Pocket infection
    - **iv.** Lead infection: usually result of pocket infection if soon after implant
  - **b.** Immediate to chronic
    - **i.** Device malfunction (very rare with modern devices).
    - **ii.** Lead fracture/malfunction: Plain x-ray usually may detect; presents as loss of capture and increased impedance—occurs at point of mechanical stress.
    - **iii.** Lead insulation break: Invisible on x-ray; presents as oversensing (inappropriate inhibition) and decreased impedance.
    - **iv.** Electromagnetic interference: Electrocautery in surgical procedures causes inhibition; set device to nonsensing mode, for example, VOO, DOO, if pacemaker dependent; can be done through reprogramming or with magnet overlying device.
    - **v.** Pacemaker infection: complication of bacteremia.
    - **vi.** Pacemaker syndrome: RV pacing negatively impacts hemodynamics→intermittent ventricular inhibited (VVI) pacing, loss of A–V synchrony compromises blood pressure; contraction of atria on closed atrioventricular (AV) valve seen on physical exam as "cannon a-wave."
    - **vii.** Upper rate-limit pacing: with rapid intrinsic atrial rates, for example, atrial flutter, multifocal atrial tachycardia (MAT), etc., pacemaker tracks fast atrial rate, paces at same fast rate in ventricle(s); mode switching prevents this by changing to nontracking mode when atrial rate exceeds set upper rate limit.

viii. Pacemaker-mediated tachycardia (PMT): Ventricle(s) paced→retrograde impulse→atrial contraction from retrograde signal→sensed by the atrial lead→sensed atrial impulse tracked→second ventricular output created→second impulse goes retrograde to atria→cycle repeats; special algorithms to interrupt upper limit tracking prevents PMT.

ix. Device erosion: occurs at point of skin tension, especially in thin patients and associated with infection and "twiddler's syndrome" (habitual manipulation of device by patient).

2. Monitoring
   a. Immediate
      i. Chest radiography (chest x-ray [CXR]; two views) after implant to confirm lead placement and rule out other complications
      ii. Programming to individualize/optimize therapy and minimize ventricular pacing
   b. Immediate to chronic
      i. Pacemaker parameters routinely interrogated after implantation and at followup.
      ii. Patients seen at 2 to 6 weeks and every 6 to 12 months thereafter with transtelephonic monitoring between visits.
      iii. Battery depletion: expected life is 6 to 10 years.
   c. Programming
      i. For DC PPM, important to minimize RV pacing→reduces incidence of AF and congestive heart failure (CHF). Achieved by extending AV delay.
      ii. AV and interventricular pacing (VV) interval optimizations recognized as increasingly important for CRT.
      iii. AF suppression algorithm paces atria to suppress premature atrial contractions (PACs) and reduce substrate for AF initiation.

II. IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

A. General principles
   1. Defibrillation threshold (DFT): minimal energy required for defibrillation
   2. Sensing: algorithm automatically adjusts to detect ventricular fibrillation (VF), but avoid inappropriate shocks (see below, Section II.,D.,2.,b)
   3. All current implantable cardioverter defibrillators (ICDs) have PPM capabilities (VVI, DC, or BiV)
   4. Defibrillation: application of electrical shock to tachycardia to reset action potential and restore sinus rhythm
   5. Antitachycardia pacing (ATP): pacing faster than arrhythmia to overdrive and terminate

B. Indications
   1. Good evidence from multiple RCTs
      a. Primary prevention:
         i. Cardiomyopathies (Table 40-2)
         ii. Clinical scenarios: syncope with clinically relevant sustained VT or VF on electrophysiology study (EPS)
      b. Secondary prevention (previous history of VT or VF): multiple prospective trials demonstrate robust and reproducible effect of improved survival compared with drug therapy (Antiarrhythmics versus Implantable Defibrillators [AVID], Cardiac Arrest Study Hamburg [CASH], Canadian Implantable Defibrillator Study [CIDS]).
         i. Post cardiac arrest
         ii. Sustained monomorphic VT if reversible causes treated and on good medical therapy.

TABLE 40-2 Ejection Fraction Requirements for ICD Implantation by Cardiomyopathy Type[a]

Ischemic	
Current guideline requirements for ICD	**Source trial(s)**
EF <35%, NYHA ≥II	SCD-HeFT, MADIT-II
EF <30%, NYHA I	MADIT-II
EF <40%, NSVT and inducible VF or sustained VT at EPS	MADIT MUSTT
Nonischemic	
Clinical requirement	**Source trial**
EF ≤35%, NYHA ≥II	SCD-HeFT

[a]EF on β-blocker and ace-inhibitor/angiotensin II receptor blocker (ARB) ≥6 weeks and patient must be at least 40 days post MI unless positive EPS.
ICD, implantable cardioverter-defibrillator; EF, ejection fraction; NYHA, New York Heart Association; SCD, sudden cardiac death; HeFT, Heart Failure Trial; MADIT, Multicenter Automatic Defibrillator Implantation Trial; NSVT, nonsustained ventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; EPS, electrophysiologic study; MUSTT, Multicenter Unsustained Tachycardia Trial.

2. May be useful in some cases, but prospective data weak
   a. Arrhythmogenic RV dysplasia (ARVD)
   b. Brugada syndrome, congenital long QT, and other genetic arrhythmia syndromes (Defibrillator versus β-Blockers for Unexplained Death in Thailand [DEBUT] study)
   c. Syncope with inducible sustained VT or VF
   d. HOCM with severe septal hypertrophy or sudden cardiac death (SCD) in close relative

C. Procedure
   1. Similar to PPM implantation
   2. If patient has a PPM, can upgrade to PPM/ICD or BiV/ICD in original pocket

D. Postprocedure considerations
   1. Programming—the following are adjustable:
      a. Rate over which VT should be paced or shocked (VT zone)
      b. Number of ATP trials before defibrillation attempted
      c. Tiered therapy: ATP, then varied energy of shocks
      d. Therapies off if patient made comfort care only or transiently during a surgical procedure
   2. Complications
      a. Immediate: similar to pacemaker complications
      b. Intermediate to long term: similar to PPM with additional concern of oversensing (may lead to inappropriate therapies shocks/ATP). Potential causes:
         i. RV pacing always bipolar in ICDs (minimizes oversensing)
         ii. supraventricular tachycardia (SVT)/AF
         iii. Prominent T or P waves
         iv. Lead insulation break (increased levels of "noise")
         v. Pacemaker artifacts
         vi. Myopotentials, especially diaphragmatic
         vii. Electromagnetic interference (e.g., electrocautery, electronic surveillance devices, cellular telephones)

- **c.** magnetic resonance imaging (MRI) and PPM/ICD
  - **i.** Damage to lead/myocardial interface possible, increased DFT and impedance

3. Maintenance
   - **a.** DFT testing at implantation, then may increase after
     - **i.** Antiarrhythmic drug initiation (especially amiodarone): DFT testing recommended 4 to 6 weeks after starting drug.
     - **ii.** Other changes in substrate, including worsening EF or LV diameter, worsened ischemic disease, or electrolyte abnormalities.
   - **b.** Pulse generator changes every 4 to 6 years

Suggested Reading

Abraham WT, Fisher WG, Smith AL, et al. MIRACLE Study Group. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845–1853.
RCT of 453 patients with moderate to severe CHF and an EF ≤35% and QRS ≥ 130 msec randomized to CRT or no CRT; optimum medical therapy given to both groups. The CRT arm had improved 6 min walk test, functional status, QOL, and EF. They also required less hospitalization.

The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;337:1576–1583.
First large, RCT of ICDs as first-line therapy for secondary prevention of sudden death. Compared with antiarrhythmic therapy (primarily amiodarone), ICDs were associated with better survival.

Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med.* 2005;352:225–237.
RCT of 2521 patients with moderately symptomatic CHF and EF ≤35% randomized to optimum medical therapy (OMT) vs. OMT and ICD. The ICD arm had a significant reduction in all-cause mortality over five year follow-up. First major RCT to demonstrate ICD benefit in non-ischemic cardiomyopathy.

Beshai JF, Grimm RA, Nagueh SF, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med* 2007;357:2461–2471.
RCT of 172 patients with standard indication for ICD randomized to CRT or no CRT (control) for six months. The primary endpoint, the percentage of patients with an increase in VO_2 max of at least 1.0 ml/kg/min, was reached only in the subgroup of patients with CHF and QRS >120 ms, further demonstrating that CHF patients without prolonged QRS do not benefit from resynchronization therapy.

Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure (COMPANION). *N Engl J Med* 2004;350:2140–2150.
RCT showing CRT reduces CHF hospitalization and cardiac death, but only when combined with backup ICD was total mortality reduced significantly.

Buxton AE, Lee KL, Fisher JD, et al. A RCT study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 1999;341:1882–1890.
Large RCT showing antiarrhythmic therapy with ICDs reduced sudden death and total mortality compared with nonantiarrhythmic medical therapy among patients with coronary artery disease, systolic dysfunction, nonsustained VT, and inducible VT.

Cleland JG, Daubert J, Erdmann E, et al. Effect of cardiac resynchronization on morbidity and mortality in heart failure (CARE-HF). *N Engl J Med* 2005;352:1539–1549.
CARE-HF randomized 813 patients with moderate or severe heart failure to standard medical therapy or medical therapy with CRT. All-cause mortality was less with CRT, and QOL, LV EF, and symptoms all improved in the CRT arm.

Connolly SJ, Gent M, Roberts RS, et al. Canadian Implantable Defibrillator Study (CIDS): a RCT trial of the implantable defibrillator against amiodarone. *Circulation* 2000;101:1297–1302.
Showed trend toward reduction in total mortality and reduction of SCD with ICDs vs amiodarone among patients with VT, VF, or syncope and inducible VT.

Connelly SJ, Kerr CR, Gent M, et al. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. *N Engl J Med* 2000;342:1385–1391.
Ventricular pacing did not significantly increase mortality compared with dual chamber pacing, but incidence of AF was significantly higher in the VVI group.

The DAVID Trial Investigators. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator. *JAMA* 2002;288:3115–3123.
506 patients with EF of ≤40% and standard indication for ICD, randomized to either VVI backup pacing at 40/min or rate responsive, DDDR pacing at 70/min, followed for death or CHF exacerbation. Results showed dual chamber pacing may increase death/hospitalization for heart failure in patients with reduced EF.

Gold MR, Feliciano Z, Gottlieb SS, et al. Dual-chamber pacing with a short AV delay in congestive heart failure: a RCT study. *J Am Coll Cardiol* 1995;26:967–973.
The first RCT study of pacing in heart failure. Demonstrated that short atrioventricular delay pacing from the RV apex did not improve functional status or ejection fraction.

Lamas GA, Lee KL, Sweeney M, et al. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction (MOST). *N Engl J Med* 2002;346:1854–1862.
Among patients with sick sinus syndrome, dual-chamber pacing reduces the incidence of atrial fibrillation and pacemaker syndrome.

Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fractions. *N Engl J Med* 2002;346:877–883.
Primary prevention study showing that ICDs reduce mortality in patients with coronary artery disease and EF <30%.

Nademanee K, Veerakul G, Mower M, et al. Defibrillator versus β-blockers for unexplained death in Thailand (DEBUT). *Circulation* 2003;107:2221–2226.
86 survivors of sudden death randomized to propranolol or ICD. Over three years there were four deaths, all in medical therapy group. Seven subjects in ICD arm had recurrent VF and were effectively treated. DEBUT is a major early trial supporting ICD as an effective therapy for secondary prevention of SCD.

ACC/AHA/NASPE. Writing Committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices. *J Am Coll Cardiol* 2008;51:e1–e62.
Most recent guidelines for device-based therapy of Cardiac Rhythm Abnormalities.

EVALUATION OF THE LOW TO INTERMEDIATE RISK PATIENT WITH CHEST PAIN: CHEST PAIN CENTERS

41

Christopher M. Schneider and Marc A. Mickiewicz

I. GENERAL PRINCIPLES

A. Each year approximately 8 million patients present to US emergency departments (EDs) for chest pain.

1. Of 3 million patients discharged from the ED without presumed acute coronary syndrome (ACS), approximately 40,000 (1% to 2%) ultimately have an acute cardiac event.

2. Many patients with true ACS have atypical symptoms and normal or nondiagnostic electrocardiograms (ECGs) on initial presentation.

3. Routine inpatient admission of low[-]risk patients with chest pain is not cost[-]effective.

B. The ED-based chest pain center (CPC) concept (Fig. 41-1) addresses four important goals:

1. Early diagnosis and treatment of ACS

2. Reduction of inappropriate ED discharges

3. Reduction of unnecessary inpatient admissions

4. Development of community outreach programs for patients with possible symptoms of acute cardiac ischemia

C. In patients with low or intermediate risk for ACS, CPCs have driven a paradigm shift from the older concept of inpatient admission to "rule-out" acute myocardial infarction (AMI) to a period of ED observation to "rule-in" ACS.

II. CHEST PAIN: CPC DIAGNOSTIC EVALUATION

A. History and physical

1. Classic anginal history is obtained in less than one half of patients having an AMI.

2. Approximately 8% of patients with AMI have no chest pain.

3. Atypical symptoms of myocardial ischemia include dyspnea, syncope, weakness, and altered mental status.

4. Those patients with history typical for accelerating angina are at high risk and should be admitted for inpatient evaluation (excluded from CPC evaluation).

B. ECG

1. Nondiagnostic in most patients with ACS; provides a specific diagnosis in only 5% of patients.

2. If possible, always compare to a prior ECG.

3. Patients with ECG changes consistent with AMI (e.g., ST-elevation or new bundle branch block) are candidates for time sensitive interventions such as primary percutaneous coronary intervention or thrombolysis and are excluded from CPC evaluation.

4. Serial ECGs (at least 2) significantly enhance detection of both AMI and ACS (Fig. 41-2).

5. Nondiagnostic/normal ECGs may require further evaluation in CPC.

C. Cardiac biomarkers (Fig. 41-3)

1. Time-dependent release of serum cardiac biomarkers identifies myocardial necrosis, provides risk stratification, and can drive earlier medical therapy and consideration of invasive reperfusion

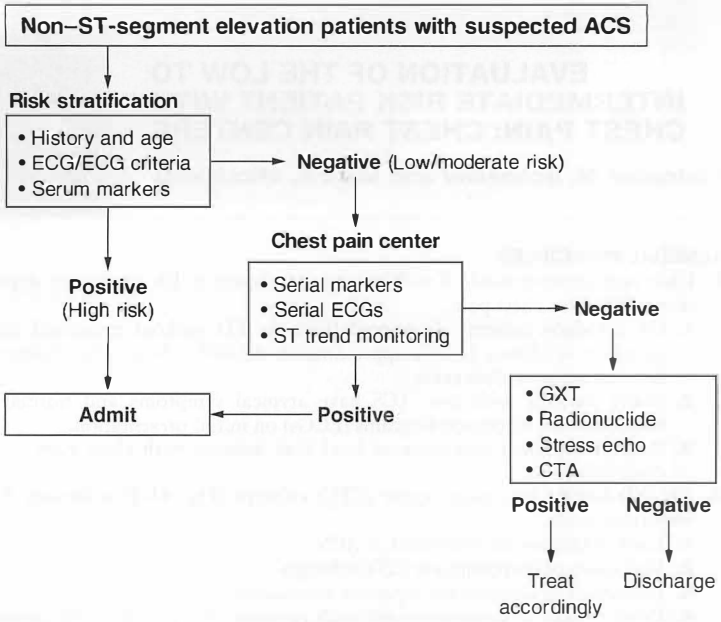

Figure 41-1. Generic chest pain center flow; ACS, acute coronary syndrome; ECG, electrocardiographic; GXT, graded exercise testing; CTA, computed tomographic angiography.

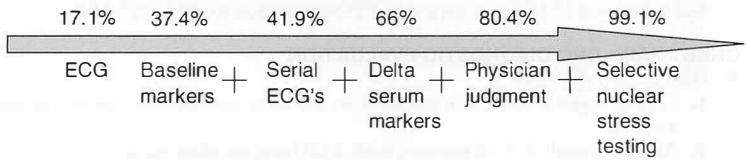

Figure 41-2. Incremental sensitivity for detecting 30-day acute coronary syndrome (ACS).

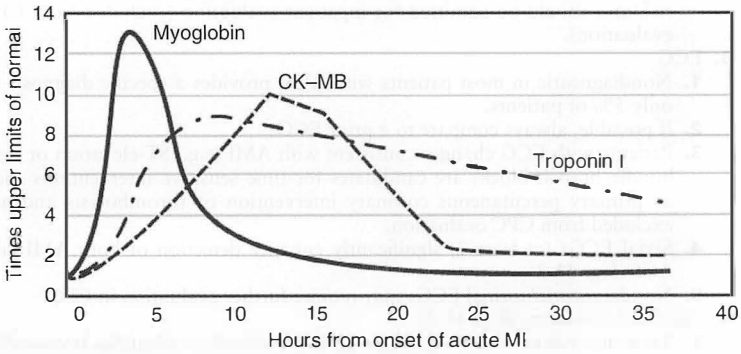

Figure 41-3. Kinetics of early serum markers. CK-MB, creatinine kinase-myocardial band; MI, myocardial infarction.

2. Rarely positive early in AMI. Serial sampling increases detection of both AMI and ACS.
3. Cardiac biomarkers
   a. Myoglobin: Earliest release marker of myocardial necrosis (initial rise at 2 hours, peak at 6 to 9 hours, return to baseline in 24 to 36 hours).
      i. Many false positives because it is found in both cardiac and skeletal muscle and accumulates in renal failure; its strength is based on a good negative predictive value.
      ii. A 2-hour change in myoglobin has been suggested as useful in excluding the possibility of myocardial necrosis, although its widespread use has been limited by concerns regarding sensitivity.
   b. Creatine kinase (CK): Typical rise 4 to 8 hours after onset of myocardial necrosis, peak at 12 hours, return to baseline in 48 hours
      i. Sensitive for detection of myocardial injury but not specific (found in both cardiac and skeletal muscle). Use of the myocardial band (MB) fraction, CK-MB, can greatly improve specificity. CK-MB only rises with AMI.
      ii. Single determinations are insensitive, but serial levels have been shown to be highly sensitive for AMI within the first 2 to 6 hours.
   c. **Cardiac** troponins. Release kinetics similar to CK-MB, but more sensitive for detection of myocardial necrosis and remain elevated in circulation for much longer time period.
      i. Troponin I (TnI) and T (TnT) remain elevated for up to 2 weeks after AMI.
      ii. Useful in delayed ED presentations of AMI.
      iii. Highly sensitive and moderately specific markers of myocardial cell damage.
      iv. Can be released during brief episodes of ischemia; therefore, troponin elevation may be encountered in situations where CK-MB is negative.
      v. A rise in a cardiac troponin now defines myocardial damage and should be included in all evaluations for ACS, alone or in combination with CK-MB or myoglobin.

D. Point-of-care cardiac marker testing
   1. Widely available, highly reliable, and may shorten the time to diagnosis of ACS and subsequent intervention.
   2. In the CHest pain Evaluation by Creatine Kinase-MB, Myoglobin, And Troponin I (CHeckmate) study, quantitative, near-patient, multimarker strategies identified more positive patients than single-marker, local laboratory testing and identified them earlier.

E. Rest nuclear imaging
   1. Patients with no perfusion defects on single-photon emission computed tomographic (SPECT) imaging during a period of chest pain have a low risk for subsequent cardiac events, and can be safely discharged from the ED.
   2. An elective outpatient stress scan is recommended for those with negative imaging.
   3. Sensitivity is best when injected during pain or within 2 hours of last pain.
   4. Cannot differentiate between ischemia and scar; therefore, patient must not have had a prior MI.

F. Provocative testing and cardiac imaging
   1. If serial serum marker determinations are negative, ST-segment monitoring unrevealing, and chest pain attributes unconvincing, CPC patients may proceed to provocative stress testing.
   2. Graded exercise testing (GXT)
      a. Excellent prognostic value and highly predictive of underlying coronary artery disease (CAD); limited by sensitivity.

   b. Positive GXT (horizontal or downsloping ST-segment depression of 1 mm or greater), accompanied by ischemic chest pain, results in hospital admission from the CPC.
   c. Normal GXT to an adequate workload after completion of observation and marker testing allows safe discharge.
3. Stress echocardiography and stress nuclear imaging
   a. Useful in patients unable to physically complete a GXT
   b. Enhance sensitivity for detection of CAD
   c. Added prognostic value for future cardiac events and CAD.
4. Computed tomographic angiography (CTA)
   a. Direct visualization of coronary arteries to assess for coronary CAD.
   b. High negative predictive value may help to rule-out ACS in low pretest risk population.
   c. Computed tomography of the chest with intravenous (IV) contrast allows possibility of simultaneously assessing for other causes of chest pain (pulmonary embolism, aortic dissection, pneumonia).
   d. Need more clinical research trials to fully clarify/establish role in the emergency department. Suggested Guidelines provided in Table 41-1.

G. CPC protocols
1. Multiple different protocols exist for triage and evaluation of the patient with suspected ACS. A representative example is provided in Figure 41-1. In general patients selected for CPC observation meet the following guidelines:
   a. Inclusion criteria: possible ACS and a nondiagnostic ECG.
   b. Exclusion criteria: ST-segment elevation or depression of 1 mm or more, unstable angina, or hemodynamic instability.

H. Rapid rule-out protocols
1. Some institutions have shortened their protocols to provide more rapid disposition
   a. Immediate GXT in patients with a nondiagnostic ECG, before obtaining results of cardiac enzymes, has been studied and suggested to be safe in low-risk patients.
   b. Other centers have shortened the interval between cardiac marker tests and are dispositioning patients after two sets of negative cardiac enzymes taken as early as 2 hours apart.

TABLE 41-1 Computed Tomographic Angiography Selection Criteria

Inclusion criteria	Exclusion criteria
Chest pain >5 min within the previous 24 h	Known CAD
No or nondiagnostic ECG changes	Age older than 60
Normal initial cardiac biomarkers	Elevated troponin or CK-MB
Sinus rhythm	ECG changes diagnostic of ischemia or infarction
Ability to perform a breathhold of 10–15 s	Hemodynamic or clinical instability
Meets radiology criteria for IV-contrast administration	Atrial fibrillation or markedly irregular rhythm
	Contraindication to β-blockers if heart rate >65

CAD, coronary artery disease; ECG, electrocardiogram; IV, intravenous.

ACKNOWLEDGMENTS

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Pulmonary Problems in the Intensive Care Unit

III

A PHYSIOLOGIC APPROACH TO MANAGING RESPIRATORY FAILURE

42

Mark M. Wilson and Richard S. Irwin

I. GENERAL PRINCIPLES

A. Respiratory failure is defined simplistically by arterial carbon dioxide tension ($Paco_2$) >50 mm Hg or arterial oxygen tension (Pao_2) < 50 to 60 mm Hg.

B. The efficiency of gas exchange is evaluated by measuring the Pao_2, the $Paco_2$, and the alveolar-arterial (A-a) Po_2 gradient on room air or the Pao_2/Fio_2 (fraction of inspired oxygen) ratio for patients on high Fio_2.

1. Pao_2. The normal value for Pao_2 depends on the age and body position of the patient:

In the upright position, $Pao_2 = 104.2 - 0.27 \times$ age (years)
In the supine position, $Pao_2 = 103.5 - 0.47 \times$ age (years)

2. $Paco_2$. The normal $Paco_2$ is 35 to 45 mm Hg and is unaffected by age or body position. Because CO_2 production does not vary widely even in critically ill patients, it can be generally assumed that $Paco_2$ will vary inversely with alveolar ventilation.

3. Pao_2–Pao_2 gradient. To help interpret a decrease in Pao_2, one must know the A-a gradient. The alveolar Po_2 (Pao_2) can be calculated from the simplified alveolar air equation:

$$Pao_2 = Pio_2 - Paco_2/R$$

At sea level and breathing room air the P_{IO_2}, the partial pressure of inspired O_2, can be assumed to be 150 mm Hg. R is the respiratory exchange ratio and is assumed to be 0.8.

After subtracting P_{aO_2}, the normal A-a gradient is 5 (in a 20-year old) to 10 (in a 35-year old) mm Hg and is a sensitive indicator of intrinsic lung disease. At any age, an A-a gradient exceeding 20 mm Hg should be considered abnormal. With an F_{IO_2} above 0.21, the A-a gradient becomes a less accurate measure of gas exchange efficiency.

4. **P_{aO_2}/F_{IO_2} ratio.** Used to estimate the severity of a gas exchange defect with patients receiving supplemental O_2. F_{IO_2} is expressed as a decimal. Values between 200 and 299 indicate moderate impairment with gas exchange (e.g., acute lung injury); values <200 indicate severe impairment and the presence of a major right-to-left shunt (e.g., acute respiratory distress syndrome).

II. PATHOPHYSIOLOGY

A. Hypoxemia

1. Five mechanisms can cause hypoxemia: low P_{IO_2}, hypoventilation, low ventilation–perfusion ($\dot{V}/\dot{Q}$) mismatch, right-to-left shunting, and diffusion impairment.
2. A low P_{IO_2} is generally seen only at high altitude.
3. Diffusion impairment alone is not the major cause of hypoxemia.
4. In the clinical setting, then, hypoventilation, low $\dot{V}/\dot{Q}$ mismatch, and right-to-left shunting or combinations of these are essentially the only important pathophysiologic causes of hypoxemia.
5. Hypoventilation, a decrease in alveolar ventilation for a given metabolic demand, results from a decrease in minute ventilation from extrapulmonary dysfunction. With no underlying abnormality of gas exchange, the A-a gradient, measured on room air, remains normal.
6. In areas of inadequate ventilation for a given level of perfusion (low $\dot{V}/\dot{Q}$ mismatch), pulmonary venous blood has a relative decrease in both P_{O_2} and percentage of oxyhemoglobin saturation. The result is a decreased P_{aO_2} and increased A-a gradient.
7. Right-to-left shunting refers to mixed venous blood going directly into the arterial circulation without having first been exposed to alveolar gas (from cardiac or great vessel, pulmonary vascular or pulmonary parenchymal conditions). When the shunted blood mixes with the rest of the arterial blood, it lowers the average O_2 content, and therefore the average P_{aO_2}. The A-a gradient is always increased.

B. HYPERCAPNIA

1. Three mechanisms can lead to an elevated P_{aCO_2}: breathing a gas containing CO_2, hypoventilation, and severe low $\dot{V}/\dot{Q}$ mismatch. Clinically, only the last two are important. Hypoventilation has already been discussed. In patients who cannot augment their alveolar ventilation (e.g., severe chronic obstructive pulmonary disease [COPD] with chronic hypercapnia), hypercapnia can worsen with fever or overfeeding because of an increase in tissue CO_2 production coupled with an impaired capacity to clear CO_2.
2. The major mechanism causing arterial hypercapnia in patients with severe intrinsic lung disease is severe low $\dot{V}/\dot{Q}$ mismatch. A substantially greater degree of low $\dot{V}/\dot{Q}$ mismatch must be present to cause arterial hypercapnia than to cause hypoxemia.
3. Although not a primary cause of hypercapnia, respiratory muscle overload (from increased work of breathing associated with severe lung derangement or fatigue) may result in a relative hypoventilation because of the inability to increase minute ventilation appropriately.

C. Respiratory acid–base disorders

1. Acid–base balance is assessed clinically from the arterial hydrogen ion (H^+) concentration. The ratio of the relative availability of acid versus base determines the H^+ concentration, as shown by the Henderson version of the Henderson–Hasselbalch equation:

$$H^+ = 24 \times (Paco_2 / HCO_3^-)$$

A pH of 7.40 corresponds to an H^+ concentration of 40 nanoequivalents/L and each change in pH of 0.01 units corresponds to an opposite deviation in H^+ concentration of 1 nanoequivalent/L when the pH is 7.28 to 7.45. Outside this range, it is still clinically useful to estimate the H^+ concentration in this manner because the estimated value will deviate from the true value by no more than 5% to 10%.

2. In primary respiratory acidosis, the $Paco_2$ is elevated because of respiratory system dysfunction. Under normal circumstances, an appropriate compensatory change (i.e., increase) will occur in the HCO_3^- level to help mitigate the effect on H^+ concentration. To estimate how long the $Paco_2$ has been elevated, the ratio of $\Delta H^+/\Delta Paco_2$ is computed. The kidneys gradually increase the HCO_3^- level to bring H^+ concentration back toward, but not to, normal. The $\Delta H^+/\Delta Paco_2$ ratios for acute and chronic respiratory acidosis are 0.8 and 0.3, respectively. When previous blood gas values are not available, assume the change in $Paco_2$ occurred from 40 mm Hg and pHa from 7.40 or H^+ 40 nanoequivalents.
3. The differential diagnosis of respiratory acidosis is the same as that of hypercapnic respiratory failure (Table 42-1). The therapeutic approach is also the same.
4. Primary respiratory alkalosis is defined by a decrease in $Paco_2$ with an accompanying compensatory decrease in HCO_3^-. The duration of respiratory alkalosis involves the same determination of $\Delta H^+/\Delta Paco_2$ ratios. The values for acute and chronic respiratory alkalosis are 0.8 and 0.17, respectively. A primary respiratory alkalosis may have a normal or an elevated A-a gradient. The differential diagnosis of respiratory alkalosis with an elevated A-a gradient is the same as that of hypoxemic respiratory failure (e.g., acute asthma, pneumonia, pulmonary embolism, pulmonary edema). The differential diagnosis of respiratory alkalosis with a normal A-a gradient includes central nervous system disorders, pregnancy, high altitude, severe anemia, hyperventilation, hepatic failure, and catecholamine, progesterone or thyroid hormone excess. The combination of an elevated anion-gap metabolic acidosis with an "overcompensated" respiratory alkalosis should alert the clinician to evaluate for salicylate intoxication.

III. DIAGNOSIS

A. To determine the cause of hypoxemia, one must evaluate the $Paco_2$, the A-a gradient, and occasionally the patient's response to 100% O_2.

B. During hypoventilation, the $Paco_2$ is always elevated, the A-a gradient is normal (20 mm Hg or less), and the decrease in Pao_2 is accounted for solely by the low PAo_2. If the patient is given 100% O_2 to breathe (rarely necessary), there will be a dramatic increase in Pao_2 (to more than 500 mm Hg).

C. During $\dot{V}/\dot{Q}$ mismatch and right-to-left shunting, the decreased Pao_2 is typically accompanied by an elevated A-a gradient. During $\dot{V}/\dot{Q}$ mismatch, the $Paco_2$ may or may not be elevated, whereas it is rarely elevated in right-to-left shunt. The Pao_2 in the patient with $\dot{V}/\dot{Q}$ mismatch shows a dramatic rise in response to 100% O_2 (to more than 500 mm Hg). The patient with right-to-left shunting shows minimal or, in severe cases, no response at all to 100% O_2.

D. Contrast echocardiography or quantitative nuclear medicine perfusion lung/brain/kidney scanning can be obtained to differentiate the right-to-left

TABLE 42-1 Causes of Hypercapnia and Their Pathophysiologic Mechanisms[a]

Site of abnormality	Disease	Mechanism
Pulmonary disorders of:		Severe ventilation–perfusion mismatch
Lower airways	Chronic obstructive pulmonary disease, asthma, cystic fibrosis	
Lung parenchyma	Environmental/occupational lung disease	
Pulmonary vasculature	Pulmonary embolism (rarely)[b]	
Extrapulmonary disorders of:		Hypoventilation
Central nervous system	Respiratory center depression due to drug overdose, primary alveolar hypoventilation, myxedema	
Peripheral nervous system	Spinal cord disease, amyotrophic lateral sclerosis, Guillain-Barré syndrome	
Respiratory muscles	Myasthenia gravis, polymyositis, severe hypophosphatemia	
Chest wall	Ankylosing spondylitis, flail chest, thoracoplasty	
Pleura	Restrictive pleuritis	
Upper airways	Tracheal obstruction, epiglottitis, adenoidal and tonsillar hypertrophy, obstructive sleep apnea	

[a]This table is not an exhaustive listing; it includes the more common causes for each involved compartment of the respiratory system.

[b]Because the drive to breathe is increased with pulmonary embolism, hypercapnea generally only occurs when the patient is unable to increase minute ventilation (e.g., patient with pulmonary embolism on controlled mechanical ventilation).

shunt of cardiac, great vessel, or pulmonary vascular origin from a pulmonary parenchymal cause. By echo, with cardiac, great vessel or pulmonary vascular shunting there will be too rapid a transit of contrast from the venous circulation into the left side of the heart and systemic arterial circulation indicative of a structural/anatomic defect. By nuclear medicine scanning, the percent of right-to-left nonpulmonary parenchymal shunt can be calculated by determining the percentage of counts that appear in the brain and kidneys.

E. With hypercapnic respiratory failure (Table 42-1), the A-a gradient may or may not be increased. Commonly, a disease process may affect oxygenation or ventilation through a combination of the mechanisms described earlier. See Chapter 46 for discussion of extrapulmonary causes of respiratory failure.

IV. TREATMENT

A. Respiratory failure is managed by combined supportive and specific therapies.

B. In hypoxemic respiratory failure, the major problem is a low Pa_{O_2}. If the mechanism is low $\dot{V}/\dot{Q}$ mismatch, supplemental O_2 will prove effective. If the disease process involves a diffuse pulmonary intraparenchymal shunt, as in the acute respiratory distress syndrome, mechanical ventilation with positive

end-expiratory pressure may be required in addition to supplemental O_2. If the problem is a right-to-left cardiac or pulmonary vascular shunt, supplemental O_2 alone will be of limited benefit; emphasis is on specific therapy (i.e., surgical repair of an atrial septal defect, obliteration of a pulmonary arteriovenous fistula).

C. The key initial decision in hypercapnic respiratory failure is whether or not the patient requires ventilatory support in the form of noninvasive positive-pressure ventilation or intubation and mechanical ventilation. In general, intubation should be strongly considered for patients with acute respiratory acidosis that has not rapidly responded to medical therapy or 1 to 2 hours of noninvasive ventilation in patients who can maintain their own airway effectively until medications have a chance to improve the patient's condition. The patient with a $\Delta H^+/\Delta PaCO_2$ ratio that signifies chronic respiratory acidosis should be followed closely, but these patients uncommonly need to be intubated. In the acute situation, noninvasive mechanical ventilation or intubation will be needed unless specific therapy can immediately reverse the crisis. In the acute-on-chronic situation ($\Delta H^+/\Delta PaCO_2 \sim 0.5$), the trend of the acidosis over time is the crucial factor in deciding on the necessity for intubation.

D. Specific therapy varies greatly by disease, and therefore no broad generalizations can be made. Examples of potential specific therapy include naloxone to offset respiratory center depression from narcotic overdose, inhaled bronchodilators and systemic corticosteroids for asthma and emphysema, or nasal continuous positive airway pressure for obstructive sleep apnea. Details of therapy for the most common of these diseases are presented in subsequent chapters.

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43 ACUTE RESPIRATORY DISTRESS SYNDROME

Mark M. Wilson and Richard S. Irwin

I. GENERAL PRINCIPLES

A. Acute respiratory distress syndrome (ARDS) is a state of acute, diffuse alveolar damage characterized by increased capillary permeability, pulmonary edema, and refractory hypoxemia due to right-to-left shunting.

B. A ratio of partial pressure of arterial oxygen (Pa_{O_2}) to fraction of inspired oxygen (F_{IO_2}) <300 indicates an acute lung injury (ALI) process.

C. ARDS is defined by the following criteria: a Pa_{O_2}/F_{IO_2} ratio <200, regardless of the level of positive end-expiratory pressure (PEEP); bilateral pulmonary infiltrates on chest radiograph (CXR); and a pulmonary artery occlusion pressure ≤18 mm Hg or no clinical evidence of elevated left atrial pressure on the basis of CXR or other clinical data.

D. ARDS has an estimated annual incidence in the United States of approximately 79 cases/100,000 person-years.

II. ETIOLOGY

A. Conditions associated with ARDS include those that cause lung injury directly (gastric aspiration, pulmonary contusion, pneumonia, or other toxic inhalational injury) and those that cause injury indirectly (sepsis, trauma, burns, drug ingestion, pancreatitis, plasma-containing blood products causing transfusion-related acute lung injury [TRALI]). Indirect mechanisms are responsible for most cases of ARDS.

B. Up to one-half of all cases of ARDS are associated with the systemic inflammatory response syndrome or sepsis syndrome.

C. The risk of ARDS increases as the number of potential causes (risk factors) increases.

III. PATHOPHYSIOLOGY

A. The initial pathology of ARDS (diffuse alveolar damage) includes interstitial swelling, proteinaceous intra-alveolar edema, alveolar hemorrhage, and fibrin deposition. Alveolar flooding characteristically occurs in only some alveoli; others appear to be normal.

B. Degenerative cellular changes occur within 1 to 2 days with deposition of hyaline membranes within the alveoli. The repair response begins quickly after the initial insult.

C. Most of the alveolar edema usually resolves after approximately 1 week. Some patients seem to resolve lung injury with little if any fibrosis, whereas others go on to develop severe parenchymal fibrosis. The reason that outcomes are so variable is unknown.

D. The extensive right-to-left shunt in ARDS (up to 25% to 50% of the cardiac output) results from persistent perfusion of atelectatic and fluid-filled alveoli caused by an ineffective or absent hypoxic pulmonary vasoconstriction response.

E. Respiratory system compliance is dramatically reduced, reflecting the amount of edema and atelectasis that is present and is not a measure of the lung injury as such. If fibrosis develops, the elastic properties of the lung parenchyma can then change permanently.

F. The work of breathing in ARDS is increased and may be responsible for the diaphragm taking up 25% to 50% of the body's total oxygen consumption. Mechanical ventilatory support in ARDS reduces the work of breathing, so oxygen can be redirected to other vital organs.

G. Given the variety of conditions associated with ALI and ARDS, it should not be surprising that no characteristic hemodynamic pattern exists. Rather, it is more common for the hemodynamic pattern to reflect the underlying condition itself.

IV. DIAGNOSIS

A. When ARDS presents without preexisting or coexisting conditions, it is easy to recognize.

B. Dyspnea and tachypnea often precede the full development of patchy, heterogeneous infiltrates on CXR; however, alveolar infiltrates invariably develop within the next several hours.

C. Crackles and scattered rhonchi may be heard throughout the lung fields. Not uncommonly, the initial chest examination is remarkably normal, despite severe alveolar infiltrates on CXR. The rest of the physical examination is usually normal, unless other organ systems are involved.

D. Because obtaining lung tissue in these critically ill patients is most often impractical, the diagnosis of ARDS is usually made by inference (see foregoing criteria).

V. TREATMENT

A. Specific treatment

1. No specific therapy exists for ARDS. Identified underlying or complicating conditions should be treated with specific therapy on individual basis.

B. Supportive treatment

1. Mechanical ventilation

a. Noninvasive positive pressure ventilation should be considered first in the setting of progressive respiratory failure from ALI, before full-blown ARDS. Should the patient's condition deteriorate further, invasive mechanical ventilation is warranted.

b. Initial ventilator management should include a volume-cycled ventilator in the assist/control mode. Convincing data now favor the use of low tidal volumes (Vt) of 6 mL/kg (of ideal body weight) over 12 mL/kg to keep airway plateau pressures no more than 30 cm H_2O in an attempt to minimize any alveolar overdistension injury. The use of such low Vt can lead to hypercapnia (not necessarily undesirable, see discussions of permissive hypercapnia or controlled hypoventilation strategies) and atelectasis.

c. Attention is being focused on the importance of first recruiting and then maintaining as many alveolar units open as possible.

d. In patients with ARDS whose oxygenation cannot be maintained with more conventional approaches, growing clinical experience with prone positioning (see the subsequent text) and/or the pressure-control mode or even the use of mechanical ventilation in the inverse-ratio mode may be useful strategies for improving gas exchange when acceptable Pao_2 ($\geq$60 to 80 mm Hg) cannot be achieved with PEEP $<$15 to 20 cm H_2O or when the use of PEEP is associated with excessive plateau pressures.

e. Clinical experience with other nonconventional modes of ventilatory support (high-frequency ventilation, liquid ventilation, inhaled nitric oxide) is too limited to allow any recommendations on their use. While the results of a recently completed randomized, controlled clinical trial assessing the efficacy of extracorporeal membrane oxygenation

(ECMO) having not been published, presentations of the results suggest that ECMO may become a conventional mode of ventilatory support in the future.

2. Patient positioning

a. Because of the nonuniform distribution of lung infiltrates in ARDS, repositioning the patient into the prone position can improve oxygenation by relieving atelectasis and by improving the distribution of perfusion relative to ventilation. Improvement occurs in approximately 66% to 75% of patients, usually within minutes. Although gas exchange is likely to improve, studies to date have failed to show an improvement in mortality with prone positioning.

3. Fluid management

a. While hypernatremia and renal hypoperfusion should be avoided, a restrictive rather than liberal fluid management strategy is recommended based upon the results of a randomized, controlled clinical trial.

4. Corticosteroids

a. Several prospective, multicenter, placebo-controlled studies have shown no benefit to the use of high-dose corticosteroids early in the course of ARDS. Corticosteroids also do not appear to be consistently beneficial if administered during the fibroproliferative phase of ARDS (7 to 10 days after onset).

5. Exogenous surfactant

a. Because normal surfactant may be dysfunctional in ARDS, the instillation of exogenous surfactant has been proposed as a means to improve airspace stability in ARDS and may add antibacterial and immunologic properties as well. Although a large, multicenter, prospective trial showed no benefit on 30-day mortality, duration of mechanical ventilation, or physiologic function, the design of the trial and the efficacy of the inhaled drug have been criticized. Interest in exogenous surfactant remains strong and additional trials with alternative agents in the future are likely.

6. Other pharmacologic therapies

a. No specific medications have been shown to be of benefit in ARDS. Ongoing clinical trials with antioxidants (procysteine), selective pulmonary vasodilators (inhaled nitric oxide, aerosolized prostacyclin), and anti-inflammatory agents (eicosanoid inhibitors, selective prostanoids, lisophylline) are currently under way.

C. Complications

1. The mortality rate for ARDS has improved over the past 4 decades and is now approximately 30% to 40%, mostly within the first 2 weeks of the illness.

2. Many patients with ARDS develop a syndrome of multiorgan dysfunction. Recovery depends on adequate support of vital organ systems. Complications of management are common and include barotrauma, nosocomial pneumonia, deep venous thrombosis, catheter-related infections, and the so-called stress-related gastrointestinal bleeding.

3. Outcome for patients is difficult to predict. The number of acquired organ system failures is often the most important prognostic indicator for patients requiring intensive care, including patients with ARDS. In general, the greater the number of failing organ systems, the worse the prognosis.

4. Recent outcomes research indicates that most ARDS survivors have long-term sequelae, including reduced exercise tolerance and diminished diffusing capacity, as long as 1 year after recovery. Further, many survivors will suffer from depression, anxiety, perceived decline in quality of life, or posttraumatic stress disorder as far as 2 years from recovery.

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Piantadosi CA, Schwartz DA. The adult respiratory distress syndrome. *Ann Intern Med* 2004;141:460.
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Tomashefski JF Jr. Pulmonary pathology of acute respiratory distress syndrome. *Clin Chest Med* 2000;21:435.
An excellent updated review of the pathology of ARDS.

44 STATUS ASTHMATICUS

J. Mark Madison and Richard S. Irwin

I. PRINCIPLES

A. Definitions

1. Asthma is an inflammatory disease of the airways featuring reversible airway obstruction.
2. Status asthmaticus describes a moderate to severe exacerbation of airway obstruction that fails to improve rapidly (usually within 1 hour) with intensive bronchodilator therapy.

II. ETIOLOGY

A. Triggers of asthma exacerbations. Environmental factors such as viral upper respiratory tract infections, inhaled allergens, pollutants, smoke exposure, and nonsteroidal anti-inflammatory drugs (NSAIDs).

B. Types of asthma exacerbations

1. Slow-onset attacks (>6 hours of deterioration) are most common (~90%).
2. Sudden-progression asthma attacks (<6 hours of deterioration) are less common (~10%).

III. PATHOPHYSIOLOGY

A. Pathology

1. Inflammation obstructs the airways by increasing mucus, causing edema and eosinophil infiltration of the airway wall, promoting spasm of smooth muscle, and damaging epithelium.
2. In sudden-progression asthma attacks, neutrophils dominate the inflammation.

B. Physiology

1. Increased airway resistance leads to hypoxemia.
   a. Ventilation–perfusion inequalities mainly account for hypoxemia.
   b. Atelectasis from mucus plugging can cause right-to-left shunt.
2. Persistence of severe, increased airway resistance may eventually lead to hypercapnia because of a patient's inability to sustain the increased work of breathing.

IV. DIAGNOSIS

A. Differential diagnosis

1. Not all wheezing is due to asthma. Obstruction of the airway at any level by any disease process can produce wheezing and dyspnea.

B. Assessment

1. Failure to appreciate the severity of obstruction contributes to mortality.
2. History: High risk for severe airway obstruction is suggested by prior endotracheal intubation and mechanical ventilation for asthma, aspirin sensitivity, frequent or recent emergency department visits or hospitalizations for asthma, current or recent use of corticosteroids, seizures or syncope during prior exacerbations, poor ongoing medical care, and delay in obtaining medical care.

3. Physical examination:
   a. High risk for severe airway obstruction is suggested by tachycardia (> 120 beats per minute), tachypnea (>30 breaths per minute), diaphoresis, bolt-upright posture in bed, pulsus paradoxus > 10 mm Hg, and accessory muscle use.
   b. Cyanosis, respiratory muscle alternans, abdominal paradox, and depressed mental status are late and ominous signs.
   c. Amount of wheezing is a poor way to assess severity of obstruction.
4. Laboratory
   a. Pulmonary function tests (PFTs)
      i. Obtain an objective measure of maximal expiratory airflow to assess the severity of obstruction whenever possible (peak expiratory flow rate [PEFR] or forced expiratory volume in 1 second [FEV1]).
      ii. PEFR (or FEV1) <40% of baseline is severe obstruction.
   b. Assessment of oxygenation
      i. Pulse oximetry if severe distress, PEFR <40% predicted, or patient unable to perform lung function testing. Oxygen saturation <90% suggests severe exacerbation.
      ii. Consider arterial blood gas (ABG) when alveolar hypoventilation suspected, patient is in severe distress, or PEFR (or FEV1) is <25% predicted. A normal P_{CO_2} is a potentially ominous finding that suggests impending respiratory failure.

V. TREATMENT

A. Bronchodilator therapy

1. β-Adrenergic agonists should be started immediately at presentation
   a. Short-acting, β_2-adrenergic agonists (SABA) (e.g., albuterol) are the mainstay. Four to eight puffs of albuterol by metered dose inhaler (MDI) with a spacer device can be given every 20 minutes for up to 4 hours and then given every 1 to 4 hours as needed thereafter.
   b. Inhaled route of administration is preferable even when severe obstruction is present. When used properly, an MDI with spacer device is as effective as small-volume nebulizer.
2. Cholinergic antagonists
   a. Muscarinic cholinergic antagonists (e.g., ipratropium) should be used as an adjunct to β_2-adrenergic agonists during initial treatment of severe exacerbations in the emergency department. Once the patient is hospitalized, cholinergic antagonists are not recommended in recent National Institutes of Health (NIH) guidelines.
   b. Four to eight puffs of ipratropium by MDI with spacer every 6 hours as needed or 0.5 mg by nebulizer every 6 hours as needed.
3. Methylxanthines
   a. Because of toxicity, methylxanthines are not recommended in the treatment of asthma exacerbations.

B. Anti-inflammatory therapy with corticosteroids

1. Corticosteroids are essential for treating status asthmaticus and should be started at presentation without delay.
2. Oral corticosteroids (e.g., prednisone) are as effective as intravenous therapy (e.g., methylprednisolone). However, for critically ill patients admitted to an intensive care unit, guidelines recommend the intravenous route because gastrointestinal absorption of drugs may be variable in critically ill patients.
3. For acute exacerbations of asthma, guidelines recommend methylprednisolone, prednisolone, or prednisone at 40 to 80 mg/day in 1 or 2 divided doses until PEFR >70% of baseline.

4. The total course of systemic corticosteroids may be from 3 to 10 days. For courses <7 days, tapering of dose is not necessary. For longer courses, some clinicians prefer gradual tapering. The recovering patient should be started on an inhaled corticosteroid (ICS).

C. Other therapy

1. Oxygen: Supplemental oxygen therapy should be started immediately. Seemingly paradoxical, inhaled β_2-adrenergic agonists may worsen ventilation–perfusion matching and cause hypoxemia unless supplemental oxygen is given.
2. Adjunct measures:
   a. Although evidence supporting the practice is mixed, guidelines recommend considering heliox-driven albuterol nebulization to possibly avoid intubation during severe, life-threatening exacerbations. Because heliox affects the inhaled mass of medication and the size of the aerosol particles, the flow to power the nebulizer should be increased when heliox is used.
   b. Although evidence is mixed, guidelines recommend considering intravenous magnesium sulfate to possibly avoid intubation during severe, life-threatening exacerbations.
   c. Administration of adjunct measures should never delay a needed intubation.
3. Mechanical ventilation
   a. Decision to intubate is based on repeated clinical assessments of response to therapy, whether hypercapnia is worsening, whether there are signs of muscle fatigue, and whether mental status is deteriorating.
   b. Heliox administration may decrease the need for intubation and mechanical ventilation in some acutely ill patients.
   c. Oral, rather than nasal, route of intubation is preferable. Use an endotracheal tube with internal diameter 8 mm or larger, if possible.
   d. Avoid barotrauma due to dynamic hyperinflation during mechanical ventilation. Controlled hypoventilation (or "permissive hypercapnia") is the main strategy that should be used to keep plateau airway pressures <30 cm H_2O. For patients deeply sedated and paralyzed with neuromuscular blocking agents, monitor lung volumes at end inspiration (VEI) to detect, monitor, and manage dynamic hyperinflation, with the goal of having VEI <20 mL/kg.
   e. The combination of neuromuscular blocking agents and corticosteroids has been associated with severe myopathy. When paralyzing agents are necessary for ventilating the patient, muscle function always should be allowed to recover partially between repetitive boluses.

D. Additional and unconventional measures. When severe airway obstruction is not responding to conventional therapy and mechanical ventilation, other measures may include helium-oxygen (heliox), general anesthetics (e.g., halothane), bronchoscopy with therapeutic lavage, hypothermia, and extracorporeal life support. Because no mechanical ventilator is calibrated for use with helium, correction factors will need to be applied by respiratory therapy in setting up mechanical ventilation with helium.

E. Therapies with no established role. There is no established role for fluid administration in excess of euvolemia, mucolytics, or chest physical therapy. Sedatives are contraindicated unless the patient is mechanically ventilated. Antibiotics are used only when there is a strong suspicion of active infection.

Suggested Reading

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Case reports of asthma complicated by functional upper airway obstruction are presented.

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This is an excellent review of corticosteroid use in asthma.

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A meta-analysis shows that bronchodilator delivered by metered-dose inhaler or nebulizer is equivalent in the treatment of acute asthma.

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Making ventilator changes to keep volume at end of inspiration by ventilator (VEI) below 20 mL/kg protects against barotrauma in status asthmaticus.

45 CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Sunil Rajan and Oren P. Schaefer

I. GENERAL PRINCIPLES

A. Definition: chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

B. COPD affects > 16 million Americans and accounts for approximately 750,000 hospital admissions and 75,000 deaths in the United States annually.

C. It is the fourth most common cause of death overall and the second most common cause of permanent disability in people older than 40 years.

D. Deaths from COPD have increased over the last two decades.

II. ETIOLOGY

A. Cigarette smoking. The major risk factor; correlates with total number of pack-years.

B. Homozygous α1-antitrypsin deficiency.

C. Other factors that may increase risk include significant childhood respiratory illnesses, air pollution, increased airway reactivity, adenovirus infection, and occupational exposures (even in the absence of cigarette smoking).

III. PATHOPHYSIOLOGY

A. Expiratory airflow obstruction results from:

1. Structural airway narrowing due to inflammatory edema, excessive mucus, and glandular hypertrophy.

2. Functional airway narrowing due to destruction of alveolar walls and loss of elastic recoil and radial distending forces; airway smooth muscle shortening and bronchoconstriction.

3. Airflow obstruction increases in a dynamic fashion with expiratory effort.

4. Consequences of severe, chronic airflow obstruction.

a. Reduced flow rates that limit minute ventilation.

b. Maldistribution of ventilation resulting in:

i. Wasted ventilation (high ventilation perfusion [$\dot{V}/\dot{Q}$] mismatch)

ii. Impaired gas exchange (low $\dot{V}/\dot{Q}$ mismatch)

c. Increased airway resistance that results in increased work of breathing.

d. Air trapping and hyperinflation. Altered geometry places the respiratory muscles at a mechanical disadvantage (reduced maximal force generation) and results in muscle fatigue.

e. CO_2 retention: the result of increased dead space and a shift of the hemoglobin-oxygen binding curve.

IV. DIAGNOSIS

A. History

1. Without a history of cigarette smoking, COPD is unlikely. The previously accepted thought that COPD develops in only 15% of smokers is an underestimation; its prevalence is likely much higher.

2. Cardinal symptoms are chronic productive cough and dyspnea on exertion.

B. Physical examination

1. Decreased breath sounds, prolonged expiration, wheezing, hyperinflation, respiratory distress.
2. Agitation, confusion, or obtundation suggests hypercapnia or hypoxia.
3. Respiratory muscle fatigue may be heralded by paradoxic respiratory motion.

C. Radiology

1. Chest roentgenogram findings may include hyperinflation with flattened diaphragms, increased retrosternal and retrocardiac airspaces, vascular attenuation or prominence of lung markings, enlarged pulmonary arteries at the hilum with right ventricular enlargement, and regional hyperlucency and bullae.
2. Chest computed tomography scan findings include:
   a. Centrilobular emphysema: upper lobe distribution of focal areas of low attenuation usually <1 cm in diameter.
   b. Panlobular emphysema: lower lobe distribution with a decrease in lung markings with few blood vessels.

D. Pulmonary function tests (PFTs)

1. Spirometry demonstrates expiratory airflow obstruction that is not fully reversible; it is required to make the diagnosis of COPD.
2. A decreased ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) [$\downarrow FEV_1/FVC$] is the hallmark of obstructive airways disease.
3. Global Initiative for Chronic Obstructive Lung Disease (GOLD)
   a. Consensus workshop report with strategy for diagnosis, management, and prevention of COPD.
   b. PFTs used to define the severity of disease. Stage I (mild), $FEV_1/FVC < 0.70$, $FEV_1 \geq 80\%$ predicted; stage II (moderate), $FEV_1/FVC < 0.70$, $50\% \leq FEV_1 < 80\%$ predicted; stage III (severe), $FEV_1/FVC < 0.70$, $30\% \leq FEV_1 < 50\%$ predicted; stage IV (very severe), $FEV_1/FVC < 0.70$, $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure.
4. FEV_1 correlates with clinical outcome and mortality.
5. Hypercapnic respiratory failure in COPD not usually seen unless FEV_1 is <1 L.
6. PFTs may reveal an increased total lung capacity and residual volume and/or a reduction in carbon monoxide diffusing capacity.
7. Arterial blood gases (ABGs) will diagnose and quantitate the severity of respiratory failure.
8. The relation between the change in $Paco_2$ and the change in hydrogen ion concentration helps determine whether hypercapnia is acute ($\Delta H^+/\Delta Pco_2$ 0.8), acute-on-chronic ($\Delta H^+/\Delta Pco_2$ 0.3 to 0.8), or chronic ($\Delta H^+/\Delta Pco_2$ 0.3). (See Chapter 42.)

E. Exacerbations of COPD

1. Definition: an event in the natural course of the disease (not due to pneumonia, pulmonary embolism, pneumothorax, congestive heart failure) characterized by a change in the patient's baseline dyspnea, cough, and/or sputum beyond day-to-day variability sufficient to warrant a change in management.
2. Acute decompensation most often associated with an acute upper or lower respiratory tract infection. More severe symptoms make bacterial infection more likely.
3. Patient describes increased dyspnea, cough, and sputum production (often with a change in color and character).
4. Airflow obstruction worsens, the work of breathing increases, and mucus production and mucociliary clearance are altered.

5. PFTs may confirm worsened expiratory airflow obstruction. They are difficult to perform and may not be accurate during an exacerbation. ABGs can document gas exchange abnormality and severity of the exacerbation.

V. TREATMENT

- **A.** Supportive therapy for acute exacerbation:
  1. Oxygen therapy is required in all hypoxemic patients (Pa_{O_2} <60 mm Hg) with an acute exacerbation. Do not withhold low-flow oxygen for fear that oxygen will aggravate CO_2 retention.
  2. Bronchodilator therapy for acute exacerbation:
     - **a.** Inhaled β-agonists (albuterol) and ipratropium, in combination. Tiotropium bromide is an effective long-acting bronchodilator. Its use in the acute setting has not been established at this time.
     - **b.** Delivery by small-volume nebulizer or by metered-dose inhaler (MDI) with a spacer is equally effective.
     - **c.** An MDI with an aerosol-holding chamber can deliver bronchodilators to patients receiving mechanical ventilation.
  3. Antibiotics for acute exacerbation:
     - **a.** Anthonisen type I and type II exacerbations warrant antibiotic therapy. Type I (most severe): presence of all three cardinal symptoms—increased shortness of breath, increased sputum volume, and sputum purulence. Type II: presence of two of the three symptoms. Type III: presence of one of the three symptoms combined with cough, wheeze or symptoms of an upper respiratory tract infection.
     - **b.** Common organisms include *Haemophilus influenzae, Streptococcus pneumoniae*, and *Moraxella catarrhalis*.
  4. Corticosteroids for acute exacerbation:
     - **a.** Short-term use of corticosteroids is recommended (10 to 15 days).
     - **b.** Outpatient or emergency department: 30 mg oral prednisolone daily or 40 mg of oral prednisone. Inpatient: up to 125 mg of intravenous methylprednisolone every 6 hours for 3 days, followed by 60 mg of oral prednisone for 4 days, and then a gradual tapering of the dose to zero.
- **B.** Specific therapy. Institute additional therapy directed at other contributory conditions (e.g., gastroesophageal reflux disease [antireflux diet, acid suppression with or without prokinetic therapy]; aspiration [NPO, speech/swallow therapy]).
- **C.** Respiratory failure:
  1. Supplemental oxygen to reverse hypoxemia and tissue hypoxia
     - **a.** Oxygen therapy and a rise in the Pa_{CO_2}
       - **i.** Expect a 10 mm Hg increase in Pa_{CO_2}. Although CO_2 narcosis may uncommonly occur with excessive oxygen therapy, it is unlikely with low flow-controlled oxygen therapy.
       - **ii.** CO_2 retention results from a change in dead space or shift of the hemoglobin-oxygen binding curve, rather than decreased respiratory drive.
       - **iii.** Should be expected and not specifically treated unless excessive, resulting in acute respiratory acidosis, with central nervous system or cardiovascular effects. Do not discontinue oxygen abruptly, but decrease slowly until the Pa_{CO_2} returns to an acceptable level.
       - **iv.** Abrupt discontinuation of supplemental oxygen may not result in a quick increase in ventilation and the withdrawal of oxygen further depresses the low alveolar P_{O_2} and worsens arterial hypoxemia.
  2. Noninvasive positive pressure ventilation (NIPPV)
     - **a.** The favored mode of assisted ventilation if no contraindication exists.

- **b.** Pressure-support ventilation administered by a tight-fitting face or nasal mask. Improves pulmonary mechanics and gas exchange. May obviate the need for invasive mechanical ventilation.
- **c.** Contraindications: respiratory arrest, cardiovascular instability, severely impaired mental status/excessive agitation, recent craniofacial or gastrointestinal surgery, inability to clear secretions or protect airway.
- **d.** Outcomes: relief of dyspnea, improved pH and ABGs, avoidance of intubation, reduced mortality at 1 year.

3. Intubation and mechanical ventilation

- **a.** Indication:
  - **i.** Failure of NIPPV: worsening ABGs and pH in 1 to 2 hours or lack of improvement after 4 hours.
  - **ii.** Severe acidosis (pH <7.2) and worsening hypercapnia ($Paco_2$ >60 mm Hg).
  - **iii.** Life-threatening hypoxemia (Pao_2/Fio_2 <200 mm Hg).
  - **iv.** Inability to clear secretions and to protect the airway.
  - **v.** Assessment of the relation between the arterial hydrogen ion concentration and $Paco_2$ helps determine whether intubation may be required urgently (acute acidosis, $\Delta H^+/\Delta Pco_2$ 0.8), be prepared for if gas exchange worsens (acute-on-chronic, $\Delta H^+/\Delta Pco_2$ 0.3 to 0.8) or delay intubation (chronic, $\Delta H^+/\Delta Pco_2$ 0.3).
- **b.** Objectives include support of gas exchange and rest of respiratory muscles.
- **c.** Carefully regulate ventilatory rate and tidal volume to avoid posthypercapnic metabolic alkalosis with risks of seizures and arrhythmias due to returning Pco_2 toward normal in a patient with chronic hypercapnia.
- **d.** "Intrinsic" or "auto" positive end-expiratory pressure (iPEEP or aPEEP).
  - **i.** Definition: the difference between alveolar pressure and proximal airway pressure measured by the ventilator at end exhalation.
  - **ii.** Results from "air trapping" from low expiratory flow through obstructed airways.
  - **iii.** Aggravated by rapid respiratory rates, high tidal volumes, low inspiratory flow rates, and ventilation through narrow endotracheal tubes.
  - **iv.** Consequences of aPEEP include elevation of inspiratory pressures, hypotension, and increased work for spontaneous or triggered breaths.
  - **v.** Overcome by decreasing minute ventilation (i.e., decreasing tidal volume or respiratory rate or both) and applying external PEEP equivalent to or slightly less than aPEEP.
  - **vi.** Externally applied PEEP reduces inspiratory work; no value in paralyzed patients.
- **e.** Consider mimics of COPD exacerbation that would be treated in different manner (Table 45-1).

VI. PREVENTION OF EXACERBATIONS OF COPD

- **A.** Smoking cessation is the most important and obvious first step in the prevention of COPD exacerbations.
- **B.** Annual influenza vaccination has been shown to decrease morbidity and mortality related to influenza among patients with chronic respiratory diseases.
- **C.** Pneumococcal vaccination is associated with a decreased rate of hospitalization and death in COPD patients.
- **D.** Inhaled corticosteroids in combination with long-acting β-agonists as well as tiotropium decrease frequency of exacerbations.

TABLE 45-1 Differential Diagnosis of Acute Exacerbation of Coronary Obstructive Pulmonary Disease (Mimics)

Aspiration
Asthma
Bronchiolitis
Cardiac arrhythmia
Chest wall injury (e.g., rib fracture)
Cystic fibrosis
Lymphangitic carcinomatosis
Metabolic derangements (e.g., hypophosphatemia)
Parasitic infection
Pleural effusion
Pneumonia
Pneumothorax
Pulmonary edema (cardiac vs. noncardiac)
Pulmonary embolism
Sedation (e.g., narcotics, benzodiazepines)
Tracheobronchial infection
Upper respiratory tract infection

Suggested Reading

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Both agents were associated with a reduction in acute exacerbations. There was a lower death rate in the fluticasone/salmeterol group.

46 EXTRAPULMONARY CAUSES OF RESPIRATORY FAILURE

Mark M. Wilson

I. GENERAL PRINCIPLES

A. The following components make up the extrapulmonary compartment: (a) central nervous system (CNS), (b) peripheral nervous system, (c) respiratory muscles, (d) chest wall, (e) pleura, and (f) upper airway.

B. Impairment of the extrapulmonary compartment produces respiratory failure through the mechanism of hypoventilation; the resultant respiratory failure is always hypercapnic.

C. Extrapulmonary causes can account for up to an estimated 17% of all cases of hypercapnic respiratory failure.

II. ETIOLOGY AND PATHOPHYSIOLOGY

A. Functionally, extrapulmonary disorders lead to hypercapnic respiratory failure because of a decrease in normal force generation (CNS dysfunction, peripheral nervous system abnormalities, or respiratory muscle dysfunction) or an increase in impedance to bulk flow ventilation (chest wall and pleural disorders or upper airway obstruction).

B. Any condition that directly or indirectly impairs respiratory muscle function can result in decreased force generation. If this impairment is severe enough, the level of minute ventilation may be insufficient for the level of production of carbon dioxide.

C. A decrease in central drive to breathe may occur from direct central loss of sensitivity to changes in $Paco_2$ and pH or as a result of a peripheral chemoreceptor loss of sensitivity to hypoxia, as with CNS depressants (narcotics, barbiturates), metabolic abnormalities (hypothyroidism, starvation, metabolic alkalosis), CNS structural lesions, primary alveolar hypoventilation, and central sleep apnea.

D. Disruption of impulse transmission from the respiratory center in the brainstem to the respiratory muscles may result in respiratory failure. The innervation of the inspiratory respiratory muscles may be involved as part of a generalized process, such as in Guillain-Barré syndrome (GBS), myasthenia gravis, amyotrophic lateral sclerosis (ALS), neuromuscular junction blockade, or as an isolated abnormality that affects the respiratory system in a variable way depending on the level of the injury, such as in phrenic nerve palsy and spinal cord trauma or lesions.

E. Peripheral nervous system dysfunction severe enough to produce hypercapnic respiratory failure is always associated with a reduced vital capacity (usually <50% of predicted value) and markedly decreased maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) at the mouth (usually <30% of predicted). A partial list of the myriad etiologies in this group include ALS, poliomyelitis, GBS, shellfish poisoning, diphtheria, tick paralysis, myasthenia gravis, Eaton-Lambert syndrome, critical illness polyneuropathy, botulism, and organophosphate poisoning.

F. Certain systemic myopathies feature prominent respiratory muscle involvement, such as muscular dystrophies, myotonic disorders, inflammatory and

endocrine myopathies, and electrolyte disturbances (hypophosphatemia, hypermagnesemia/hypomagnesemia, hypokalemia, hypercalcemia).

G. Any disorder that causes a decrease in chest wall or pleural compliance (kyphoscoliosis, pleural fibrosis, flail chest, obesity-hypoventilation syndrome, ankylosing spondylitis) or increases airflow resistance from upper airway obstruction (foreign body aspiration, tracheal stenosis, epiglottitis, laryngeal edema, laryngeal/tracheal tumors, obstructive sleep apnea) may culminate in hypercapnic respiratory failure if the resultant respiratory muscle force requirements cannot be sustained.

H. Lateral curvature of the spine (scoliosis) is generally a more important factor in the development of hypercapnic respiratory failure than is dorsal curvature of the spine (kyphosis). Persons with severe deformity (angle of lateral curvature 120 degrees or more) are at the greatest risk of eventual development of respiratory failure.

III. DIAGNOSIS

A. Arterial hypercapnia in the presence of a normal alveolar-arterial oxygen tension gradient (A-a gradient) on room air is the *sine qua non* of pure extrapulmonary respiratory failure. An A-a gradient <20 mm Hg in the presence of an elevated $PaCO_2$ is, with few exceptions, diagnostic of extrapulmonary respiratory failure.

B. The major differential diagnosis of extrapulmonary respiratory failure is hypercapnic respiratory failure from intrinsic lung disease (chronic obstructive pulmonary disease or asthma).

C. Pulmonary parenchymal disease can coexist with extrapulmonary respiratory failure and may be suggested by the combination of hypercapnia and mild widening of the A-a gradient up to 30 mm Hg. Even when the A-a gradient exceeds 30 mm Hg, some degree of extrapulmonary dysfunction may be present. When primary pulmonary disease is severe enough to cause hypercapnia, the gradient is generally >30 mm Hg.

D. A careful medical history should include an assessment of (but not limited to) the presence of muscle weakness and any specific muscle groups involved, duration of symptoms, sleep patterns and daytime somnolence, history of trauma or recent viral illness, dietary habits, and drug ingestions or chemical exposures.

E. Measurements of MIP and MEP at the mouth are easy to perform, noninvasive, and highly predictive of the development of hypercapnic respiratory failure when the problem is decreased respiratory muscle force generation. Although normal predicted values vary (primarily on the basis of age and sex), an MIP not as negative as -30 cm H_2O or reduced to up to 30% of normal is likely to be associated with arterial hypercapnia. MEP is also reduced in this setting and an MEP <40 cm H_2O is generally associated with a poor cough and difficulty clearing secretions.

F. Vital capacity measurements may be valuable predictors of the development of arterial hypercapnia and can be performed at the bedside. Although a vital capacity $\leq$1 L or <15 mL/kg body weight is commonly associated with arterial hypercapnia in patients with neuromuscular weakness, this is a less sensitive predictor than the MIP, particularly in patients with chest wall disorders such as kyphoscoliosis.

G. Significant upper airway obstruction should be considered in the patient who complains of dyspnea in association with stridor (extrathoracic obstruction) or expiratory wheezing (intrathoracic obstruction), particularly if other symptoms suggest an upper airway process (e.g., dysphagia in epiglottitis). Unless the patient is acutely ill, the presence of upper airway obstruction can usually be confirmed in the pulmonary function laboratory with the results of flow-volume loop analysis or by direct visualization.

H. Specific laboratory testing (toxicology screens, thyroid function tests, and levels of magnesium, phosphate, potassium, calcium, and creatinine phosphokinase) and other diagnostic studies (computed tomography, lumbar puncture, electromyography, muscle or nerve biopsy, polysomnogram) should be guided by the patient's presentation and physical examination.

IV. TREATMENT

A. The treatment of extrapulmonary respiratory failure can be divided into specific and supportive therapy. A description of specific therapies for each of the numerous potential causes of extrapulmonary respiratory failure is beyond the scope of this chapter.

B. Supportive therapy involves the use of mechanical ventilatory assistance, supplemental oxygen, and techniques of airway hygiene.

C. In the setting of chronic or progressive disease, reversible factors such as pulmonary congestion, infection, retained secretions, and other intercurrent illnesses should be carefully sought and treated.

D. Regardless of the primary cause of respiratory muscle weakness, malnutrition exacerbates muscle weakness, and proper nutritional replacement can be beneficial in increasing respiratory muscle strength and function.

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47 ACUTE RESPIRATORY FAILURE IN PREGNANCY

Oren P. Schaefer

I. GENERAL PRINCIPLES

A. Acute respiratory failure is an important cause of maternal and fetal morbidity and mortality.

B. Thromboembolism, amniotic fluid embolism, and venous air embolism together account for approximately 20% of maternal deaths. Other causes of respiratory failure account for 10% to 15% of maternal deaths.

II. ETIOLOGY

A. Thromboembolic disease

1. Pulmonary embolism: second leading cause of maternal mortality
2. Increases in factors VII, VIII, and X, and fibrinogen; decreased fibrinolytic activity
3. Additional risks: venous stasis from uterine pressure on the inferior vena cava (IVC), cesarean (C-) section; increased maternal age, multiparity, obesity, and surgery during pregnancy and the early puerperium, inherited thrombophilia
4. Symptoms, signs, laboratory, radiographic, and electrocardiographic (ECG) findings not specific

B. Amniotic fluid embolism

1. Ninety percent occur before or during labor; mortality rate up to 86%.
2. Predisposing factors: older maternal age, multiparity, amniotomy, C-section, intrauterine fetal monitor, term pregnancy in the presence of an intrauterine device.
3. Ante mortem diagnosis based on clinical setting and exclusion of other causes of respiratory failure.
4. Finding fetal elements in maternal circulation in blood aspirated from right heart catheters lacks both sensitivity and specificity.
5. Cardiorespiratory collapse and disseminated intravascular coagulation (DIC) occur simultaneously or in sequence.
6. Dyspnea, tachypnea, and cyanosis during labor or early puerperium is classic. Shock is first manifestation in 10% to 15%. Excessive bleeding may be the first sign.
7. Longer survival increases the likelihood of respiratory failure, vascular collapse, and DIC.

C. Venous air embolism

1. Presentation: sudden, profound hypotension, usually followed by respiratory arrest. Cough, dyspnea, dizziness, tachypnea, tachycardia, and diaphoresis may occur.
2. Other potential findings: "mill-wheel" murmur; ECG evidence of ischemia, right heart strain, and arrhythmias; metabolic acidosis.
3. Obstruction of the pulmonary circulation from air that blocks the apical tract of the right ventricle and fibrin microemboli that obstruct pulmonary arterioles and capillaries. Polymorphonuclear leukocytes may be recruited and activated and lead to tissue damage.

D. Gastric aspiration

1. Clinical syndromes
   a. Chemical pneumonitis and noncardiogenic pulmonary edema
   b. Immediate asphyxia
   c. Pneumonia from aspiration of oropharyngeal bacteria
2. Clinical course
   a. Rapid improvement over 4 to 5 days
   b. Initial improvement followed by deterioration caused by supervening bacterial pneumonia
   c. Early death due to intractable hypoxemia
3. Pathogens usually oropharyngeal anaerobes
4. Predictors of poor outcome: low pH, large volume, greater amount of particulate content of the aspirate
5. Risk factors: increased intragastric pressure caused by gravid uterus, progesterone-induced relaxation of the lower esophageal sphincter, delayed gastric emptying during labor, and analgesia-induced decreased mental status

E. Respiratory infections

1. Community-acquired pneumonia. Organisms to consider: *Streptococcus pneumoniae, Mycoplasma pneumoniae, Haemophilus influenzae*, and respiratory viruses.
2. Influenza, varicella, coccidioidomycosis, tuberculosis, listeriosis, and severe acute respiratory syndrome (SARS) have been associated with increased maternal and fetal morbidity and mortality.
3. Primary varicella-zoster infection may progress to pneumonia more commonly than seen in the nonpregnant patient.
4. Listeriosis is rare; commonly results in abortion or neonatal sepsis.

F. Asthma

1. The most common respiratory problem during pregnancy.
2. Assessment includes history, examination, and objective measure of lung function (peak expiratory flow rate [PEFR], forced expiratory volume in 1 second [FEV_1]).
3. Predictors of hospitalization similar to those of the nonpregnant patient.
4. Adequate oxygenation must be ensured.
5. Baseline $PaCO_2$ in the pregnant woman is often already depressed; a $PaCO_2$ of 35 mm Hg may represent "pseudonormalization" caused by fatigue and possibly impending respiratory failure.
6. Persistent hypocapnia with respiratory alkalosis (pH >7.48) may result in uterine artery vasoconstriction and decreased fetal perfusion.

G. Tocolytic-induced pulmonary edema

1. β-Adrenergic agonists are used to inhibit preterm labor.
2. β_2-Selective agents (ritodrine, terbutaline) have diminished the frequency of maternal tachycardia, but pulmonary edema remains a serious side effect.
3. Newer tocolytics are cyclooxygenase-2 inhibitors and oxytocin antagonists; they are more specific for preterm labor and less toxic than β-agonists.
4. Presentation: chest discomfort, dyspnea, tachypnea, rales, and edema on chest radiograph (CXR).
5. May develop after 24 hours; usually after 48 hours of therapy.

H. Pneumomediastinum and pneumothorax (Pntx)

1. Most often seen in the second stage of labor.
2. Presentation: chest or shoulder pain that radiates to neck and arms, mild dyspnea, subcutaneous emphysema.
3. Prolonged, dysfunctional labor is a predisposing factor.

III. DIAGNOSIS

A. Radiology

1. No appreciable increased risk of gross congenital abnormalities or intrauterine growth retardation with exposure to <5 to 10 rads. Oncogenic risk also small; risk of leukemia may be increased (1 in every 2,000 vs. background rate 1 in every 3,000).
2. Shielding of the abdomen reduces this further.
3. Estimated fetal radiation exposure: CXR, <1 mrad; helical chest computed tomography (CT), 0.3 to 13 mrad (varies per trimester); pulmonary angiography, <50 mrad; perfusion lung scan, 6 to 12 mrad. The average fetal radiation dose with CT is less than that with V/Q lung scanning during all trimesters, and is preferred in the evaluation of PE.

B. Hemodynamic monitoring

1. Indications for invasive monitoring are similar to those in the nonpregnant patient but also include monitoring the critically ill patient with severe preeclampsia or eclampsia.
2. Pregnancy-related hemodynamic changes:
   a. Cardiac output and heart rate elevated
   b. Central pressures, pulmonary artery occlusion pressure, and mean arterial pressure unchanged
   c. Systemic and pulmonary vascular resistances, colloid oncotic pressures reduced
3. Monitor fetal heart rate daily or continuously.

IV. TREATMENT

A. Supportive therapy

1. Mechanical ventilation (MV)
   a. Guidelines for intubation and MV same as for nonpregnant patient
   b. Intubation of the pregnant patient:
      i. Hyperemia can narrow upper airway; patient at increased risk of upper airway trauma during intubation. Small endotracheal tube may be required.
      ii. Decreased functional residual capacity will lower the oxygen reserve. Short period of apnea may result in abrupt decrease in Pa_{O_2}. Before intubation, administer 100% oxygen.
      iii. Avoid hyperventilation: respiratory alkalosis can decrease uterine blood flow.
      iv. Cricoid pressure to decrease gastric inflation and prevent regurgitation.
   c. MV of pregnant patients with acute respiratory distress syndrome (ARDS) should follow the guidelines of the ARDS Network study (see Chapters 43 and 53).
   d. Adjust minute ventilation for a Pa_{CO_2} of 30 to 32 mm Hg (normal in pregnancy).
   e. Aim for usual gestational Pa_{O_2} of >95 mm Hg.
   f. Weaning parameters for pregnant patients similar to those for nonpregnant patients. Weaning in the lateral decubitus position may be preferable to avoid compression of the IVC by the gravid uterus.
2. Reversal of hypotension
   a. Trendelenburg position may further decrease venous return due to IVC compression by the uterus.
   b. Position with right hip elevated 10 to 15 cm (15 degrees) or in the lateral decubitus position.
   c. Hypotension unresponsive to repositioning or fluid resuscitation requires vasopressors.

i. α-Adrenergic agents (norepinephrine) improve maternal blood pressure but decrease uterine blood flow (uterine artery vasoconstriction).
ii. Ephedrine (both α- and β-stimulant) tends to preserve uterine blood flow. Therefore, this is the vasopressor of choice.

3. Nutrition
   a. Maternal malnutrition may correlate with intrauterine growth retardation and development of preeclampsia. Maternal weight gain correlates with fetal weight gain and a successful outcome.
   b. Enteral route is preferred.
   c. If delivery occurs while mother is receiving total parenteral nutrition, observe the neonate closely for hypoglycemia.

B. Specific therapy

1. Thromboembolism
   a. Adequate oxygenation; treat hypotension and organ hypoperfusion.
   b. Initial therapy
      i. Intravenous unfractionated heparin (UFH) or low molecular weight heparin (LMWH). UFH and LMWH do not cross the placenta and are not teratogenic.
      ii. LMWH is the drug of choice because of practical advantages over UFH and because of a lower risk of side effects.
      iii. Pregnancy and the immediate postpartum period are relative contraindications to thrombolysis but can be considered with life-threatening embolism. Recombinant-tissue plasminogen activator (rTPA) and streptokinase can be used.
      iv. IVC filter: consider with cardiopulmonary compromise when patient who does not receive thrombolysis has a contraindication to heparin, or has recurrent emboli despite anticoagulation.
   c. Longer term anticoagulation
      i. UFH given for at least 5 days, then administer subcutaneously in doses adjusted to prolong the activated partial thromboplastin time (aPTT) to 1.5 to 2.5 times control.
      ii. LMWH is safe. May not be associated with osteopenia. Possibly reduced rate of bleeding and thrombocytopenia.
      iii. The half-life of LMWH is reduced in pregnancy. Twice-daily regimens should be titrated to antifactor Xa levels of 0.5 to 1.2 U/mL post injection.
      iv. Warfarin, a potent teratogen, should not be used.
      v. Continue therapy throughout pregnancy and 4 to 6 weeks postpartum.
      vi. For pulmonary embolism in late pregnancy or postpartum period, continue anticoagulation at least 3 months.
2. Amniotic fluid embolism
   a. Treatment is supportive: adequate ventilation and oxygenation, blood pressure support, and management of bleeding. With active bleeding, transfuse with fresh frozen plasma, cryoprecipitate, and platelets.
   b. Reduce uterine bleeding by manual massage, oxytocin, ± methylergonovine maleate.
   c. With persistent bleeding, consider uterine exploration for tears or retained placenta.
3. Venous air embolism
   a. Left lateral decubitus position may allow air to migrate from right ventricular (RV) outflow tract.
   b. Aspiration of air can be attempted with a central venous or pulmonary artery catheter.
   c. Emboli may be decreased in size by providing 100% oxygen.

   d. Anticoagulation, corticosteroids, hyperbaric oxygen suggested but not of proven benefit.
4. Gastric aspiration
   a. Prophylactic antibiotics, corticosteroids are not beneficial in gastric aspiration.
   b. Antibiotics are used when infection complicates chemical pneumonitis.
   c. Antibiotic choice is guided by evaluation of respiratory secretions and other cultures.
5. Respiratory infections
   a. Antibiotics are similar to those used for nonpregnant patients.
   b. For community-acquired pneumonia: penicillins, cephalosporins, azithromycin, and erythromycin (excluding the estolate) are safe.
   c. Other infections are treated according to usual standards; the safety of drug therapy weighed against the risk of untreated infection.
6. Asthma
   a. Pharmacotherapy is similar to that used for the nonpregnant patient.
   b. Prevention or reversal of hypoxemia is paramount. Oxygenation may worsen with bronchodilators; oxygen required in all patients.
   c. High doses of β-agonist carry risk of hypokalemia and pulmonary edema.
   d. High-dose intravenous corticosteroids to help reverse airflow obstruction.
   e. With life-threatening refractory asthma, consider emergency delivery of the fetus by C-section. Decision in part depends on the age and viability of the fetus.
7. Tocolytic-induced pulmonary edema
   a. Discontinuation of tocolytic agent; supplemental oxygen; diuresis; other support as indicated
8. Pneumomediastinum and Pntx
   a. Pneumomediastinum
      i. Spontaneous resolution is usual in 3 to 14 days; almost never requires drainage.
      ii. Direct treatment at any underlying cause (e.g., asthma).
   b. Pneumothorax
      i. Chest tube drainage: symptomatic patients; patients on mechanical ventilation; enlarging Pntx.
      ii. Observation: asymptomatic patient with Pntx of <20% hemithorax.

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48 VENOUS THROMBOEMBOLISM: PULMONARY EMBOLISM AND DEEP VENOUS THROMBOSIS

Todd M. Bishop and Oren P. Schaefer

I. GENERAL PRINCIPLES

A. Incidence of pulmonary embolism (PE) is >600,000 cases per year in the United States.

B. Mortality of untreated PE is approximately 30%; with diagnosis, treatment mortality is 2.5%.

C. Up to 90% of PEs arise from deep venous system of the legs, less commonly in the proximal thigh and iliac veins or inferior vena cava (IVC).

D. Thrombosis and subsequent embolism can occur in upper extremity veins. Risks: central venous catheters, upper extremity exercise, history of congestive heart failure (CHF).

II. PATHOGENESIS

A. Risk factors, acquired

1. Most common: immobilization, surgery within the last 3 months (especially pelvis and hip)
2. Others: advancing age, malignancy, history of venous thromboembolism (VTE), central venous catheters, (incidence up to 65% of patients with indwelling catheters), trauma to the lower extremity, CHF, therapeutic estrogen use, postpartum state, obesity

B. Risk factors, inherited

1. Most common: activated protein C (APC) resistance (factor V Leiden mutation). In the United States, >11 million persons, and 20% to 60% of patients with VTE, have APC resistance.
2. Others: prothrombin variant 20210, antiphospholipid antibodies, hyperhomocysteinemia (unclear if VTE [vs. arterial thrombosis] risk).
3. Rare: deficiencies of antithrombin III, protein C, and protein S; abnormalities in plasminogen or tissue plasminogen activator (tPA).

III. PREVENTION

A. Rationale

1. Almost all hospitalized patients have at least one risk factor for VTE, and approximately 40% have three or more.
2. Without thromboprophylaxis, the incidence of confirmed hospital-acquired deep venous thrombosis (DVT) is 10% to 40% for medical and surgical patients and 40% to 60% for patients after major orthopedic surgery.
3. PE is the most common preventable cause of hospital death. Prophylaxis is associated with minimal risk of complications, including bleeding.

B. Risk stratification

1. Models for DVT risk stratification, though not widely used, are an effective way to ensure prophylaxis is universally applied.
2. Risk is generally based on patient-specific groups.
   - **a.** Low risk: minor surgery in mobile patients; medical patients who are fully mobile, <10% risk of DVT without prophylaxis
   - **b.** Moderate risk: most general surgery, gynecologic, urologic patients, and medical patients on bed rest; 10% to 40% risk of DVT without prophylaxis

c. High risk: hip or knee arthroplasty, major trauma, or spinal cord injury; 40% to 80% risk of DVT without prophylaxis

C. Treatment

1. Mechanical thromboprophylaxis alone:
   a. Should be reserved for patients with high risk of bleeding
   b. May enhance the effectiveness of anticoagulant prophylaxis
   c. Generally less efficacious than anticoagulant prophylaxis
   d. Lacks clinical supporting data compared to anticoagulant prophylaxis
2. In patients initially at high risk of bleeding, prophylaxis should change to include anticoagulant prophylaxis once the risk of bleeding decreases.
3. Mobilization alone does not provide adequate thromboprophylaxis for hospital patients.
4. Treatment with anticoagulants:
   a. Low-risk patients: low molecular weight heparin (LMWH), unfractionated heparin (UFH), or fondaparinux can be considered along with early ambulation.
   b. Moderate risk patients: LMWH, UFH bid or tid, or fondaparinux should be administered and mechanical thromboprophylaxis should be considered in combination.
   c. High-risk patients: LMWH, fondaparinux, or oral vitamin K antagonists (goal international normalized ratio [INR] of 2 to 3).
      i. High-risk surgical patients should be considered for VTE prophylaxis during and after hospitalization.
   d. Renal dosing is recommended when using LMWH and fondaparinux, especially in elderly patients, those with diabetes, and at high risk of bleeding.
   e. Morbidly obese patients: consider for higher doses of LMWH, UFH.

IV. DIAGNOSIS

A. Signs and symptoms

1. DVT: most common—leg swelling and tenderness. However:
   a. Ninety-five percent of patients with symptoms suggestive of DVT have another diagnosis.
   b. Fifty percent to 85% of patients with DVT present without symptoms.
   c. Homan's sign is neither sensitive nor specific for the diagnosis of DVT.
   d. If left untreated, 50% of patients will go on to have a PE
2. PE: dyspnea, tachypnea, pleuritic chest pain, signs and symptoms of DVT seen in 97%. Findings are nonspecific; symptoms are as likely to be present in those without PE. Syncope is an uncommon presenting symptom. An increased pulmonary second heart sound (P2) and fourth heart sound more common in patients with PE but found in <25%. Consider PE when patients present with three different syndromes.
   a. Acute pneumonia. The most common syndrome mimics acute pneumonia. May be accompanied by pleuritic pain and/or hemoptysis.
   b. Unexplained dyspnea.
   c. Shock. The normal right ventricle fails acutely when it cannot generate a systolic pressure >40 mm Hg.
3. Clinical prediction models, for example, Wells score, help risk stratify patients, and in combination with other tests (D-dimer, computed tomographic [CT] scan), can be useful in the diagnostic evaluation.
   a. Wells score can help assess likelihood of DVT. A modified Wells score has been used to assess probability of PE (Table 48-1)

B. General diagnostic tests

1. Chest radiograph: abnormal in >80% with PE. Consolidation, atelectasis, pleural effusions, and enlarged central pulmonary arteries with decreased

TABLE 48-1 Determining Pretest Probability of Acute PE Using a Standardized Prediction Model

Variable	Points
Symptoms/signs of DVT	3.0
Alternative diagnosis deemed less likely than PE	3.0
Heart rate >100 beats per min	1.5
Immobilization/surgery in previous 4 wk	1.5
Previous venous thromboembolism	1.5
Hemoptysis	1.0
Recent or current malignancy	1.0

Clinical probability of PE can be assigned using a scoring system as above. Less than 2 points, low probability; 2–6 points, moderate probability; >6 points, high likelihood.
PE, pulmonary embolism; DVT, deep vein thrombosis.
(Adapted from Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000;83:416.)

pulmonary vasculature are common. The classic Hampton hump (pleural-shaped density noted in the costophrenic angle on the posteroanterior projection) and Westermark sign (focally decreased vascularity distal to the occlusion) are uncommon.

2. Electrocardigraph (ECG): commonly abnormal (in 70%). Most common findings of sinus tachycardia and ST-segment and T-wave changes are too nonspecific to be of value. The classic S1-S2-S3 and S1-Q3-T3 patterns suggesting cor pulmonale are uncommon, but when present may be a sign of massive PE.
3. Arterial blood gases (ABGs): commonly abnormal. Mean Pa_{O_2} 70 ± 16 mm Hg in patients with PE (no different in those without PE). Of patients with proven PE, 15% have a Pa_{O_2} of ≥85 mm Hg, and 10% to 15% of patients with PE have a normal $P_{A-a}O_2$ gradient [$(A\text{-}a)P_{O_2}$]. Owing to increased ventilation, patients with PE have normal or reduced Pa_{CO_2}.
4. Cardiac troponin: specific for cardiac myocyte damage. Patients with right ventricular strain related to PE may have elevated troponin T and I.
   a. At increased risk for cardiogenic shock.
   b. A normal value is not sufficiently sensitive to rule out PE.
5. Plasma brain natriuretic peptide (BNP): released in response to increased cardiac filling pressures and can serve as a marker of right ventricular overload.
   a. Elevated BNP and troponin levels at admission have been correlated with in-hospital mortality and complicated hospital course.

V. DIAGNOSIS OF DEEP VENOUS THROMBOSIS

A. Venography

1. The reference standard for the diagnosis of DVT.
2. Complications include pain, superficial phlebitis, DVT, and contrast media reactions.
3. Noninvasive tests have supplanted the venogram.

B. Impedance plethysmography (IPG)

1. Overall sensitivity is approximately 65%.

2. False-positive results with tensing of the leg muscles, compression by an extravascular mass, elevated central pressure obstructing venous outflow, or reduced arterial flow.
3. Not sensitive to calf vein thrombosis.
4. Initial negative test in 6% to 26% of symptomatic patients who later develop an abnormal test.

C. Real-time B-mode ultrasonography with color Doppler flow (Duplex scan)

1. Permits direct visualization of major vascular channels.
2. Doppler signal provides an audible and graphic depiction of blood flow direction and speed.
3. Failure to collapse the vascular lumen completely with gentle probe pressure and the finding of intraluminal echogenic material resulting from clot are diagnostic.
4. Predictive value of duplex ultrasound is greater than that of IPG.
5. Sensitivity for proximal DVT is 97%; specificity is 99%.
   a. False positive with failure to compress femoral vein due to pregnancy or pelvic tumor
   b. False negative from missing small clots or misinterpreting total occlusion of the femoral vein because of dilated collateral veins
   c. Compression and Doppler ultrasonography also accurate in detecting upper extremity DVT
   d. Less sensitive in identifying asymptomatic, isolated calf vein and recurrent thrombosis

D. Computed tomographic venography (CTV) and magnetic resonance imaging (MRI)

1. Useful to detect pelvic and IVC clot. May help differentiate acute from chronic disease.

VI. DIAGNOSIS OF PULMONARY EMBOLISM

A. Ventilation-perfusion lung scan

1. Scans categorized as normal, very low probability, low probability, intermediate, or high probability based on the number and size of the perfusion abnormalities present and whether or not they are matched with abnormalities of ventilation.
2. Positive predictive value (PPV) of a high-probability lung scan is approximately 88%. A prior history of PE decreases the PPV value to 74%.
3. Definition of high-probability lung scan: two or more large (>75% of segment) segmental perfusion defects without corresponding ventilation or radiographic abnormalities or substantially larger than either matching ventilation or chest radiograph abnormalities; two or more moderate segmental ($\geq$25% and $\leq$75% of segment) perfusion defects without matching ventilation or chest radiograph abnormalities and one large mismatched segmental defect; four or more moderate segmental perfusion defects without ventilation or chest radiograph abnormalities.
4. Normal lung perfusion scan effectively rules out clinically important PE.
5. High-probability (approximately 12%) or normal/near-normal scans (approximately 12%) occur infrequently.
6. Assigning prior clinical probabilities helpful only in concordant situations
   a. High clinical suspicion *and* high-probability lung scan—PE in 96%.
   b. Low clinical suspicion *and* low-probability lung scan—PE in only 4%.
7. With underlying cardiopulmonary disease (chronic obstructive pulmonary disease, CHF), the frequency of a nondiagnostic scan is higher than in those without underlying disease. Predictive value remains unchanged.

8. In intensive care unit (ICU) patients in respiratory failure, the clinical, radiographic, ABG, and $\dot{V}/\dot{Q}$ scan findings are unsatisfactory in making a diagnosis. Ventilation scans generally cannot be performed on mechanically ventilated patients.

B. Contrast-enhanced helical (spiral) CT (CT angiography)

1. Sensitivity for central emboli is approximately 95% (overall sensitivity 72%); specificity 95%.
2. Emboli in segmental or small vessels occur in 15% to 30% and may be missed.
3. As found in prospective investigation of pulmonary embolism diagnosis (PIOPED) II trial, newer multidetector scanners have increased the overall sensitivity to 83% and specificity to 95%.
4. Patients with a negative contrast CT have a rate of subsequent embolism similar to that seen with a negative $\dot{V}/\dot{Q}$ lung scan and similar to patients with positive CT and treatment for VTE.
5. In the high-risk patient, despite negative CT, the clinician should consider additional investigation. PIOPED II showed a 40% false-negative rate of CT angiography in patients with high clinical probability.
6. CT angiography coupled with CTV of the lower extremities increases the sensitivity for the diagnosis of PE to 90%.

C. Echocardiography

1. Transthoracic echocardiography is insensitive for diagnosis of PE but can be useful in the overall evaluation of PE.
2. Speed and portability make echocardiography useful in patients who are too unstable to undergo diagnostic testing.
3. Dilatation and hypokinesis of the right ventricle, paradoxical motion of the interventricular septum, and right ventricular free wall hypokinesis (McConnell's sign) are signs of right ventricular strain and may suggest acute massive PE.

D. D-Dimer

1. Degradation products of cross-linked fibrin. A marker of endogenous fibrinolysis.
2. D-Dimer assays differ in sensitivity, specificity, likelihood ratios, and variability among patients with suspected DVT or PE. Enzyme-linked immunosorbent assay (ELISA) and quantitative rapid ELISA D-dimer in general are most clinically useful because they are highly sensitive. The value of the test is in ruling out VTE.
3. Negative predictive value of >95% for DVT and PE.
4. Multiple assays available. Less-sensitive assays cannot be used in isolation to rule out VTE.
5. D-Dimer has not been studied extensively in critically ill patients. However, it is of value in ruling out VTE in stable outpatients in the office or emergency department setting.

E. Pulmonary angiography

1. The gold standard by which to diagnose PE.
2. Intravascular filling defects and the trailing embolus sign are diagnostic.
3. Mortality risk is 0.1% to 0.5%.
4. Complications: cardiac perforation, hematoma, contrast media reaction.
5. A negative angiogram with balloon occlusion excludes the diagnosis of PE.

F. Diagnostic algorithm; PE in the critically ill (Fig. 48-1)

VII. TREATMENT

A. Low molecular weight heparin

1. LMWH is as effective as or superior to UFH in the treatment of acute DVT and PE and considered by most to be the drug of choice.
2. No difference seen in recurrent VTE, bleeding, or mortality.

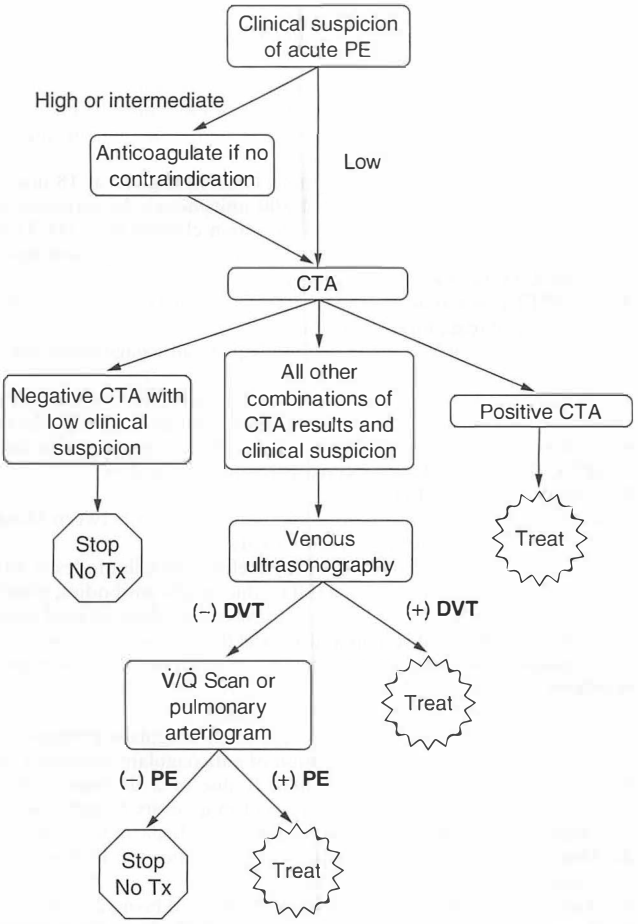

Figure 48-1. Diagnostic algorithm for pulmonary embolism (PE) in the critically ill. Chest computed tomographic angiography (CTA) algorithm for suspected acute (PE) in stable intensive care unit (ICU) patients is noted above. Chest CTA may not be feasible in patients with significant renal dysfunction or contrast allergy. Clinical probability scores and rapid enzyme-linked immunosorbent assay D-dimer testing are not included due to insufficient validation in the ICU setting. Though the ventilation/perfusion (V̇/Q̇) scan may be useful in certain cases (e.g., clear chest x-ray [CXR]) the scan is technically difficult in the critically ill patient and therefore may not be valuable. DVT, deep venous thrombosis; Tx, treatment.

3. Dosing is weight based and depends on the particular LMWH.
4. Titrating dose to anti–factor Xa levels should be considered in patients with significant renal impairment, those with bleeding, abnormal coagulation patterns, pregnancy, obesity, and low-weight patients and children.
5. Advantages: subcutaneous administration with fixed dose, once or twice a day, no laboratory monitoring.
6. LMWH contraindicated in renal failure; dose adjustments required with renal insufficiency.

7. LMWH is not easily reversible and in the ICU patient UFH may be the preferred agent in the setting of unanticipated bleeding and procedures.

B. Unfractionated heparin

1. UFH is given as a continuous intravenous infusion with an initial loading dose of 60 units/kg (maximum bolus 5,000 units) given on the basis of a strong clinical suspicion unless a high risk or contraindication to anticoagulation exists.
2. After the loading dose, a continuous infusion is given at 18 units/kg/hour (maximum initial infusion rate 1,800 units/hour). Adjustments are made using a nomogram, to achieve a thrombin clotting time (TCT) of 0.2 to 0.4 heparin U/mL, or an activated partial thromboplastin time (aPTT) 1.5 to 2.0 times mean normal range.
3. The aPTT is not as accurate as the TCT; use the latter when baseline aPTT is prolonged (e.g., lupus-type inhibitor).
4. Risk of recurrent VTE increased if adequate anticoagulation not achieved within 24 to 48 hours.
5. Recheck aPTT in 4 to 6 hours after bolus and then every 6 hours for the first 24 to 36 hours or until the therapeutic range has been achieved.
6. If, after the initial loading dose, there is little or no change in the TCT or aPTT, the patient should receive a second loading dose.
7. Complications of UFH:
   a. Bleeding occurs in 5% to 20%. A relationship between bleeding and higher levels of anticoagulation exists.
   b. Thrombocytopenia. In most, the platelet count falls modestly. In heparin-induced thrombocytopenia (HIT), due to IgG antibodies, platelet count falls abruptly to <50%. Heparin should be discontinued immediately because of risk of venous and arterial thrombosis. Anticoagulation with nonheparin anticoagulants is required; consider IVC interruption.

C. Warfarin

1. Initiate warfarin at the time of heparinization.
2. Leads to depletion of vitamin K-dependent coagulant proteins: factors II, VII, IX, and X; limits carboxylation of anticoagulant proteins C and S.
3. INR may become therapeutic quickly due to a decrease in factor VII; other coagulant factors may be present in quantity to generate thrombin. Therefore, warfarin must be overlapped with heparin for 5 days.
4. After this interval, heparin may be stopped once the INR is in the therapeutic range for 2 consecutive days.
5. Daily dosing is based on the INR, with the goal being 2 to 3.
6. Duration of warfarin therapy. Initial DVT/PE: treat for 6 months; data suggest that the course should possibly be longer. Recurrent VTE: treat for 1 year or longer. Inherited and acquired risk factors and pulmonary hypertension: treatment is indefinite.
7. Complications: bleeding, most commonly in the gastrointestinal and urinary tracts, in 4.3% to 6%. Risk related to intensity of anticoagulation (14% to 42% when INR is ≥3), concomitant use of aspirin, and with comorbid conditions (central nervous system, renal, hepatic, and cardiac disease).

D. Thrombolytic therapy

1. Indication: acute, massive PE with hypotension/hypoxemia despite resuscitation.
2. No consensus exists on the use of thrombolytic therapy for acute DVT or PE; no reduction in mortality or rate of recurrence has been shown at 90 days.
3. Administration of thrombolysis:
   a. Discontinue UFH/do not give additional LMWH. Resume this therapy after thrombolysis when the aPTT is less than two times control value.

   b. Given bleeding risk with thrombolytics, consider UFH for 24-hour period following lytic; UFH has short half-life and can be reversed more quickly than LMWH. LMWH has not been studied with thrombolytic therapy.
   c. Agent of choice: tPA given as 100 mg over 2 hours.
   d. Restart heparin when aPTT returns to two times control or less, followed by warfarin.
4. Contraindications: Identical to those for coronary thrombolysis (see Table 35-3).

E. Vena caval interruption

1. Indications: contraindication to or complication of anticoagulation, documented recurrent VTE despite adequate anticoagulation, chronic recurrent embolism with pulmonary hypertension, and pulmonary embolectomy.
2. IVC filters may be placed above the renal veins if necessary.
3. Can be placed in superior vena cava in cases of upper extremity DVT.
4. If possible, anticoagulation should be resumed.
5. Effective in primary prophylaxis in patients with a high risk of bleeding; temporary filters can be employed in patients in whom the risk of bleeding appears short term
6. Complications: thrombus at the site of insertion, filter migration, improper filter deployment, proximal clot formation with propagation and embolization, venous insufficiency, and IVC obstruction. Rare: myocardial infarction, vessel perforation, pericardial tamponade, arrhythmia.

F. Pulmonary embolectomy

1. Indications: angiographically documented massive PE with hemodynamic instability and a contraindication to thrombolysis.
2. Mortality rates for surgical embolectomy range from 10% to 75%.
3. Complications: acute respiratory distress syndrome, renal failure, cardiac arrhythmias, mediastinitis, and severe neurologic sequelae.
4. Percutaneous mechanical embolectomy (transvenous catheter extraction) is a less well-studied method of reducing clot burden.

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MANAGING HEMOPTYSIS

Oren P. Schaefer and Richard S. Irwin

49

I. GENERAL PRINCIPLES

A. Definitions

1. Hemoptysis: expectoration of blood from the lungs or bronchial tubes
2. Massive hemoptysis: expectoration of 600 mL of blood within 24 to 48 hours
3. Pseudohemoptysis: expectoration of blood from other than the lower respiratory tract

II. ETIOLOGY

A. Nonmassive hemoptysis. Table 49-1 lists the more common causes of hemoptysis, including bronchitis, bronchiectasis, lung carcinoma, and tuberculosis.

B. Massive hemoptysis

1. All causes of hemoptysis may result in massive hemoptysis. Most frequent causes are infection (tuberculosis, mycetoma, bronchiectasis, lung abscess), lung cancer, and diffuse intrapulmonary hemorrhage.
2. Catastrophic, albeit rare causes, include rupture of a pulmonary artery from a balloon flotation catheter and tracheoarterial fistula.

C. Idiopathic hemoptysis

1. Despite a systematic diagnostic approach hemoptysis may be idiopathic in 2% to 32%.
2. Most commonly seen in men between ages of 30 and 50 years.
3. Usually presents as nonmassive hemoptysis but can be massive.
4. Ten percent have recurrence.
5. Consider Dieulafoy's disease of bronchus (superficial bronchial artery) in context of idiopathic hemoptysis.

III. PATHOGENESIS

A. Bronchial arterial circuit supplies blood to the airways (main stem bronchi to the terminal bronchioles), pleura, intrapulmonary lymphoid tissue, and large branches of the pulmonary vessels and nerves in the hilar regions. The bronchial circulation is responsible for bleeding in approximately 92% of cases.

B. Pulmonary arterial circuit supplies the pulmonary parenchymal tissue, including respiratory bronchioles.

IV. DIAGNOSIS

A. Medical history

1. Consider frequency, timing, duration, anticoagulant use, and travel history (endemic fungi and parasites).
2. Chronic sputum production suggests chronic bronchitis, bronchiectasis, or cystic fibrosis.
3. Orthopnea and paroxysmal nocturnal dyspnea suggests cardiac failure or mitral stenosis.
4. Always consider pulmonary embolism.
5. Consider suction catheter trauma in the intensive care unit.
6. Diffuse intrapulmonary hemorrhage: hemoptysis typical but absence does not rule this out.

TABLE 49-1 Common Causes of Hemoptysis[a]

Tracheobronchial disorders
Acute tracheobronchitis
Bronchiectasis
Bronchogenic carcinoma
Chronic bronchitis
Gastric acid aspiration
Cystic fibrosis
Tracheobronchial trauma
Tracheoarterial fistula
Cardiovascular disorders
Congestive heart failure
Mitral stenosis
Pulmonary arteriovenous fistula
Pulmonary embolism
Hematologic disorders
Anticoagulant therapy
Thrombocytopenia
Disseminated intravascular coagulation
Localized parenchymal disease
Acute and chronic pneumonia
Aspergilloma
Lung abscess
Pulmonary tuberculosis
Diffuse alveolar hemorrhage
Goodpasture's syndrome
Systemic lupus erythematosus
Trimellitic anhydride toxicity
Cocaine inhalation
Viral pneumonitis
Wegener's granulomatosis
Bone marrow transplantation
Pulmonary capillaritis
Other
Idiopathic
Iatrogenic (e.g., bronchoscopy, cardiac catheterization)

[a]This list is not meant to be all inclusive. See Hemoptysis chapter in *Intensive Care Medicine*, 6th edition for an expanded list with references.

B. Physical examination

1. Evaluation of the respiratory system
   - **a.** Inspection: evidence of recent or old chest trauma
   - **b.** Auscultation
     - **i.** Unilateral wheeze or rales suggest localized disease.
     - **ii.** Diffuse crackles in congestive heart failure (CHF) and diffuse intrapulmonary hemorrhage.
2. Evaluation of other systems
   - **a.** Skin and mucous membranes.
     - **i.** Telangiectasias suggest hereditary hemorrhagic telangiectasia.
     - **ii.** Ecchymoses and petechiae suggest hematologic abnormality.
   - **b.** Neck: with pulsations transmitted to a tracheostomy cannula consider a tracheoarterial fistula or the risk of one.
   - **c.** Cardiovascular: mitral stenosis, pulmonary artery stenosis, or pulmonary hypertension.

C. Laboratory studies

1. Chest radiograph (CXR)
   a. Obtain in every patient (may suggest diagnosis or help localize bleeding site).
      i. However, do not assume that an abnormality always accurately identifies the site of bleeding.
   b. CXR normal in up to 30%.
2. Complete blood count for evidence of infection, hematologic disorder, or chronic blood loss.
3. Urinalysis may show hematuria or suggest systemic disease associated with diffuse intrapulmonary hemorrhage (vasculitis, pulmonary-renal syndrome, antiglomerular basement membrane antibody-mediated disease).
4. Coagulation studies: primary or contributing hematologic disorder.
5. Electrocardiogram; consider echocardiogram (CHF, mitral stenosis).
6. High-resolution chest computed tomography (CT) scan may improve yield of bronchoscopy in localizing a bleeding source and point to a diagnosis.
7. Additional more specialized evaluation based on history and examination may be warranted.

D. Bronchoscopy

1. For diagnosis and localization of the pulmonary hemorrhage.
2. Greatest yield when performed during or within 24 hours of active bleeding.
   a. With active bleeding, localization in up to 91%.
   b. Within 48 hours, localization drops to 51%.
   c. After bleeding stops, localization reduced further.
3. Flexible bronchoscopy: ideally used to diagnose lower respiratory tract problems.
4. Rigid bronchoscopy: ideally used for massive hemorrhage.

E. Angiography

1. Can determine the site of bleeding in up to 90%. Not useful in diffuse alveolar hemorrhage syndromes.
2. Can establish a diagnosis not identified by bronchoscopy in only 4%.

V. TREATMENT

A. General considerations

1. Quantify the amount of bleeding; massive hemoptysis is associated with significant mortality.
2. Consider the cause of bleeding.
3. Consider the patient's underlying lung function.

B. Supportive care

1. Bed rest and mild sedation.
2. Cough suppressants should not be used.
3. Supplemental oxygen may be required.
4. Evaluate need for endotracheal intubation (airway protection, assisted mechanical ventilation).
5. If intubation is required, an endotracheal tube with an internal diameter of at least 8.0 mm will facilitate flexible bronchoscopy.
6. Fluid and blood resuscitation as indicated.
7. Chest physical therapy and postural drainage should be avoided.

C. Definitive care

1. For nonmassive hemoptysis, treatment is directed at the specific cause.
2. Massive hemoptysis is an emergency. The likelihood of death, primarily due to asphyxiation, is directly related to the rate of bleeding.
   a. Treatment aimed at the specific cause
   b. Treatment aimed to stop the bleeding
   c. Lung isolation
      i. Initial management requires protection of the uninvolved lung from aspiration of blood.
      ii. The bleeding lung should be kept dependent.

iii. Placement of a double-lumen endotracheal (Carlen) tube can favorably affect bronchial isolation, but these tubes can be difficult to place and may be dislodged easily, and their small diameter may prevent subsequent bronchoscopy.
iv. Bronchial blockers can be placed endoscopically.

d. Rigid bronchoscopy under general anesthesia may be required to clear the airway of aspirated blood
e. Therapeutic maneuvers—bronchoscopy
   i. Fogarty balloon catheter, bronchoscopically positioned, may provide effective tamponade when the bleeding bronchial segment is located.
   ii. Iced saline lavage of the bronchus leading to the bleeding site may stop hemorrhage by local vasoconstrictor effect.
   iii. Laser coagulation can be used to control bleeding in patients with cancer. Recurrence of bleeding within a few weeks is typical.
f. Therapeutic maneuvers—angiography
   i. Embolization can successfully stop bleeding in massive hemoptysis in >90% of cases. Rebleeding within 1 to 4 days can occur, and therefore multiple procedures may be necessary. Within 6 months, 20% of patients bleed again.
   ii. Complications that are rare, but serious, include embolization of the spinal arteries and transverse myelitis.
g. Specific maneuvers for uncommon causes of massive hemoptysis
   i. Rupture of the pulmonary artery from Swan–Ganz catheter. Deflate balloon, withdraw catheter 5 cm, reinflate balloon with 2 mL of air, allow balloon to float back and occlude vessel. The catheter usually floats to the right pulmonary artery. If not known which artery has ruptured, place patient in the right lateral decubitus position. Once the patient has been stabilized, study the patient angiographically. If a pseudoaneurysm has formed, ablate the feeding vessel with coil.
   ii. Tracheoarterial fistula: Overinflation of the tracheostomy cuff may stop the hemorrhage as an emergency procedure.
h. Emergency surgery
   i. With the exception of immediate intervention to repair a tracheoarterial fistula, the role of emergency surgery remains controversial. It is unclear whether emergent surgery for massive hemoptysis provides a survival benefit. Mortality is related to the diagnosis and whether the patient is an operable candidate.
i. Conservative nonsurgical treatment
   i. Advocated when hemoptysis has an infectious cause.
   ii. In patients with cystic fibrosis, as recurrent hemoptysis in other areas is likely.
   iii. Severe lung disease: When forced expiratory volume in 1 second (FEV1) is <2 L withhold surgery if assessment suggests a postoperative severe respiratory impairment (FEV1 ≤800 mL).

D. Approach

Therapy in a given patient depends on etiology, lung function, availability of resources, and local expertise.

1. Nonsurgical candidates: poor lung function, significant comorbid illness, diffuse lesions. Treat with selective angiography and embolization.
2. Surgical candidates: resectional surgery should be performed when it will be definitive treatment for the underlying disease.
3. Diffuse intrapulmonary hemorrhage:
   a. Selective arterial embolization and surgery are not options.
   b. For immune-mediated diseases (e.g., Goodpasture's syndrome, systemic lupus erythematosus [SLE]) high-dose steroids and cytotoxic agents are recommended.

c. Post–bone marrow transplantation alveolar hemorrhage requires high-dose steroids.
d. Consider recombinant activated factor VII as a temporizing measure in unstable patients without coagulopathic bleeding.

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50 ASPIRATION AND DROWNING

Nicholas A. Smyrnios and Richard S. Irwin

I. ASPIRATION

A. General principles

1. Definitions

a. Aspiration: inhaling fluid or a foreign body into the bronchi and lungs. The material may be particulate matter (food particles), irritating fluids, or oropharyngeal secretions containing infectious agents.

B. Pathogenesis

1. Normal respiratory defenses against aspiration. An aspiration event requires bypassing or overwhelming one or more of these mechanisms.

a. Aerodynamic filtration—nose, mouth, larynx—particles >10 μm in diameter.

b. Mucociliary clearance—for particles 2 to 10 μm in diameter

c. Alveolar detoxification—alveolar macrophage and neutrophil nonspecific killing for particles <2 μm in diameter

d. Cough—provides clearance when mucociliary clearance is inadequate

e. Immunologic mechanisms—augment the nonimmunologic mechanisms

f. Swallowing mechanism—hypopharyngeal muscles move food into the esophagus, the epiglottis covers the larynx, the vocal cords close, and the upper esophageal sphincter relaxes. Pharyngeal swallowing initiates peristaltic waves in the esophagus, which carry the bolus through a relaxed lower esophageal sphincter (LES) to the stomach.

2. Factors predisposing to aspiration in critically ill patients

a. Translaryngeal intubation—swallowing impairment persists after extubation.

b. Tracheostomy—interferes with proper laryngeal elevation necessary for glottic closure.

c. Enteral feeding tubes—causes vagally induced LES relaxation and also prevents mechanical closure of the LES.

d. Large residual volumes in stomach—exact volume is unknown, presumed to be approximately 200 mL.

C. Diagnosis

1. Diagnostic tests available for aspiration are listed in Table 50-1.

D. Treatment

1. Mendelson's syndrome: Aspiration of gastric contents may cause the development of acute respiratory distress syndrome (ARDS). Management of ARDS is described in Chapter 43.

2. Foreign body aspiration

a. Particles that do not totally obstruct the trachea removed by bronchoscopy.

b. Completely obstructing particles removed by subdiaphragmatic thrusts in unconscious patient or chest thrusts in obese or pregnant patient.

3. Bacterial pneumonia and lung abscess

a. Community-acquired pneumonia most often due to *Streptococcus pneumoniae*. Lung abscess most often due to anaerobes.

TABLE 50-1 Diagnostic Protocol for Aspiration Syndromes

History
Physical examination
Baseline examination
Observation of patient drinking water
Chest radiographs
Lower respiratory studies
Expectorated samples
Protected specimen brush with quantitative cultures
Bronchoalveolar lavage
Lung biopsy
Upper gastrointestinal studies
Contrast films/modified barium swallow
Endoscopy
Scintiscan
24-h esophageal pH/impedance monitoring
Speech and swallowing bedside methods for detecting aspiration in tube-fed patients

b. Nosocomial most often (50% to 75%) due to enteric gram-negative bacilli and *Staphylococcus aureus*.

c. Speech pathologist can assess risk of aspiration and often help a patient to develop strategies for swallowing that minimize the risk of further aspiration. Following endotracheal extubation or with tracheostomy tube in place, do not start oral nutrition until patient has been evaluated and their swallowing status has been determined to be appropriate for oral intake.

4. Chemical pneumonitis—rapid, self-limited course requires no specific treatment.

5. Exogenous lipoid pneumonia

a. Caused by aspiration of oil or fat from animal, plant, or mineral.

b. Exogenous lipoid pneumonias usually resolve on their own.

c. Surgical repair of achalasia and Zenker's diverticulum.

d. Patients with swallowing problems may require stoppage of oral feedings and initiation of gastrostomy or jejunostomy feedings.

e. Patients with tube feedings: elevate head of bed to 45-degree angle.

f. Gastroesophageal reflux disease treatment: head-of-bed elevation; acid suppression; prokinetic drugs; antireflux diet; nothing to eat for 2 hours before bedtime.

6. Tracheobronchitis

a. Intensive care unit patients generally stop aspirating large volumes when oral intake is stopped. Do not resume until modified barium swallow confirms swallowing without aspiration.

II. DROWNING

A. General principles

1. Definitions

a. Fatal drowning: death from suffocation by submersion in water.

b. Nonfatal drowning: survival, at least temporarily, after respiratory impairment by submersion in water.

c. Submersion or immersion injury: both fatal and non-fatal drowning taken together.

2. Statistics
   a. The seventh most common cause of accidental injury death in the United States.
   b. More than 3,300 drownings in the United States annually
   c. Incidence 1.14 per 100,000
   d. Most common in children younger than 5 years, young adults 15 to 29 years, males, Native Americans, African Americans.
   e. States with the highest drowning rates are Alaska and Mississippi.

B. Etiology
1. Risk factors
   a. **Alcohol.** It is most common risk factor; 30% to 70% associated with alcohol.
   b. **Inadequate adult supervision.** Pool, bathtub, large industrial buckets are common sites of childhood immersions. Fences, sign posting, educational programs, and lifeguards minimize risk and improve survival.
   c. **Child abuse.** 29% to 38% of pediatric submersions are related to abuse or neglect.
   d. **Seizures.** Submersion occurs more frequently in children with epilepsy, perhaps due to poor adherence to anticonvulsant regimen.
   e. **Boating.** Alcohol and lack of personal flotation devices contribute.
   f. **Aquatic sports.** Diving, surfing, and water-skiing implicated. Diving and sliding headfirst produce most serious injuries. Personal watercraft contributes.
   g. **Drugs.** Induce sleep, disorientation, impair coordination, and swimming.

C. Pathogenesis
1. Anoxia
   a. Drowning sequence: panic, breath-holding, struggle to surface, gasping, water swallowed and eventually regurgitated, "break point" reached when breath-holding overcome by hypercapnia. Involuntary breaths taken with aspiration of water.
   b. "Dry" drowning in 10% to 15% with little fluid aspirated due to laryngospasm.
2. Hypothermia
   a. Produces both favorable and unfavorable effects.
   b. For survival after long-term submersion, the core body temperature must be reduced quickly and brain metabolic activity slowed rapidly to prevent damage.
   c. Most hypothermic effects are adverse. Causes death in three ways:
      i. Vagally mediated asystolic cardiac arrest (immersion syndrome)
      ii. Tendency to malignant arrhythmia (separate from immersion syndrome); cardiac arrest from ventricular fibrillation below 25°C and asystole below 18°C.
      iii. Loss of consciousness and aspiration as head falls into water.

D. Pulmonary effects
1. Atelectasis due to increased surface tension
2. Bronchoconstriction
3. Noncardiogenic pulmonary edema/ARDS
4. Fresh water inactivates existing surfactant and prevents production for 24 hours.
5. Hypertonic seawater draws fluid from plasma into the alveoli, causing pulmonary edema. May also damage type II pneumocytes.
6. Aspiration of gastric contents and particles in fresh and saltwater may lead to ARDS.
7. Post-cardiopulmonary resuscitation (CPR) damage, barotrauma, pneumonitis, central apnea, O_2 toxicity.

E. Neurologic effects. These have greatest effect on prognosis. Central nervous system injury due to anoxia.
1. The time course of anoxia is uncertain. Duration of submersion often unclear and hypothermia may have a protective effect.
2. Histology: edema, necrosis, mitochondrial swelling in cortex/hippocampus/cerebellum.
3. Severe anoxic encephalopathy with persistent coma, seizures, delayed language development, spastic quadriplegia, aphasia, and cortical blindness are reported.
4. Virtually all patients who present with fixed, dilated pupils and coma die.

F. Musculoskeletal effects. Children with anoxic encephalopathy often develop musculoskeletal problems such as contractures, hip subluxation/dislocation, and scoliosis.

G. Serum electrolytes. Minimal impact of electrolyte changes because humans rarely take in enough fluid to cause problems and easily correct small changes that do occur.

H. Hematologic effects. Patients rarely require medical intervention for anemia.

I. Renal effects
1. Acute tubular necrosis, hemoglobinuria, and albuminuria are all reported.
2. Diuresis was considered due to hypothermia but is seen in submersion at any temperature.
3. Metabolic acidosis is frequently present as a result of lactate accumulation.

J. Cardiac effects
1. Atrial fibrillation and sinus dysrhythmias are common but rarely require therapy.
2. P–R, QRS, Q–T prolongation and J-point elevation due to hypothermia.
3. Death due to ventricular fibrillation or asystole.
4. Transient increase in central venous pressure and wedge pressures and decrease in cardiac output.

K. Infectious complications. Pneumonia is the predominant infection described.

L. Diagnosis
1. History
   a. Obtain age; history of cardiac, respiratory, neurologic diseases; medications; activities precipitating submersion (i.e., boating, diving, or ingestion of drugs/alcohol); duration of submersion; temperature and type of water.
2. Physical examination
   a. Tachypnea most common. Tachycardia also common. Use hypothermia thermometer. Standard thermometer underestimates hypothermia and may cause premature stopping of CPR.
   b. Examination done to uncover injuries that caused or resulted from submersion.
   c. Neurologic classification:
      i. Category A: alert within 1 hour of presentation. These patients do well.
      ii. Category B: obtunded and stuporous but arousable at evaluation. Most of these patients survive and permanent neurologic deficits rare.
      iii. Category C: comatose/abnormal respirations/abnormal response to pain. High mortality and survivors have high rate of neurologic dysfunction.
3. Laboratory studies: Obtain hemoglobin, hematocrit, electrolytes, arterial blood gas analysis, blood alcohol level, prothrombin time/partial thromboplastin time (PT/PTT), serum creatinine, urinalysis, drug screen, cervical spine films, chest radiograph, electrocardiogram.

M. Treatment

1. Initial resuscitation
   a. Mouth-to-mouth resuscitation begun in the water.
   b. Carefully support victim's neck to prevent exacerbation of vertebral injuries.
   c. Full CPR should begin immediately on shore.
   d. Resuscitation must be continued at least until the patient has been rewarmed.
   e. Remove wet clothing and begin external rewarming plus heated O_2 in the field. Target temperature for victims of cardiac arrest is between 32°C and 34°C.
   f. Cardiopulmonary bypass should be used in severe cases on arrival at the trauma center.
2. Therapy of underlying cause
   a. Prompt administration of necessary antidotes or other measures.
   b. Anticonvulsant levels in known epileptic patients.
   c. Neck immobilization until C-spine films are cleared of possible head/neck trauma.
   d. Correct hypoglycemia and severe electrolyte abnormalities.
3. Treatment of respiratory and other organ failure
   a. Administer oxygen for hypoxemia.
   b. Manage ARDS per conventional protocols. Low tidal volume ventilation is essential.
   c. Optimize fluid status and renal blood flow. Severe cases may require dialysis.
   d. Correct cardiac dysrhythmias by rewarming.
4. Neurologic therapy—recommendations of the World Congress on Drowning are as follows:
   a. Restoration of circulation is top priority.
   b. Therapeutic hypothermia to a core temperature of 32°C to 34°C should be maintained for 12 to 24 hours.
   c. Hyperthermia should be prevented at all times in the acute recovery period.
   d. Seizures should be looked for and treated as necessary.
   e. Blood glucose concentrations should be monitored frequently and normoglycemia maintained.
   f. Hypoxemia should be avoided.
   g. Hypotension should be avoided.

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51 PULMONARY HYPERTENSION

Kimberly A. Fisher and Oren P. Schaefer

I. GENERAL PRINCIPLES

A. Definition: A mean pulmonary artery pressure (mPAP) that exceeds 25 mm Hg at rest or 30 mm Hg with exercise.

B. Classification. Revised clinical classification of pulmonary hypertension (PH) (Venice, 2003). Categories share similar pathophysiology, clinical presentation, and therapeutic options.

1. Pulmonary arterial hypertension (PAH)
   - **a.** Idiopathic pulmonary arterial hypertension (IPAH)
   - **b.** Familial pulmonary arterial hypertension (FPAH)
   - **c.** Associated with (associated pulmonary arterial hypertension [APAH]): collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, human immunodeficiency virus (HIV) infection, drugs/toxins (anorexigens, cocaine), others (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies [e.g., sickle cell disease], myeloproliferative disorders, splenectomy)
   - **d.** Associated with significant venous or capillary involvement: pulmonary venoocclusive disease (PVOD), pulmonary capillary hemangiomatosis (PCH)
2. Pulmonary venous hypertension
   - **a.** Left-sided atrial or ventricular heart disease
   - **b.** Left-sided valvular heart disease
3. PH associated with chronic lung disease and/or hypoxemia (Table 51-1)
   - **a.** Chronic obstructive pulmonary disease (COPD)
   - **b.** Interstitial lung disease
   - **c.** Sleep-disordered breathing
   - **d.** Alveolar hypoventilation syndrome
   - **e.** Chronic exposure to high altitude
   - **f.** Developmental abnormalities
4. PH due to chronic thrombotic and/or embolic disease
   - **a.** Thromboembolic obstruction of proximal pulmonary arteries
   - **b.** Thromboembolic obstruction of distal pulmonary arteries
   - **c.** Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous: sarcoidosis, histiocytosis X, lymphangiomatosis (LYMF), compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

II. ETIOLOGY

A. Three major pathophysiologic categories of PH

1. Passive—results from elevated postcapillary pressure:
   - **a.** Right heart catheterization: elevated pulmonary artery balloon occlusion pressure (PAOP), elevated pulmonary artery end diastolic pressure (PAed), normal PAed-PAOP gradient
   - **b.** Examples: left ventricular failure, mitral valve disease, obstruction of major pulmonary veins

TABLE 51-1 Pulmonary Hypertension due to Disorders of Ventilation

Vasoconstriction of precapillary and capillary vascular bed
Structurally normal pulmonary parenchyma and vascular bed
High-altitude pulmonary hypertension (residence >3,000 m)
Primary central hypoventilation
Obstructive sleep apnea
Obesity-hypoventilation syndrome
Paralytic poliomyelitis
Myasthenia gravis
Pulmonary parenchymal disease
Chronic obstructive pulmonary disease
Cystic fibrosis
Anatomic restriction of the pulmonary capillary bed
Diffuse parenchymal lung disease
Sarcoidosis
Progressive systemic sclerosis
Idiopathic interstitial pulmonary fibrosis
Acute respiratory distress syndrome
Extensive lung resection
Extensive fibrothorax
Vasoconstriction plus anatomic restriction of the vascular bed
Kyphoscoliosis
Chronic fibrotic tuberculosis

2. Active—results from constriction, obstruction, or destruction of capillary or precapillary vessels that increases resistance to flow:
   a. Right heart catheterization: normal PAOP, elevated PAed-PAOP gradient
   b. Examples: pulmonary embolism, PAH, PH due to hypoxia, congenital heart disease
   c. Vasoconstrictive stimuli: alveolar hypoxemia, acidemia, hypercarbia
3. Reactive—PH is initially passive. Upstream pulmonary vasculature responds to chronic passive congestion with active component superimposed on passive component.
   a. Right heart catheterization: elevated PAOP, elevated PAed-PAOP gradient
   b. Examples: mitral valve disease (especially mitral stenosis), PVOD

III. DIAGNOSIS

A. Signs and symptoms

1. Exertional dyspnea, fatigue, weakness, chest pain, exertional syncope, peripheral edema, abdominal distension (Table 51-2)
2. Examination findings: large jugular A wave, left parasternal (right ventricular [RV]) heave, pulmonic ejection click and flow murmur, enhanced pulmonic component of second heart sound (P2), RV fourth heart sound, signs of RV failure (hepatomegaly, peripheral edema, ascites), prominent jugular V waves, RV third heart sound, tricuspid or pulmonic regurgitation murmur
3. Non-IPAH: signs and symptoms of the underlying disease prominent

B. Chest radiograph

1. Characteristic findings: enlargement of the main pulmonary artery, dilation of the central hilar pulmonary artery branches to the origin of the segmental vessels, constriction of the segmental arteries

TABLE 51-2 New York Heart Association/World Health Organization Functional Classification of Patients with Pulmonary Hypertension

Functional Class	Description
I	No limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope
II	Mild limitation of physical activity; normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope
III	Marked limitation of physical activity; less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope
IV	Unable to perform any physical activity Dyspnea and/or fatigue present at rest, and symptoms increase with any activity; may have signs of right ventricular failure

2. Signs of passive PH (pulmonary venous hypertension)
   a. Prominence of upper lobe vessels over lower lobe vessels
   b. Presence of interstitial edema and alveolar edema, not specific for PH

C. Electrocardiography

1. Severe PH: right axis deviation in 79%; RV hypertrophy in 87%
2. Electrocardiograph (ECG) less predictive in COPD due to downward intrathoracic displacement of the heart

D. Transthoracic Doppler echocardiography (DE)

1. Role of DE in diagnosing PH:
   a. Assess RV and left ventricular (LV) morphology and function.
   b. Exclude congenital heart disease, mitral valve disease, and left atrial myxoma.
   c. Estimate severity of PH by examination of regurgitant tricuspid jet (sensitivity 0.79 to 1.00; specificity 0.60 to 0.98).
   d. Follow changes after introduction of therapy.
2. Consider transesophageal echocardiography in patients with COPD (hyperinflation makes transthoracic echocardiography technically difficult).

E. Pulmonary function tests (PFTs)

1. Role of PFTs in diagnosing PH is to exclude or characterize the contribution of underlying airway or parenchymal disease.
2. In IPAH and chronic thromboembolic pulmonary hypertension (CTEPH): 20% patients have restrictive defect; diffusing capacity often reduced to 60% to 80% predicted.
3. Arterial blood gas: normal or mild hypoxemia. If hypoxemia severe, consider right-to-left shunting or interstitial lung disease.

F. Right heart catheterization

1. Documents elevated pulmonary arterial (PA) pressure; elevated right atrial pressure (RAP >20 mm Hg) or mPAP >85 mm Hg and decreased cardiac output (CO <4 L/min/m^2) associated with increased mortality.
2. Can classify as active, passive, or reactive based on the PAed-PAOP gradient, or calculation of pulmonary vascular resistance (PVR) (>240 dyne/second/cm^5, abnormal).
   a. Active: PAed-PAOP >5 mm Hg, normal PAOP
   b. Passive: PAed-PAOP <5 mm Hg, PAOP elevated
   c. Reactive: PAed-PAOP >5 mm Hg, PAOP elevated
3. Assess pulmonary vasoreactivity.
   a. Use short-acting pulmonary vasodilator (prostacyclin, adenosine, nitric oxide)

   b. Defined as 20% decline in PVR and mPAP to absolute value mPAP <40 mm Hg with preserved or increased CO
   c. Predictive of long-term responsiveness to treatment with calcium channel blockers

G. Other studies

1. Left heart catheterization: consider when the origin of passive PH is not clear, congenital heart disease, or when pulmonary vein obstruction is considered.
2. Ventilation-perfusion lung scan ($\dot{V}/\dot{Q}$ scan): with CTEPH, $\dot{V}/\dot{Q}$ scan is often high probability; in IPAH, normal or low probability.
3. Pulmonary angiography: can assess for proximal or distal disease in CTEPH.
4. High-resolution chest computed tomography (CT): assess for underlying interstitial lung disease.
5. Laboratory evaluation: HIV serology, antinuclear antibody and rheumatoid factor titers.

IV. TREATMENT

A. General measures

1. Oxygen, to keep Sao_2 >90%
2. Diuretics if patient has right heart failure and volume overload
3. Anticoagulation, may improve survival

B. Disease-specific treatment

1. Pulmonary embolism: anticoagulation, thrombolytics
2. CTEPH: pulmonary endarterectomy if proximal, surgically amenable disease
3. Congestive heart failure: diuretics, afterload reduction
4. Ventilatory disorders (e.g., COPD): treat with specific intervention (e.g., bronchodilators)
5. Alveolar hypoxemia (of any source): supplemental oxygen to achieve Sao_2 >90%
6. Obstructive sleep apnea: nasal CPAP; weight loss

C. Pulmonary vasodilator therapy (indicated for patients with symptomatic PAH, i.e., group 1 by Venice classification)

1. Calcium channel blockers: diltiazem, nifedipine; use only in patients with acute vasoreactivity.
2. Prostanoids: epoprostenol, treprostinil, inhaled iloprost.
   a. Continuous intravenous epoprostenol improves symptoms, hemodynamics, and survival.
   b. Epoprostenol benefits those without vasoresponsiveness (vascular wall remodeling and platelet inhibitory effects).
   c. Common side effects: flushing, headache, jaw pain, diarrhea, nausea, rash, aches.
   d. Complications: line-related infection, catheter-associated venous thrombosis, thrombocytopenia. Pulmonary edema has resulted when prostanoids given to patients with PVOD and PCH.
3. Endothelin receptor antagonists: bosentan, ambrisentan; result in improved functional class, hemodynamics, six-minute walk test (6-MWT) and delayed time to clinical worsening.
4. Phosphodiesterase type IV inhibitor: sildenafil; results in improved functional class, hemodynamics, and 6-MWT.
5. Choice of treatment guided by disease severity as measured by functional classification (Table 51-2).
   a. Epoprostenol: first-line treatment for patients with New York Heart Association/World Health Organization (NYHA/WHO) class IV and/or hemodynamic profile associated with worsened outcome (RAP >20 mm Hg, mPAP >85 mm Hg, CO <4 L/min/m^2); can also be used in

NYHA/WHO class III patients, although may prefer to start with oral medication.

b. Oral therapy (bosentan, ambrisentan, or sildenafil): most appropriate for NYHA/WHO class II or III patients; can be used in NYHA/WHO class IV patients who decline treatment with epoprostenol.

c. Treprostinil (intravenous or subcutaneous): consider in NYHA/WHO II–IV, cumbersome delivery.

d. Iloprost (inhaled): demonstrated benefit in NYHA/WHO III/IV, cumbersome delivery.

6. Response to treatment: follow for improvement in symptoms, functional class, 6-MWT, echocardiogram; consider combination therapy and/or repeat right heart catheterization if no improvement.

D. Surgical treatment

1. Lung transplantation: refer patients for evaluation if NYHA functional class III/IV after 3 months of optimal medical therapy (epoprostenol), cardiac index <2 L/min/m^2, RAP exceeding 15 mm Hg.

2. Atrial septostomy: improved CO in patients with severe right heart failure, but may worsen oxygenation due to creation of right-to-left shunt, and high procedure-related mortality, rarely used "salvage" therapy.

E. Prognosis

1. Untreated: mean survival 3 years from diagnosis, with severe PH or right heart failure, death usually within 1 year.

2. In IPAH patients treated with epoprostenol, 1-year and 3-year survival rates 88% and 62%, respectively.

3. Prognosis clearly better with NYHA class I or II versus NYHA class III or IV (Table 51-2).

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52 PLEURAL DISEASE IN THE CRITICALLY ILL PATIENT

Mark M. Wilson

I. PLEURAL EFFUSIONS

A. General principles

1. Pleural disease itself is an unusual cause for admission to the intensive care unit (ICU).
2. Exceptions are a large hemothorax for monitoring the rate of bleeding and hemodynamic status, an unstable secondary spontaneous pneumothorax (PTX), and a large unilateral or bilateral pleural effusion causing acute respiratory failure.
3. Pleural disease may be overlooked in the critically ill patient; it is often a subtle finding on clinical examination and chest radiography (CXR).

B. Etiology

1. Pleural effusions are most commonly caused by primary lung disease, but may also result from systemic illnesses.
2. Atelectasis is a common cause of small pleural effusions in the ICU.
3. Congestive heart failure (CHF) is the most common cause of all pleural effusions. Most patients have the classic signs and symptoms and have CXR changes of cardiomegaly and bilateral small to moderate effusions of similar size on CXR.
4. Hepatic hydrothorax occurs in 6% of patients with liver cirrhosis and clinical ascites.
5. Parapneumonic effusions due to community-acquired and nosocomial pneumonia are common in critically ill patients.
6. If the CXR demonstrates loculation of fluid and pus is aspirated at thoracentesis, the diagnosis of empyema is established, and immediate drainage is needed.
7. Pleural effusions are seen in 3% to 17% of patients with pancreatitis.
8. Pleural effusions occur in approximately 40% of patients with pulmonary embolism.
9. A potential life-threatening event, esophageal rupture requires immediate diagnosis and therapy. The history is usually of severe retching or vomiting or instrumentation of the esophagus.

C. Pathophysiology

1. Atelectasis causes pleural fluid by decreasing local pleural pressure, thereby favoring movement of fluid from the parietal pleural surface into the pleural space. Analysis of the pleural fluid reveals a serous transudate that dissipates once atelectasis resolves.
2. Hepatic hydrothorax results from movement of ascitic fluid through congenital or acquired diaphragmatic defects.
3. Pleural effusions from pancreatitis result from direct contact of the diaphragm with pancreatic enzymes (so-called sympathetic effusion), transfer of ascitic fluid through diaphragmatic defects, a fistulous tract between a pseudocyst and the pleural space, or retroperitoneal movement of fluid into the mediastinum and rupture into the pleural space.

4. Effusions from pulmonary emboli result from increased capillary permeability, imbalance in microvascular and pleural hydrostatic pressures, and pleuropulmonary hemorrhage.
5. Pleural effusion, with or without PTX, occurs in 75% of cases of esophageal rupture and are secondary to mediastinitis.
6. Hemothoraces (fluid with a pleural fluid-to-blood hematocrit ratio >30%) result from penetrating or blunt chest trauma; as complications of invasive procedures; with pulmonary infarction, malignancy, or ruptured aortic aneurysm; or as a complication of anticoagulation.

D. Diagnosis

1. Pleural effusions appear on supine CXR as increased homogeneous densities over the lower lung fields compared with the upper lung fields.
2. Underlying diffuse parenchymal lung disease is common in patients in the ICU and may make the CXR diagnosis of pleural effusion problematic.
3. The diagnostic separation of transudates from exudates is discussed in detail in Chapter 10.
4. With hepatic hydrothorax, the CXR usually reveals a normal cardiac silhouette and a right-sided pleural effusion in 70% of patients. The diagnosis is confirmed by demonstrating that pleural and ascitic fluids have similar protein and lactate dehydrogenase concentrations.
5. The CXR in parapneumonic effusions commonly shows a small to large pleural effusion ipsilateral to a new alveolar infiltrate.
6. Effusions from pancreatitis are usually small and left-sided (60%) but may be isolated to the right (30%) or bilateral (10%). The fluid is an exudate with glucose values approaching those of the serum and amylase values greater than those of serum.
7. Pulmonary emboli usually produce exudative effusions; however, 20% are transudates as a result of associated atelectasis. Pleural fluid analysis is highly variable and nondiagnostic.
8. A presumptive diagnosis of esophageal rupture requires immediate confirmation with lateral decubitus esophagrams. Amylase of salivary origin appears in pleural fluid in high concentration. With seeding of anaerobic organisms from the mouth, the pH falls rapidly and progressively to approach 6.00.

E. Treatment

1. Thoracentesis should be performed if the diagnosis is in question or if the patient's course is other than expected (patient is febrile or has pleuritic pain, unilateral or disparate sized effusions, absence of cardiomegaly, or a partial pressure of arterial oxygen inappropriate for the degree of pulmonary edema).
2. When sampling of fluid is indicated clinically and the effusion is small, thoracentesis should be performed under ultrasonographic guidance.
3. Therapeutic thoracenteses are primarily indicated for the relief of dyspnea.
4. Therapy for effusions due to CHF involves decreasing venous hypertension and improving cardiac output with preload and afterload reduction.
5. Treatment of hepatic hydrothorax is directed at resolution of the ascites with sodium restriction and diuresis. Chemical pleurodesis is often unsuccessful. Prolonged chest tube drainage is to be avoided due to an increased risk for infection, malnutrition, immunosuppression, and renal failure. This group of patients should be evaluated for potential transjugular intrahepatic portosystemic shunt (TIPS) procedure.
6. When a parapneumonic effusion is free flowing on lateral decubitus, CXR and thoracentesis shows a nonpurulent, polymorphonuclear neutrophil–predominant exudate with a fluid pH >7.30, the patient has a high likelihood of resolution without sequelae over 7 to 14 days using antibiotics alone.

7. Draining the pleural space should be considered in the case of fluid with a positive Gram stain or culture, or when the fluid pH is <7.20 (complicated effusion), given the associated increase in morbidity and mortality.
8. No specific therapy is usually necessary for effusions due to pancreatitis; the effusion resolves as the pancreatic inflammation subsides.
9. The diagnosis of spontaneous esophageal rupture dictates immediate intervention; survival is >90% if primary closure and drainage occurs within the first 24 hours.
10. Traumatic hemothorax should be treated with immediate tube thoracostomy.

F. Complications

1. Absolute contraindications for thoracentesis include an uncorrectable bleeding diathesis or an uncooperative patient; the major relative contraindications are the presence of a small amount of pleural fluid and a low benefit-to-risk ratio for the procedure.
2. The risk of PTX with thoracentesis is inversely correlated with operator experience.
3. In experienced hands, PTX is no more likely to occur in the patient receiving mechanical ventilation than in the patient who is not; however, if a PTX does develop, the patient receiving mechanical ventilation will likely develop a tension PTX (see subsequent text).
4. Complications resulting from diagnostic or therapeutic thoracentesis are similar. There is, however, an increased risk of PTX with a therapeutic procedure and three complications unique to therapeutic thoracentesis may be seen—hypoxemia, unilateral pulmonary edema, and hypovolemia.

II. PNEUMOTHORAX

A. General principles

1. PTX refers to the presence of free air in the confines of the chest cavity (pleural space).

B. Etiology

1. Spontaneous PTX occurs without an obvious cause, either without findings of lung disease (primary spontaneous PTX) or with clinically manifest lung disease (secondary spontaneous PTX) such as chronic obstructive pulmonary disease, status asthmaticus, interstitial lung disease, *Pneumocystis jiroveci*, necrotizing pneumonias, or cystic fibrosis.
2. Traumatic PTX results from penetrating or blunt chest trauma.
3. Iatrogenic PTX, the most common cause of PTX in the ICU, is a consequence of barotrauma associated with mechanical ventilation or invasive procedures (thoracentesis, central venous catheters).
4. PTX occurs in 1% to 15% of all patients receiving mechanical ventilation.

C. Pathophysiology

1. If the pressure gradient between the airways and pleural space is transiently increased, alveolar rupture may occur; air enters the interstitial tissues of the lung and may then enter the pleural space or decompress to the mediastinum and subcutaneous tissues.
2. When PTX occurs, the elasticity of the lung causes it to collapse until the pleural defect seals or the pleural and alveolar pressures equalize.
3. Progressive accumulation of air (and positive pressure) within the pleural space produces a tension PTX. Tension PTX compresses mediastinal structures, impairing venous return to the heart and decreasing cardiac output, and causes potential fatal cardiovascular collapse. In the setting of mechanical ventilation, 30% to 97% of patients with PTX develop tension.

D. Diagnosis

1. Most iatrogenic PTXs occur at the time of the procedure from direct lung puncture, but delayed (up to 12 to 24 hours later) PTXs have been noted.

2. In the supine patient, PTX gas accumulates in a subpulmonic location and outlines the anterior pleural reflection, the costophrenic sulcus (deep sulcus sign), and the anterolateral border of the mediastinum. The base, lateral chest wall, and juxtacardiac areas should be carefully visualized for evidence of PTX. Up to 30% of PTXs may not be detected initially and half of these will subsequently progress to tension PTX.
3. PTX in the mechanically ventilated patient usually presents as an acute cardiopulmonary emergency with a mortality rate of 7% if it is rapidly diagnosed clinically, versus a mortality rate of 31% to 77% for delayed diagnoses.
4. The most common CXR signs of a PTX under tension are contralateral mediastinal shift, ipsilateral diaphragmatic depression, and ipsilateral chest wall expansion.

E. Treatment

1. Up to half of spontaneously breathing patients with needle-puncture (iatrogenic) PTX may be managed expectantly without the need for tube drainage.
2. If the patient is receiving mechanical ventilation or if the PTX is large or has caused substantial symptoms or gas exchange abnormalities, then tube thoracostomy should be performed as soon as possible. Treatment should not be delayed to obtain CXR confirmation. If a chest tube is not immediately available, placement of a large-bore needle into the anterior second intercostal space on the suspected side will be lifesaving.

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53 MECHANICAL VENTILATION: INVASIVE AND NONINVASIVE

Scott E. Kopec and Richard S. Irwin

I. GENERAL PRINCIPLES. Needs for mechanical ventilation (MV) include hypoxic respiratory failure and hypercapnic respiratory failure. Intrinsic lung disease can result in hypoxemia and/or pump failure manifested by hypercapnia and hypoxemia. Pure hypercapnic respiratory failure can result from central nervous system depression, respiratory muscle fatigue or weakness, chest wall mechanical defects, and mediators of ongoing disease such as sepsis that affect respiratory muscles. Positive pressure MV is currently the predominant means of providing ventilatory support, as opposed to negative pressure ventilation. MV may be invasive, delivered through an endotracheal tube (ETT) or tracheostomy tube. Noninvasive positive pressure ventilation (NIPPV) is delivered to the patient through a full-face or nasal mask.

A. Modes of invasive MV

1. **Volume cycled MV.** Delivers a guaranteed preset volume (Vt) with each breath that is specified by the operator. Peak inspiratory pressures (PIP) generated by the ventilator are variable with each breath, depending on airway resistance or compliance. A "pop-off" pressure can be assigned to prevent excessive peak pressures that abort the breath when that pressure limit is reached. The time that it takes to deliver the Vt (inspiratory time, or Ti) is also controlled by the operator because it is dependent on the volume, inspiratory flow rate (Vi), and wave form characteristics (square or decelerating wave forms), which are all specified by the operator.
   a. **Assist control (AC).** All breaths are assisted. The patient initiates a breath and a set inspiratory flow and Vt are delivered with each breath. However, if the patient's intrinsic rate falls below the preset basal rate, then all the breaths delivered are control breaths, spaced at regular time intervals. AC is also a time-triggered mode that delivers a preset volume if the patient does not initiate any spontaneous breaths. During the control and assisted breaths, the Vt and inspiratory flow and characteristics are exactly the same with each breath.
      i. Advantages: the patient receives a guaranteed Vt and the most widely used mode of MV. When patients are in synchrony with the ventilator, this mode allows for minimal patient effort and rest for fatigued respiratory muscles.
      ii. Disadvantages: can potentially induce respiratory alkalosis if high respiratory drive (e.g., liver failure). Patient asynchrony and respiratory muscle fatigue can occur if a different Vi is required by the patient. I:E ratio can vary because the variable respiratory rate (RR) can alter the expiratory phase.
   b. **Synchronized intermittent mandatory ventilation (SIMV).** SIMV can deliver three kinds of breaths—spontaneous, assisted, and mandatory breath. If no breaths are initiated within a period of time, a mandatory breath will be delivered. If the machine senses that the patient has taken a spontaneous breath just before the mandatory breath, the machine will recycle and then wait for the next spontaneous breath and assist it.
      i. Advantages: ensures a minimum V_E.

ii. Disadvantages: it has been shown to be the least beneficial weaning mode. Cannot fully control the I:E ratio given the variability in RR and presence of spontaneous breaths.

2. **Pressure-limited MV** delivers a flow until a preset pressure limit that is set by the operator is reached. PIP is therefore always the same and is the sum of the preset pressure limit for each breath and the positive end-expiratory pressure (PEEP) value. Vt is variable with each breath, according to airway resistance and compliance.
   a. **Pressure support (PS).** Every breath is an assisted breath. Each breath is triggered by the patient's respiratory effort. The patient determines the inspiratory flow rate and shape of the wave form as well as the RR. When a preset pressure limit is reached, inspiratory flow slows to <0.5 L/minute and the machine cycles off.
      i. Advantages: better patient synchrony, limits PIP. As effective as spontaneous breathing trial weaning.
      ii. Disadvantages: if the patient stops breathing then an apnea backup breath is given that is infrequent and less responsive than the backup from AC. Inadequate volumes could be delivered if the ETT is blocked or decreased lung compliance causes present pressure limit to stop inspiratory flow before an adequate Vt is delivered (e.g., pneumothorax).
   b. **Pressure control (PC).** PC is similar to AC in that control breaths are delivered at a preset time interval, but with a preset pressure limit rather than a preset volume. RR and time to maximal pressure limit are both operator set, and spontaneous breaths can be interspersed between the mandatory breaths.
      i. Advantages: can limit PIP and plateau pressure (Pplat) to minimize ventilator-associated lung injury. Can control or extend Ti for inverse ratio ventilation (IRV) to increase mean airway pressure (MAP) and augment oxygenation. Therefore, given these two advantages, this mode is often used for advanced acute lung injury (ALI).
      ii. Disadvantages: cannot ensure minimal V_E with airway obstruction or poor compliance, as in PS mode, because delivered volumes may be low if compliance is high. For normal I:E ratios, PC mode is a standard controlled mode and does not need additional sedation. For IRV (I:E 4:1), sedation with or without paralysis is necessary because of patient discomfort. Circuit leaks can extend inspiratory time. Exaggeration of inspiratory time can limit time for passive exhalation and induce autoPEEP.
   c. **Bilevel.** A form of pressure-support ventilation that allows for unrestricted spontaneous breathing, that switches between a high and low airway pressure based on an adjustable time sequence. Cycling between the two pressure settings can be synchronized with the patient's spontaneous breathing to maximize the I-pressure during inspiration, and the E-pressure during expiration.
      i. Potential advantages: theoretically more comfortable to the patient, resulting in less agitation and less need for sedation.
      ii. Potential disadvantages: not well studied, safety not established
   d. **Airway pressure release ventilation (APRV).** An extreme form of bilevel ventilation, maintaining a long period of high pressure followed by a very short period of low pressure (the "release"). This results in an inverse I:E ratio of 8–9:1. It is a time-triggered, pressure-limited, time-cycled mode that also allows for the patient to have spontaneous breathing.
      i. Potential advantages: improve oxygenation in patients with severe acute respiratory distress syndrome (ARDS), decrease the frequency of opening and closing the alveoli, and limit the amount of alveolar

stretching-factors thought to promote lung injury. Decrease airway pressures.

ii. Potential disadvantages: not well studied, safety not established. High number of reported pneumothoraces in small studies.

3. **Continuous positive airway pressure (CPAP)** occurs when the inspiratory and expiratory limbs are pressurized to a preset end-expiratory pressure. CPAP functions primarily as an oxygenation and weaning modality.
   a. No inspiratory flow is delivered, so it is not a true positive-pressure MV mode. The patient assumes most of the work of breathing (WOB) by generating his or her own RR, Vi, Vt, and therefore V_E, closely simulating unassisted spontaneous breathing.
   b. WOB is reduced compared to complete discontinuation from the MV circuit and delivery of only F_{IO_2} ("T-piece"). Application of PEEP stents the airways open and allows for better exhaled Vt. CPAP can be used in coordination with flow-by. Flow-by occurs when a stream of gas is delivered across the ventilator circuit, assisting the patient in drawing his or her own Vi and Vt.
      i. Expiratory positive airway pressure (EPAP): only the expiratory phase is pressurized. Compared to CPAP, EPAP has a lower MAP and higher WOB.
      ii. For those dependent on MV for only oxygenation and not ventilation, CPAP can improve oxygenation without subjecting the patient to the harmful effects of MV.

B. Ventilator settings for invasive positive pressure MV

1. **Fraction of inspired oxygen (F_{IO_2}).** Supplemental oxygen is adjusted to target an oxygen saturation (Sa_{O_2}) >90% and/or Pa_{O_2} >60 mm Hg. O_2 should not be withheld for any concern of CO_2 narcosis on MV. O_2 should not be withheld for concern of toxicity, if required. It is believed that clinically significant O_2 toxicity is unlikely to occur with F_{IO_2} <0.6 even with prolonged delivery. Balance between side effects of PEEP, used to lower F_{IO_2}, and O_2 toxicity concern.
2. **Tidal volume (Vt)** is constant in volume-cycled modes and varies with each breath in pressure-limited modes. In patients without lung disease, Vt of 8 mL/kg of ideal body weight are used provided the Pplats remain <30 cm H_2O. Lower tidal volumes are recommended for ALI and ARDS of 6 mL/kg of ideal body weight. Vt ≤8 mL/kg is recommended in patients with obstructive lung disease (asthma, chronic obstructive pulmonary disease [COPD]). Limiting Vt decreases expiratory time (Te) and minimizes autoPEEP.
3. **Inflation pressure limit.** High inflation pressures cause barotrauma. Increased Pplat (end inspiratory airway plateau pressure), rather than PIP, is most injurious, reflecting alveolar overdistension and not airway resistance. No threshold is safe but Pplat ≤30 cm H_2O is recommended. Use of sedation with or without paralytics can decrease dynamic hyperinflation and allow for lower Pplat. MV pop-off pressure should be set approximately 10 cm above the PIP.
4. **Sighing. The need for** periodic "sighs" is not currently recommended for routine MV.
5. **Respiratory rate.** RR and Vt determine V_E. For SIMV and PC modes, RR is preset and rates of 12 to 20 beats per minute are reasonable. The AC rate is set below the patient's spontaneous RR to minimize the chance of controlling ventilation with its attendant risk of respiratory muscle atrophy. RR and/or Vt should be adjusted down for autoPEEP.
6. **Sensitivity.** This adjustment affects the amount of drop in airway pressure that is required before the ventilator senses the patient's effort and assists them during AC and PS. Sensitivities of approximately 0.5 to 1 cm H_2O allow very weak patients to initiate a breath. Higher values make triggering

more difficult and are used in conditions with a high respiratory drive (e.g., liver failure) to prevent respiratory alkalosis. The sensitivity is usually set by the respiratory therapist. But one needs to consider whether both the sensitivity value is too high and autoPEEP is present if the patient is making an effort to breathe and the machine is not triggering in assisted modes.

7. **Minute ventilation (V_E).** V_E is the product of the Vt and RR. Normal individuals maintain normocapnia with a resting V_E of approximately 5 L/minute. Adjustment of V_E is based on $Paco_2$ as a marker of ventilatory requirements. "Permissive hypercapnia" is employed in ARDS and status asthmaticus to minimize the risk of barotrauma. Most experts do not recommend administering buffer solutions unless the pH is <7.15. Permissive hypercapnia is felt to be contraindicated in patients with increased intracranial pressure. Do not overventilate patients with chronic CO_2 retention because it can lead to posthypercapnic metabolic alkalosis with its attendant complications. On the other hand, high ventilatory requirements are present in hypermetabolic states (sepsis), or high caloric intake where excess CO_2 production needs to be eliminated. High dead space increases ventilatory requirements for the same CO_2 target.
8. **Inspiratory flow rate (Vi).** Inspiratory flow is usually specified rather than I:E ratio (except in PC mode). The ratio of Vt (liters) to Vi (L/minute) determines Ti (minute). Because RR determines total respiratory cycle time and exhalation is passive, I:E ratio is determined by the above-mentioned three fixed parameters.
   a. For volume-cycled modes, Ti will be longer and PIP lower for a decelerating wave form and mimics PS mode. Higher Vi decreases Ti to allow for greater time for passive exhalation and reduce autoPEEP in obstructive lung diseases. Higher Vi increases PIP but should not affect Pplat. However, there is a theoretic concern that too-rapid lung inflation can cause "deformation injury."
   b. In PS mode, patients determine their own Vi. Vi is specified for PC ventilation in that one can determine how quickly to achieve the pressure limit.
   c. In asthma and COPD, the expiratory time needs to be lengthened to allow for adequate exhalation of trapped gas. Therefore, the I:E ratio needs to be as low as possible, achieved by a short inspiratory time of lower Vt or higher inspiratory flow rates.
9. **Inspiratory hold and IRV.** No flows are delivered, but passive exhalation is prevented. Ti is regulated in PC mode to precisely control I:E ratio, tantamount to an "inspiratory hold." It is used to recruit collapsed lung units in ALI and increase Pao_2, as an alternative to increasing PEEP, which increases Pplat and risks barotrauma. IRV occurs when Ti is greater than Te and is used in severe ARDS to treat hypoxemia.
10. **Mean airway pressure.** MAP is the airway pressure averaged over the entire respiratory cycle time, inspiration and exhalation. Attention to MAP is important in ALI in treating hypoxemia, because more time in inspiration, keeping the lung inflated with an inspiratory hold, increases the oxygen driving pressure. An inspiratory hold or IRV, increasing Vt and RR, increases the time spent in inhalation and therefore the amount of time in positive pressure. Increasing PEEP and thereby exhalation phase pressure increases MAP.
11. **Positive end-expiratory pressure.** PEEP is the maintenance of positive pressure after expiratory flow is completed until the next inspiratory flow is initiated.
    a. Applied PEEP distends airways down to the alveoli to allow for more complete exhalation and CO_2 removal by reducing air trapping. PEEP improves $\dot{V}/\dot{Q}$ matching, by stenting open alveoli with patent capillaries. It helps distribute alveolar debris and decreases O_2 diffusion distance but does not drive fluid out of the lung.

b. Intrinsic PEEP (PEEPi) or autoPEEP is the positive pressure that occurs from incomplete exhalation before the initiation of the next breath. Dynamic hyperinflation causes a pressure gradient and a persistent flow. PEEPi is detected on the flow versus time curve when expiratory flow does not return to baseline before the next inhalation. Also, if the end-expiratory airway Pplat is greater than applied PEEP, then PEEPi is present.

c. Applied PEEP usually ranges between 0 and 20 cm H_2O and is usually adjusted up or down in 2.5- to 5-cm H_2O increments.

d. In obstructive diseases, applied PEEP can mitigate the effects of PEEPi in spontaneously breathing patients.

e. Complications of excessive applied or intrinsic PEEP include overdistension, barotrauma, hypotension from limiting venous return, and decrease in left ventricular diastolic compliance due to lung hyperinflation compressing the lateral cardiac wall.

f. When applied prospectively, a low PEEP strategy yielded the same outcomes as the high PEEP strategy. Therefore, the lowest possible PEEP that promotes adequate oxygenation, in conjunction with other ventilatory strategies, is recommended.

12. Recruitment maneuvers occur when an expiratory hold is applied with high PEEP levels for an extended time to increase Pao_2 by opening collapsed lung units. Levels of 35 to 40 cm H_2O PEEP are held for up to 90 seconds. PEEP $\geq$15 cm H_2O is used after the recruitment maneuver to prevent derecruitment. However, there is no consensus as to the optimal PEEP level, the duration of expiratory hold, or the frequency of repeating the maneuver. There are also no data that show that recruitment maneuvers affect outcomes in ARDS.

C. NIPPV refers to the delivery of ventilatory support without placement of an ETT. Many patient interfaces are available, including mouth pieces and face masks.

1. Ventilator interfaces. Oral mouthpieces are subject to excessive air leakage. Masks are more secure and tighter fitting. Nasal masks and pillows are comfortable, allow for talking and even swallowing, but have greater air leaks for that reason. Oronasal or full-face masks are most common in critical care settings to minimize air leaks and ensure quick control over ventilation, but oronasal masks prevent oral secretion evacuation, risk aspiration should emesis occur, risk asphyxiation should the ventilator circuit be interrupted, and cause more nasal bridge skin breakdown.

2. Ventilators. Almost any critical care ventilator can be used with the NIPPV interfaces; these are sometimes preferable given the higher flow rates that can be delivered and the ability to monitor RR, Vt and V_E. However, intensive care unit (ICU) ventilators may alarm excessively, thereby interrupting effective ventilation. More portable ventilators that are primarily available for home usage can be used.

3. Modes of NIPPV. The most commonly used mode of NIPPV is bilevel positive-pressure ventilation (*Bi*PAP is the trade name of a ventilator that delivers bilevel positive-pressure ventilation). Bilevel is a pressure-limited mode in which an inspiratory positive airway pressure (IPAP) and EPAP are set. Bilevel positive-pressure ventilation allows for patient triggering, and most machines have a backup-rate mode that allows for both spontaneous and timed delivered ventilations.

4. Patient selection. Patients obviously need to be in respiratory failure and require ventilatory assistance. Ideal candidates for NIPPV are those who are more awake and can protect their airway from aspiration and clear airway secretions by coughing. Less agitated patients are ideal and can tolerate the mask interface without claustrophobia.

5. **Disease states.** The patient groups that are most likely to benefit from NIPPV is the patient suffering from COPD exacerbation, followed by cardiogenic pulmonary edema, hypoxic respiratory failure, use in the emergency department for marginal patients to avoid intubation, and for those patients in respiratory distress not desiring intubation for end-of-life considerations. NIPPV should be considered only as a bridge to hopefully avoid intubation while correcting the underlying disease state. Its use should probably be limited to 24 to 48 hours. Approximately 50% of patients do not tolerate or improve with NIPPV. Any condition with copious secretions, such as pneumonia, that requires suctioning is not appropriately treated with NIPPV.
6. NIPPV can be used as a mode for weaning (see Chapter 54).

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54 MECHANICAL VENTILATION: DISCONTINUATION

Scott E. Kopec and Richard S. Irwin

I. GENERAL PRINCIPLES

A. Outcome for patients with respiratory failure:

1. Mechanical ventilation (MV) can be discontinued in 80% to 90% of patients within 3 weeks. Of this group, 77% can be extubated within 72 hours of the start of MV.

2. Ten percent to 20% require prolonged MV >21 days. Weaning from MV in this group may take >3 months. One-year survival ranges widely between 12% and 93%. Survivor quality of life may be minimally to moderately impaired when assessed 2 years later.

B. Four potentially reversible causes of prolonged MV:

1. Inadequate respiratory drive due to:

a. Nutritional deficiencies

b. Sedatives

c. Central nervous system (CNS) abnormalities

d. Sleep deprivation

2. Inability of the lungs to carry out gas exchange without MV if the underlying cause of respiratory failure has not significantly improved.

3. Inspiratory respiratory muscle fatigue due to:

a. Neuromuscular diseases

b. Sepsis

c. Nutritional and metabolic deficiencies

d. Corticosteroids

e. Chronic renal failure

f. Increased work of breathing (WOB) from intrinsic disease, ventilator loads or cardiovascular failure.

g. Hypoxia and hypercapnia

4. Psychological dependency.

C. Pump failure from inspiratory respiratory muscle fatigue is probably primarily responsible for failure of discontinuation of MV in most patients on prolonged MV.

D. Cardiovascular failure may prolong MV due to:

1. Passive pulmonary congestion, leading to increased WOB

2. Poor cardiac performance causes inadequate oxygen supply to the respiratory muscles

3. Removal of positive intrathoracic pressures during spontaneous breathing (SB) that can paradoxically unload the left ventricle

II. INDICATIONS

A. When to initiate discontinuation trials

Because no objective data exist on when to begin the weaning process, clinical judgment is necessary. A monitored SB screening trial is recommended when the following criteria are met:

1. Underlying reason for MV has been stabilized and patient is improving

2. Hemodynamically stable and on minimal and unchanging doses of pressors

3. Adequate oxygenation (Pao_2/Fio_2 >200, PEEP <7.5 cm H_2O, Fio_2 <0.5)

B. Principles of weaning

1. Breathing is a form of continuous muscular exercise and MV discontinuation should reflect principles of muscle training that include stressing respiratory muscles to early fatigue and then resting them. Maintain a structured, progressive program because benefit is transient.
2. Sudden increased WOB with MV discontinuation can cause harmful effects. Monitor closely during the first 5 minutes and return to MV if there is deterioration.
3. Both physiologic failure and anxiety cause tachycardia, tachypnea, and hypertension; therefore, do not assume anxiety alone is the cause.
4. Screening patients daily may reduce intensive care unit (ICU) stay and time of MV.
5. Studies have shown that when a standardized, hospital-based protocol is used that incorporates a team approach between physicians, nurses, and respiratory therapist success rates for weaning are significantly improved.

C. Predictive indices for successful discontinuation

1. Indices to predict weaning success yield conflicting data. It does not appear that any single parameter can consistently and accurately predict success in weaning. The following parameters have the highest accuracy:
   a. Rapid breathing (respiratory frequency [f] over 1 minute divided by tidal volume [Vt] averaged over 1 minute) (f/Vt in L). f/Vt should be measured while patients are spontaneously breathing.
      i. f/Vt < 105 has a positive predictive value of 0.78.
      ii. f/Vt ≤ 105 has a negative predictive value of 0.95.
   b. Maximal inspiratory pressure (MIP) of <15 cm H_2O had a negative predictive value of 100%.
2. The predictors for successful discontinuation of MV are even less accurate the longer a patient is dependent on MV.
3. Clinical observation of respiratory muscles is not reliable in predicting failure. Both muscle fatigue and any increase in respiratory muscle load cause a change in rate, depth, and pattern of breathing. Nevertheless, close monitoring is necessary because discontinuation failure is inevitable if these signs are due to fatigue. If these signs never appear, successful discontinuation is likely.

III. PROCEDURE

A. Modes of discontinuation from MV

Successful discontinuation of MV is less determined by the mode of weaning than by identification and correction of medical barriers to weaning. However, when compared to other modes, synchronized intermittent mandatory ventilation (SIMV) has nearly consistently performed the worst in clinical trials. The three commonly used modes of weaning are:

1. SB discontinuation trial

   a. Sudden, complete withdrawal of machine-supported breaths.
   b. Only one SB trial is recommended in a 24-hour period.
   c. A "T-piece" is attached to the enclotracheal tube (ETT) to deliver humidified oxygen for the SB trial. T-tube flow should exceed the patient's inspiratory flow requirement.
   d. SB trial can also be performed using continuous positive airway pressure (CPAP), typically set at a pressure of 5 cm H_2O through the ventilator.
   e. The CPAP trial allows for the monitoring of respiratory rate, minute ventilation (V_E), and Vt during weaning.
   f. A weaning trial should not be attempted until it has been determined that the patient can breathe on his or her own spontaneously.
   g. Placing the patient on a sedation holiday starting approximately 1 hour before starting the SB trial appears to improve the success of the weaning trial.

2. **Pressure support ventilation discontinuation trial**
   a. Gradual decrease of augmented inspired pressure so that the patient gradually assumes the WOB.
   b. Although it is commonly thought that 5- to 7-cm H_2O of pressure support (PS) compensates for ETT and circuit resistance, this has not been shown to be consistently true.
   c. A major adverse effect of PS discontinuation trials is PS-induced central apneas.
3. **Noninvasive positive pressure ventilation (NPPV) weaning**
   a. The first approach is to extubate directly to NPPV once screening and predictive indices suggest that weaning is close but not likely successful in the short term.
   b. The second uses NPPV as a bridge to avoid reintubation after discontinuation from MV has failed. In this setting, mortality may actually be worse.

B. When to extubate

1. Most patients who have well-tolerated SB trials lasting 30 to 120 minutes can be considered for extubation.
2. Patients with the following conditions should probably have well-tolerated SB trials lasting >2 hours before considering extubation:
   a. On prolonged MV (>21 days)
   b. Neurologic patients who are predicted to have difficulty clearing their airway secretions
   c. Patients who have failed recent extubations
3. For patients being weaned on PS mode, extubation can be considered after the patient tolerates PS of 5 to 7 cm H_2O for 2 hours.
4. The two most common causes of failed extubations are upper airway obstruction and inability to protect the airway and clear secretions.
5. Risk factors for upper airway obstruction include:
   a. Prolonged MV
   b. Female sex
   c. Repeated or traumatic intubations
6. The cuff-leak test does not consistently predict clinically significant upper airway obstruction.
7. Patients at high risk for postextubation upper airway obstruction should be considered for extubation in a well-equipped setting such as an operating room environment, be extubated over an ETT exchange catheter, and/or have a helium-oxygen tank and reintubation equipment bedside.
8. Predictors for patients failing extubation due to inability to protect the airway and clear secretions include:
   a. Cough peak flow measurements of <60 L/minute
   b. Secretion volume of ≥2.5 mL/hour
   c. Poor mentation, as defined by the inability to perform the following commands:
      i. Open eyes.
      ii. Follow the observer with eyes.
      iii. Grasp hand.
      iv. Stick out tongue.

C. Recommended SB discontinuation protocol

The salient features are as follows:

1. Sit the patient in an upright position.
2. Avoid sedation unless anxiety is overwhelming and a barrier to weaning.
3. "T-piece" with humidified oxygen at inspiratory flow rates to match inspiratory requirements or keep patient connected to the ventilator and use CPAP mode and 5 cm H_2O.

4. Continue the trial unless clinical findings, judgment, oxygenation, and cardiac monitoring suggest respiratory muscle fatigue or clinical deterioration with the following parameters:
   a. Clinical criteria of diaphoresis and increased respiratory effort, paradoxical breathing, or use of accessory respiratory muscles are present.
   b. Heart rate >30 beats per minute over baseline, profound bradycardia, ventricular ectopy, or supraventricular tachyarrhythmias.
   c. Mean arterial blood pressure >15 mm Hg or <30 mm Hg from baseline.
   d. Respiratory rate >35 breaths per minute for at least 5 minutes, Sao2 <90%, or dyspnea rated by the patient as >5/10
   e. Routine arterial blood gas (ABG) analysis is not thought necessary in all cases, because blood gas alterations may be a late finding in respiratory muscle fatigue.
5. When the trial is terminated due to failure, resume the prior MV settings.
6. Once-a-day SB trials are recommended over other modes.

D. Managing discontinuation failure

1. The respiratory muscles are pivotal in the onset and perpetuation of respiratory failure.
2. Interventions to increase respiratory muscle strength:
   a. Reverse malnutrition.
   b. Correct electrolyte abnormalities (PO_4^-, Mg^{+2}, Ca^{+2}, K^+).
   c. Correct hypoxemia.
   d. Correct chronic hypercapnia during MV.
   e. Reverse hypothyroidism.
   f. Improve cardiovascular function.
   g. Minimize sedation unless anxiety is overwhelming and inhibiting weaning.
   h. Consider the use of progesterone as a respiratory center stimulant.
   i. Consider and evaluate for the possibility of myopathy, polyneuropathy.
   j. Treat sleep deprivation and central fatigue with short-acting sedatives at night.
   k. Improve diaphragmatic function by sitting the patient up during weaning.
   l. Consider using theophylline to stimulate the respiratory center and augment diaphragmatic contraction and suppress its fatigue. Avoid drug interactions with calcium channel blockers that could inhibit the beneficial effects on the diaphragm.
3. Interventions to decrease respiratory muscle demand:
   a. Maximize treatment of systemic disease to decrease metabolic requirements and mitigate cytokine production that can adversely affect muscle function.
   b. Prescribe bronchodilators and discontinue β-blockers for increased airway resistance when not needed for comorbid diseases.
   c. Give a course of systemic corticosteroids in exacerbations of chronic obstructive pulmonary disease (COPD) and asthma.
   d. Prescribe diuretics to reduce pulmonary edema.
   e. Routinely evaluate and treat cardiac dysfunction including myocardial ischemia.
   f. In average size adults, ETT size <8 mm internal diameter may increase airway resistance. Therefore, if an ETT size is very small (e.g., 6.5 mm internal diameter), consider replacing the tube with a larger one.
   g. Add CPAP for marginal cardiac function to decrease left ventricular preload.

h. Determine whether the ventilator is increasing WOB; whether the sensitivity or trigger threshold is appropriate; and whether the inspiratory flow rate or pattern matches patient demand.

i. Avoid hyperinflation; apply extrinsic PEEP in the presence of inspiratory triggering threshold load from intrinsic PEEP; consider the type of humidification devices because dead space and airway resistance are increased with heat and moisture exchangers rather than heated humidifiers.

j. Evaluate overfeeding causing increased CO_2 production in chronic hypercapnic patients and the need for increased alveolar ventilation to remove this excess product of metabolism. Overfeeding may precipitate respiratory acidosis or ongoing respiratory muscle fatigue in patients unable to increase alveolar ventilation adequately. Increased total calories, rather than percentage carbohydrates, is the more likely cause of the increased CO_2 production.

4. Potential advantages of tracheostomy tube placement for prolonged failure to wean patients:

a. Recent studies have demonstrated that tracheostomy preformed early (i.e., 7 days of mechanical ventilatory support after ETT placement) have resulted in decreased length of stay and risk for ventilator-associated pneumonia, and may aid in weaning by decreasing the WOB.

b. Patients intubated with an ETT should be accessed after several days on MV. Those patients who are deemed unlikely to wean in within the next 1 to 2 days should be evaluated for a tracheostomy.

c. Tracheostomy has other advantages:

i. More stable means of ventilating and allows for greater flexibility to perform CPAP or SB trails with a tracheostomy mask.

ii. The presence of an ETT in the patient's nose or mouth may cause anxiety due to discomfort and frustration from the inability to communicate effectively. Both may interfere with effective discontinuation trials and prolong the duration of MV.

iii. The presence of a tracheostomy tube may alleviate patient frustration by allowing for better communication through mouthing words. Partial cuff deflation may allow vocal cord stimulation and vocalization, even when the patient is still dependent on positive pressure ventilation. During SB trials, vocalization can be attempted with full-cuff deflation with gloved finger occlusion of the tube or placement of a one-way valve.

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55 RESPIRATORY ADJUNCT THERAPY AND NONINVASIVE RESPIRATORY MONITORING

Scott E. Kopec and J. Mark Madison

I. AEROSOL THERAPY

A. General principles

1. Inhaled aerosols deliver drugs directly to the airways and lungs, and this decreases doses and side effects and speeds onset of action.

B. Medications and indications

1. Bland aerosols of sterile water or saline theoretically humidify inspired gas, hydrate dry mucosal surfaces, and enhance expectoration. Routine use to treat respiratory diseases is not established except the use of 7% hypertonic saline in patients with cystic fibrosis (CF).

2. Mucolytic agents theoretically facilitate expectoration of secretions. Aerosolized *N*-acetylcysteine (Mucomyst) has low efficacy, may induce bronchospasm, and has been shown to be ineffective in patients with chronic obstructive pulmonary disease (COPD) and CF. Recombinant human DNAse may be helpful in CF.

3. Aerosolized antimicrobials have no role in treating acute bacterial pneumonia.

a. Inhaled tobramycin for CF if patient is at least 6 years of age, has forced expiratory volume (FEV1) 25% to 75% predicted and is colonized with *Pseudomonas aeruginosa*.

b. In limited studies, inhaled tobramycin appears to decrease the sputum bacterial density in patients with pseudomonal infections from non-CF bronchiectasis.

c. Inhaled pentamidine is second-line agent for *Pneumocystis* (*P. jirovici*) pneumonia prophylaxis.

d. Inhaled ribavirin does not have a well-established role in treating respiratory syncytial virus (RSV), severe acute respiratory syndrome (SARS), or influenza A and B infections.

4. Racemic epinephrine (Racepinephrine) decreases laryngeal edema by causing vasoconstriction, but its effectiveness in treating epiglottitis and postextubation stridor is unclear. Mixtures of helium and oxygen appear to be a better option in treating these airway emergencies.

a. Adults: 0.5 mL of 2.25% solution in 3 mL normal saline every 4 to 6 hours.

5. Bronchodilators

a. Inhalation of short-acting β_2-selective adrenergic agonists (e.g., albuterol, pirbuterol) is first-line therapy for asthma and COPD exacerbations.

b. Long-acting inhaled β_2-selective adrenergic agonists are currently not recommended as treatment for acute exacerbations of asthma or COPD.

c. Inhaled albuterol can acutely but transiently lower serum potassium levels in patients with severe hyperkalemia.

d. Inhaled anticholinergics (e.g., ipratropium bromide) have a role in acute asthma when combined with short-acting β_2-selective adrenergic agonists, may be useful in intubated patients to prevent bradycardia during suctioning and may be useful in select patients with severe bronchorrhea.

6. Inhaled corticosteroids are used to treat stable asthma and COPD and prevent exacerbations.
   a. Delivered by metered-dose inhaler (MDI) or dry-powder inhaler
   b. No established role during acute exacerbations of obstructive lung disease
7. Others
   a. Inhaled insulin has not been evaluated in the management of critically ill patients.
   b. Inhaled cyclosporine may improve survival in lung transplant patients.
   c. Inhaled iloprost, a prostacyclin analog, is available for the treatment of primary pulmonary hypertension, and pulmonary hypertension associated with connective tissues disease, appetite suppressants, and chronic thromboembolic disease. Doses of 2.5 to 5 μg are administered 6 to 9 times a day through the Prodose adaptive aerosol delivery (AAD) nebulizer system (Respironics, Murryville, PA)

C. Procedure
1. Nebulizers
   a. Air-jet nebulizers are a nonpropellant-based option for aerosol delivery. Method is not superior to properly used MDI with spacer/holding chamber.
   b. Recommended when patient cannot coordinate use of MDI or drug not available in MDI form.
2. MDIs
   a. Pressurized canister that contains drug suspended in propellant, typically hydrofluroalkene (HFA).
   b. Delivery dependent on technique, which requires slow, deep inhalation followed by a breath hold of approximately 10 seconds.
   c. Effectiveness improved by spacer and holding chamber.
3. Dry-powder aerosols
   a. Available for β-adrenergic agonists and corticosteroids.

D. Postprocedure considerations
1. Routine use of bland aerosols may cause bronchospasm.
2. After racemic epinephrine, rebound laryngeal edema may occur. Other complications include cardiac side effects, including tachycardia and angina. Because of these side effects, Heliox is preferred to decrease airway resistance due to upper-airway obstructions (see Section IV).

II. LUNG EXPANSION TECHNIQUES

A. General principles. Techniques used to duplicate a normal sigh maneuver.

B. Indications. To prevent atelectasis and pneumonia by providing periodic hyperinflations.

C. Procedure. Techniques include coached sustained maximal inspiration with cough, incentive spirometry, volume-oriented intermittent positive-pressure breathing, intermittent continuous positive airway pressure (CPAP), or positive expiratory pressure mask therapy.

III. AIRWAY CLEARANCE

A. General principles. Mucociliary clearance and cough are mechanisms for clearing respiratory secretions. Their effectiveness can be augmented therapeutically.

B. Treatment
1. Mucociliary clearance can be enhanced pharmacologically with inhaled β-agonists or aminophylline in same doses used for bronchodilation.
2. Chest physical therapy includes therapeutic positioning, percussion and vibration of the chest wall, and coughing. Indicated in patients with CF and bronchiectasis, and in the unusual patient with COPD who expectorates >30 mL of sputum/day, and in patients with lobar atelectasis.

Not effective, if cough is weak. It is not indicated in the treatment of asthma or uncomplicated pneumonia.

3. Cough effectiveness may be improved by positive mechanical insufflation followed by manual compression of the lower thorax and abdomen in quadriparetic patients, an abdominal push maneuver that assists expiratory efforts in patients with spinal cord injuries, abdominal binding and muscle training of the clavicular portion of pectoralis major in tetraplegic patients, and chest physical therapy. Other techniques include the flutter valve mucus clearance device, positive expiratory pressure mask therapy, autogenic drainage, and cough mechanical assist device (insufflator/exsufflator). While these modalities help with the clearance of secretions, clinically important patient outcome studies are lacking.
4. Endotracheal suctioning is used when artificial airway present. Preoxygenate with 100% oxygen. Nasotracheal suctioning is not recommended because it is associated with significant complications including death; and, if secretions cannot be mobilized, the patient can be intubated. Nasopharyngeal suctioning is for clearing the upper airway.

C. Postprocedure considerations

1. Chest physical therapy is infrequently complicated by pulmonary hemorrhage, hypoxemia, rib fractures, increased intracranial pressure, decreased cardiac output, and increased airway obstruction.
2. Mechanical suctioning may be complicated by tissue trauma, laryngospasm, bronchospasm, hypoxemia, cardiac arrhythmias, respiratory and cardiac arrest, atelectasis, pneumonia, and misdirection of catheter and, rarely, may result in death.

IV. ADMINISTRATION OF MEDICAL GASES

A. Indications

1. Oxygen therapy is indicated if Pa_{O_2} <60 mm Hg, arterial saturation (Sa_{O_2}) below 90%, and in certain conditions with normal laboratory values or suspicion of tissue hypoxia: acute respiratory failure (hypoxemic or hypercapnic), acute myocardial infarction, acute asthma, normoxemic hypoxia (e.g., carbon monoxide poisoning), preoperative and postoperative states, and cluster headaches. Administer empirically in cases of cardiac or respiratory arrest, status asthmaticus, respiratory distress, hypotension, shock, and severe trauma.
2. Helium–oxygen mixtures (Heliox) indicated for postextubation upper-airway obstruction, children with severe croup, laryngeal edema, and in upper-airway obstruction due to tracheal tumors or extrinsic compression. Current studies do not support its use in managing acute severe asthma and bronchiolitis.
3. Nitric oxide is a potent pulmonary vasodilator. While it has been used to manage acute respiratory distress syndrome (ARDS), pulmonary hypertension, status asthmaticus, acute sickle-cell crisis, and right heart failure after cardiovascular surgery, the benefits of using nitric oxide in these conditions is questionable.
4. Hyperbaric oxygen therapy (100% oxygen at two to three times atmospheric pressure at sea level) is used to treat decompression sickness, arterial gas embolism, and severe carbon monoxide poisoning (see Chapter 56). Used as adjunctive therapy in osteoradionecrosis, clostridial myonecrosis, and compromised skin grafts. There is no evidence to support its use in treating severe brain injuries, acute cerebral vascular accidents, or acute coronary syndrome.

B. Procedure

1. Standard dual-prong nasal cannulas deliver oxygen comfortably and allow eating and talking. Flow rates of 0.5 to 1.0 L/minute approximate an inspired oxygen fraction (F_{IO_2}) of 0.24; 2 L/minute approximate 0.28.

2. Simple oxygen masks deliver F_{IO_2} of 0.35 to 0.50 with flow rates of 5 L/minute or greater. Masks can be uncomfortable, need to be removed during eating, and should be used cautiously on sedated, obtunded, or restrained patients. Flows of at least 5 L/minute are used to avoid rebreathing CO_2 from mask's reservoir space.
3. Venturi masks deliver oxygen most accurately and up to F_{IO_2} of 0.50.
4. Nonrebreathing and partial-rebreathing oxygen masks with reservoir bags can deliver high F_{IO_2} (>0.50) when oxygen flows are 8 to 10 L/minute.
5. In the hypercapnic–hypoxemic patient, therapy should begin with F_{IO_2} of 0.24 or 0.28 by nasal cannula or mask (venturi is most accurate mask). If the P_{aO_2} is still <55 mm Hg after 30 minutes, increase oxygen flow incrementally and measure arterial blood gases every 30 minutes for the first 1 to 2 hours or until it is certain that a P_{aO_2} of at least 55 mm Hg is being achieved and CO_2 narcosis is not developing. An initial modest increase in P_{aCO_2} (5 to 10 mm Hg) is expected in many hypercapnic patients given oxygen and this should not deter delivery of adequate oxygen.
6. Heliox mixtures should contain a minimum of 40% helium to be effective. Higher concentrations of helium can be used as permitted by oxygenation needs.

C. Postprocedure considerations

1. In hypercapnic respiratory failure, there is small risk that supplemental oxygen will worsen alveolar ventilation and lead to CO_2 narcosis.
2. Oxygen therapy should never be abruptly discontinued when hypercapnia has worsened and CO_2 narcosis is a possibility because P_{aO_2} may fall lower than it was before any oxygen was given.
3. Complications of oxygen therapy are decreased mucociliary clearance, tracheobronchitis, and pulmonary oxygen toxicity. F_{IO_2}'s >0.50 should be restricted, whenever possible, to <48 hours.

V. NASAL CPAP

A. General principles

1. Nasal CPAP applies CPAP during the respiratory cycle. Bilevel continuous positive airway pressure (BiCPAP) allows independent adjustments of inspiratory and expiratory pressures.
2. CPAP splints the upper airway in obstructive sleep apnea.

B. Indications

1. Nasal CPAP is used to treat obstructive sleep apnea/hypopnea syndrome, chronic left ventricular failure, and Cheyne-Stokes respirations.
2. See Chapter 53 for a discussion of noninvasive positive-pressure ventilation (NIPPV).

C. Procedure

1. Patients usually respond to 3 to 15 cm H_2O of nasal CPAP by tight fitting nasal or full-face mask.

D. Postprocedure considerations

1. Different masks and BiPAP may be tried to improve patient tolerance.

VI. COMMUNICATION ALTERNATIVES

A. General principles. Speech requires air flowing through the vocal cords.

B. Indications. Patients with tracheostomy tubes and need for speech.

C. Procedure

1. Ventilator-dependent with tracheostomy tube:
   a. Partial cuff deflation techniques require close monitoring and ventilator adjustments. Not used routinely.
   b. One-way, positive-closure, no-leak valve (e.g., Passy-Muir valve) should be used only with a fully deflated tracheostomy cuff and extremely close monitoring and adjustments of ventilator. Do not use if cuff is inflated, there is tracheal/laryngeal obstruction, or secretions preventing air from

moving around or above the tube, laryngectomy, bilateral vocal cord paralysis, unconsciousness, or unstable medical condition. Not used routinely while patients are on the ventilator.

c. If cuff deflation is not tolerated, talking tracheostomy tube (Trach Talk, Portex, Inc.) is used for whispered speech.

d. Computer-assisted communication for long-term mechanical ventilation.

2. Nonventilator dependent with tracheostomy tube:

a. Deflation of the tracheostomy cuff (or a cuffless tube) with intermittent gloved finger occlusion.

b. One-way, positive-closure, no-leak valve (e.g., Passy-Muir valve) attached to tracheostomy tube (cuffless fenestrated and nonfenestrated tubes, metal tubes, and cuffed tubes fully deflated).

c. Postlaryngectomy consider electronic larynx and Blom-Singer tracheostoma valve for prosthesis-assisted tracheoesophageal speech.

D. Postprocedure considerations

1. Deflating the cuff during mechanical ventilation may decrease gas delivery to the lungs. Close monitoring of tidal volumes and gas exchange are mandatory.
2. Patients with one-way valves should be conscious, able to remove the valve in the event of sudden respiratory distress, and able to clear secretions.
3. Some studies suggest patients are at increased risk of aspiration if they are eating by mouth with a one-way valve in place.

VII. RESPIRATORY MONITORING

A. Respiratory rate is an important predictor of outcome, yet it is frequently inaccurately reported

B. Respiratory impedance monitors

1. Measure respiratory rate and estimate tidal volumes.
2. Are poor detectors of apnea.
3. Less accurate in patients who frequently move.
4. Have been associated with a false positive alarm rate of approximately 30%.

C. Respiratory inductive plethysmography

1. Measures changes in the cross-sectional area of the chest and abdomen, thereby measuring respiratory rate and estimating tidal volume.
2. More accurate than impedance monitors.
3. Only approximately two third of the estimated tidal volumes are within 10% of actual tidal volumes.
4. Can monitor for asynchronous and paradoxic breathing.

D. Pulse oximetry

1. Measures hemoglobin saturations in tissue during the arterial and venous phase of pulsation, then derives the arterial saturation.
2. Causes of poor signal detection
   a. Probe malposition
   b. Hypothermia
   c. Hypoperfusion
   d. Vasoconstriction
   e. No pulse
   f. Dark skin
3. Causes of falsely low arterial saturations
   a. Nail polish
   b. Ambient light
   c. Methylene blue and other dyes
   d. Elevated serum lipids

4. Causes of falsely high arterial saturations
   a. Carboxyhemoglobin
   b. Methemoglobin
   c. Hypothermia
   d. Ambient light

E. Capnography
1. Measurement of expired P_{CO_2} concentrations.
2. End-tidal CO_2 is the level of CO_2 measured during the last 20% of exhalation.
3. In the intensive care unit (ICU), capnography is most useful for detecting extubation, determining the presence or absence of respiration, and detecting the return of spontaneous circulation after cardiac arrest.
4. End-tidal CO_2 measurements are unreliable indicators of P_{aCO_2} in critically ill patients.

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56 ACUTE INHALATIONAL INJURY AND CHEMICAL AND BIOLOGICAL AGENTS OF MASS DESTRUCTION

Federico Vallejo-Manzur and Mark M. Wilson

I. GENERAL PRINCIPLES

A. Inhalational injuries may occur due to workplace exposures, natural disasters, or terrorist attacks and result in a variety of syndromes based on the chemical and physical properties of the toxicant involved and the intensity and duration of exposure.

B. Agents may be inhaled as gases, vapors, dust, fumes, or smoke.

C. Disease is caused by asphyxia, direct toxicity, or systemic reactions.

II. ASPHYXIANTS

A. General principles

1. Simple asphyxiants include carbon dioxide (CO_2), methane, nitrogen (N_2), natural gas, propane, and acetylene.
2. Chemical asphyxiants are present in the atmosphere in minute amounts or are released by manufacturing processes or combustion; they asphyxiate at low concentration and include carbon monoxide (CO), hydrogen sulfide (H_2S), oxides of N_2 and hydrogen cyanide (HCN).

B. Etiology

1. CO and CO_2, the most common asphyxiants, accumulate in sealed or poorly ventilated areas. They are generated during the combustion of any carbon-containing fuel.
2. HCN is used as inorganic salts in metallurgy, electroplating, and photo processing, and in the combustion of N_2-containing polymers.

C. Pathophysiology

1. Simple asphyxiants displace or dilute ambient oxygen (O_2) causing tissue hypoxia; chemical asphyxiants interfere directly with O_2 uptake, transport, or utilization.
2. The affinity of CO for hemoglobin is 240 times that of O_2. The formation of carboxyhemoglobin (COHgb) causes a reduction in the total O_2-carrying capacity of the blood, a left shift of the oxyhemoglobin dissociation curve, and an increased affinity for O_2 at the remaining binding sites. Because of the increased affinity of CO for fetal hemoglobin, infants and fetuses are at greater risk for poisoning.
3. The clinical effects of HCN and H_2S intoxications are directly related to the inhibition of cellular respiration in the mitochondria and occur rapidly after inhalation.

D. Diagnosis

1. Breathlessness, tachycardia, headache, fatigue, delirium, syncope, coma, and cardiac arrest may suggest exposure to asphyxiants; severity varies on duration of exposure and underlying health of the victim.
2. In CO poisoning, although arterial O_2 tension (Pao_2) is normal or near normal, measured O_2 saturation and content are reduced. Ordinary pulse oximetry is unable to distinguish which specific gas (CO vs. O_2) is bound to hemoglobin; therefore, the more specific co-oximetry is needed to measure COHgb levels. Signs and prognosis of acute poisoning correlate imprecisely with COHgb levels. Generally, levels $< 10\%$ are usually not

associated with symptoms; levels of 10% to 20% may be associated with headache, tinnitus, dizziness, nausea, and mild behavioral abnormalities; levels of 20% to 40% can present with coma and seizures; levels >40% suggest an increased risk of cardiac arrest.

3. Both HCN and H_2S typically cause metabolic acidosis with an elevated anion gap, an elevated serum lactate and a mixed venous O_2 saturation higher than normal.

E. Treatment

1. The basic management for any asphyxiation includes removal of the source, 100% O_2, and support of cardiorespiratory function.
2. O_2 is the major therapy for CO poisoning. It decreases the half-life of COHgb by competing with CO for hemoglobin binding sites. Patients with COHgb levels >25% (>20% if pregnant), loss of consciousness, severe metabolic acidosis (pH <7.10), or who have evidence of possible end-organ ischemia (e.g., electrocardiogram [ECG] changes, chest pain, altered mental status) are candidates for hyperbaric O_2 therapy (strength of recommendation is weak).
3. Treatment of HCN and H_2S are similar (see Section V). Sodium thiosulfate is not necessary for H_2S intoxication, however.

III. IRRITANT GASES

A. General principles

1. Various agents act as toxic irritants to the respiratory tract and cause mucosal edema, impaired mucociliary function, and pulmonary edema with high-concentration exposures.
2. Agents in this class include ammonia (NH_3, and ammonium hydroxide in solution), chlorine (Cl_2), phosgene ($COCl_2$, which hydrolyzes to form hydrochloric acid [HCl]), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), formaldehyde, cadmium, mercury, and the metal hydrides.

B. Etiology

1. NH_3 is found in fertilizer production, chemical, plastic, and dye manufacture.
2. Cl_2 is used in the production of alkali bleaches and disinfectants and in paper and textile processing. Most exposures result from industrial spills.
3. Firefighters, welders, and paint strippers are exposed to heated chlorinated hydrocarbons, and $COCl_2$ is released in these settings. Because $COCl_2$ is less irritating to the eyes and mucous membranes than Cl_2 or HCl and may be inhaled for prolonged periods without discomfort, the risk of serious injury to the lower respiratory tract is greatly increased.

C. Pathophysiology

1. NH_3, SO_2, and HCl have high water solubility and tend to be highly irritating to conjunctivae, mucous membranes, and upper air passages. Laryngospasm, bronchospasm, and mucous membrane necrosis ensue.
2. Less water-soluble agents (oxides of N_2, $COCl_2$) can penetrate more deeply into the respiratory tree and can cause damage at the alveolar and lower airway levels, resulting in pulmonary edema and bronchospasm. The absence of immediate symptoms with these less water-soluble agents can prolong exposure.

D. Diagnosis

1. These disorders usually occur in the setting of an industrial- or transport-related accident.
2. Patients present in acute respiratory distress with evidence of burn injury; skin lesions; intense edema, erythema, and ulceration of the conjunctival and mucous membranes; and possible laryngeal obstruction.
3. Auscultation of the chest may reveal stridor, crackles, and expiratory wheezing.

4. The typical bat-wing distribution of cardiogenic pulmonary edema is less likely on chest radiograph (CXR) than the patchy infiltrates of noncardiogenic pulmonary edema.

E. Treatment

1. Mainstay of management is removal from the site of exposure and immediate O_2.
2. Airway patency should be ensured because of the risk of progressive laryngeal edema over several hours. Bronchospasm is treated with bronchodilators.
3. Intravenous fluids to offset fluid losses from mucosal edema and sloughing from burns.
4. Empiric antibiotics are not indicated, and the early use of corticosteroids is controversial.

IV. SMOKE INHALATION

A. General principles

1. Approximately 80% of fire-associated deaths are from smoke inhalational injury.
2. Inhalational injury has a greater effect on mortality than burn size or patient age.

B. Pathophysiology

1. Respiratory injuries in fire victims with smoke inhalation can be the result of asphyxia, heat, and exposure to multiple toxic products of combustion (e.g., HCN, aldehydes, acrolein, dioxides of N_2 and sulfur, vaporized HCl).
2. Most deaths are the result of asphyxia, primarily due to CO intoxication.
3. Direct heat injury is usually limited to the upper respiratory tract. Edema formation and upper airway obstruction occur in up to 30% of burn patients and present 4 to 24 hours after exposure.
4. Smoke irritation can cause tracheobronchitis, severe bronchoconstriction, and frank pulmonary edema. Although pulmonary edema is rare (<10%), it has an associated high mortality (83%).

C. Diagnosis

1. Classic predictors of smoke inhalation injury include: a consistent exposure history; respiratory signs and symptoms (dyspnea, hoarseness, cough, chest discomfort, wheezing, stridor); cervical, facial, and oropharyngeal burns (especially between the nose and mouth); and expectoration of carbonaceous sputum.
2. Initial evaluation should focus on recognition and treatment of CO poisoning and airway obstruction, the major early problems. A delay in symptom onset (hours to days) is not uncommon. Lung examination and chest x-ray are inconsistent and may not be abnormal until 24 hours later.
3. COHgb levels >10% are markers of the potential for inhalation of other toxins. Unexplained metabolic acidosis or a lactate concentration >10 mM/L in the presence of normal or mildly elevated COHgb levels and normal Pao_2 suggests cyanide exposure.

D. Treatment

1. Control of the airway is the initial priority. Immediate endotracheal intubation is indicated for stridor, facial burns, central nervous system depression, or with evidence of upper or lower airway edema. Because airway edema evolves over time and intubation may become increasingly more difficult if it is delayed, all patients with significant smoke inhalation should have urgent laryngoscopy to assess the risk for airway compromise by monitoring the development of any oropharyngeal erythema, edema, or blistering of the mucosa.
2. Nasotracheal intubation may be preferred over orotracheal intubation in the presence of mouth burns.

3. All patients should be started on 100% humidified O_2. Nebulized β_2-agonists should be given to treat bronchospasm.
4. Consider hyperbaric O_2 therapy, if available, for CO intoxication. (see Section II.E)
5. Methemoglobinemia, from the oxidation of hemoglobin by cyanide, causes impaired O_2 binding and tissue delivery. It is treated with intravenous methylene blue.
6. Anecdotal evidence suggests that corticosteroids should be reserved for severe upper airway obstruction and bronchospasm resistant to bronchodilator therapy.

V. CHEMICAL AND BIOLOGICAL AGENTS OF MASS DESTRUCTION

A. General principles

1. Chemical and biologic agents can be used by terrorists against the general population or can be accidentally released. These include gases, liquids, or solids with direct toxic effects in relatively low concentrations.

B. Pathophysiology

1. Chemical agents include: (a) Nerve agents (organophosphorous compounds that irreversibly inhibit acetylcholinesterase; most toxic) such as sarin and tabun; (b) vesicants ("blister agents") such as sulfur mustard and lewisite; (c) toxic asphyxiants such as cyanide; (d) lung irritants ($COCl_2$, Cl_2) that can cause acute lung injury; and (d) nonlethal, temporary incapacitating agents such as tear gas.
2. Biologic agents that have the greatest potential to cause mass casualties (Category A agents) include: anthrax, plague, smallpox, botulism, tularemia, and viral hemorrhagic fevers. Category B agents that have some potential for mass casualties include Q fever, brucellosis, Staphylococcal enterotoxin B, ricin, and *Clostridium perfringens*.

C. Diagnosis

1. A classic clue of a chemical weapon release is the rapid onset of symptoms in the context of mass casualties. Bioweapons release may take many hours or days to become apparent.
2. Nerve agent exposure results in excess cholinergic activity ("SLUDGE" syndrome of *S*alivation, *L*acrimation, *U*rination, *D*efecation, *G*astric distress, *E*mesis). Ventilatory failure is the primary cause of death.
3. Vesicants result in early development of sore throat, cough, and hoarseness followed by dyspnea, skin erythema, and eye irritation. Acute mortality is low; morbidity may be high.
4. Cyanide exposure results in tachypnea and tachycardia, followed by agitation, muscle weakness, seizures, and even the development of acute respiratory distress syndrome (ARDS) and cardiac arrest.
5. Pulmonary or "choking agents" hydrolyze with exposure to water to form HCl. Symptoms start with irritation of the eyes, nose, and airways and may progress to vomiting, headache, noncardiogenic pulmonary edema, and respiratory failure.
6. Smallpox (variola major) is transmitted person-to-person by respiratory droplets. Clinical manifestations occur in distinct phases with a prodrome of high fevers, nausea/vomiting, and backache followed by a sequential rash (distinctly synchronous and centrifugal spreading lesions from face and hands to extremities and then the trunk over approximately 1 week). Patients are infectious until all crusts fall off. Disease is confirmed by analysis of skin scrapings, vesicular fluid, or oropharyngeal swabs. Strict containment procedures are required for agents, such as Smallpox, that pose a high risk of aerosol-transmitted infection or life-threatening disease and handling of all specimens requires a Biosafety Level 4 facility.

7. Anthrax (*Bacillus anthracis*) occurs in cutaneous, gastrointestinal, and inhalational forms based on route of entry of spores. The inhalational version leads to fulminant respiratory failure, pleural effusions, hemorrhagic mediastinitis, and massive bacteremia. Organism is easily cultured from blood and other body fluids.
8. Plague (*Yersinia pestis*) is highly contagious from person-to-person and is rapidly fatal in the pneumonic form. Presenting features are fever/chills, dyspnea, chest pain, and cough with hemoptysis. Buboes are not always present.
9. Botulinum is an extremely potent toxin produced by *Clostridium botulinum* and may cause a life-threatening paralytic illness.
10. Ricin is a potent toxin that inhibits protein synthesis at the ribosome. It requires extraction from castor bean seeds. Inhalation may lead to airway necrosis, severe pulmonary edema, fibrinopurulent pneumonia, and mediastinal lymphadenitis. Ricin toxicity is not contagious to others.

D. Treatment

1. The steps that need to be taken after a bioterrorist attack include detection, containment, rapid decontamination, prophylaxis, and direct treatment against the specific agent.
2. Removal of contaminated clothing can eliminate 80% to 90% of chemical contaminants.
3. For nerve agents: administer O_2, atropine, pralidoxime, diazepam for any seizures, and supportive measures.
4. For cyanide: 100% O_2, intravenous hydroxycobolamine or sodium nitrite and sodium thiosulfate (specific antidotes), and supportive care.
5. There are no approved drugs for the treatment of smallpox. Strict airborne and contact isolation are necessary. Therapy is based on supportive care and vaccination at an early stage.
6. Prompt intravenous ciprofloxacin or doxycycline with clindamycin and/or rifampin is used for inhalational anthrax. All exposed cases should have 60 days of prophylaxis. Anthrax vaccine is not available to the general public at this time.
7. Traditionally, streptomycin or gentamicin is the mainstay of therapy for *Y. pestis*. Alternate antibiotics include ciprofloxacin, doxycycline, or chloramphenicol. All individuals who come within 2 m of a patient with pneumonic plague should receive postexposure prophylaxis with doxycycline or ciprofloxacin. There is no approved vaccine against plague presently.
8. Treatment of botulism includes supportive care, mechanical ventilation, if necessary, and early administration of antitoxin.
9. Management of ricin exposure involves decontamination and general supportive care. There is no specific antidote available as yet for humans.

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57 DISORDERS OF TEMPERATURE CONTROL: HYPOTHERMIA

Mark M. Wilson

I. GENERAL PRINCIPLES

A. Hypothermia exists when the core temperature is <35°C (95°F).

B. On average, 700 people die in the United States each year from accidental hypothermia. The mortality rate for treated hypothermia ranges from 12% to 73%.

C. Heat may be exchanged with the environment by radiation, conduction, convection, or evaporation. *Radiation*, the transfer of thermal energy between objects with no direct contact, accounts for 50% to 70% of heat lost by humans at rest. *Conduction* involves the direct exchange of heat with objects in direct contact with the body. *Convection*, the exchange of heat with the warmer or cooler molecules of air that passes by the skin, may produce rapid heat exchange (the wind chill factor). *Evaporation* of sweat from the skin results in net heat loss. Evaporative heat loss occurs even if a warmer environment surrounds the skin.

D. Impairment of the ability to alter our environment in response to thermal stress (adding or removing clothes, changing level of activity, moving to a different climate) predisposes to an imbalance in heat exchange.

E. Temperature regulation declines with age as a result of deterioration in sensory afferents.

II. ETIOLOGY

A. The most frequent causes of hypothermia are exposure to cold, use of depressant drugs (alcohol, phenothiazines, barbiturates, neuroleptics, paralytics), and hypoglycemia.

B. Other common causes include hyperglycemia, hypothyroidism, adrenal insufficiency, central nervous system disorders, extensive burns, sepsis, and trauma.

C. Iatrogenic-induced hypothermia is now frequently used short term (24 hours) in the postarrest care of patients surviving ventricular fibrillation (VF).

III. PATHOGENESIS

A. The incidence of hypothermia doubles with every 5°C drop in ambient temperature. Wet clothing effectively loses up to 90% of its insulating value. Convective heat loss because of the wind may increase to more than five times baseline values.

B. Alcohol contributes to hypothermia in 14% to 91% of cases. Persons under the influence of alcohol are less likely to perceive danger or to conserve heat by vasoconstriction.

C. Most sedative-hypnotic drugs cause hypothermia by inhibiting shivering and impairing capability for voluntary control of temperature.

D. When the hypothalamus perceives a temperature decrease, it modulates autonomic tone to cause: a decrease in or cessation of sweat production, constriction of the cutaneous vasculature, and involuntary increase in muscle tone so that shivering begins.

E. The shivering phase of hypothermia generally occurs in the range of 35°C to 30°C and is characterized by intense energy production from increased

muscle tone and the powerful rhythmic contractions of small and large muscle groups.

F. In the nonshivering phase (<30°C), metabolism slows dramatically, at times causing multiple organ failure.

G. Increasing degrees of hypothermia produce malignant dysrhythmias, depressed cardiac function, and hypotension. The electrocardiogram (ECG) in mild hypothermia shows bradycardia with prolongation of the PR interval, QRS complex, and QT interval. At temperatures lower than 30°C, the first-degree block is not unusual. At temperatures lower than 33°C, the ECG commonly shows a characteristic J-point elevation. Atrial fibrillation is extremely common at temperatures of 34°C to 25°C, and VF is frequent below 28°C. Third-degree block and asystole are common when core temperatures drop to <20°C.

H. Although blood pressure is initially maintained by an increase in vascular resistance, systemic resistance falls and hypotension is common at temperatures lower than 25°C.

I. Pulmonary mechanics and gas exchange appear to change little with hypothermia. Both tidal volume and respiratory rate decline as core temperature lowers. At temperatures <24°C, respiration may cease.

J. As blood pressure decreases during the nonshivering phase, renal blood flow may decrease by 75% to 85%, without a significant change in urine production. This process is termed *cold diuresis* and is due to a defect in tubular reabsorption. The net result is dehydration and a relatively hyperosmolar serum.

K. The brain tolerates hypothermia extremely well; complete neurologic recovery has been described in hypothermic adults after 20 minutes of complete cardiac arrest and after up to 3.5 hours of cardiopulmonary resuscitation.

L. The white blood cell count in mild hypothermia remains normal to slightly elevated; it may drop severely at temperatures lower than 28°C. The hematocrit usually rises in hypothermic patients at a temperature of 30°C (due to dehydration and splenic contraction). Platelet counts drop as temperature decreases (hepatic sequestration), and prolongation of the bleeding time has been noted at 20°C. Platelet levels and function return to normal on rewarming.

M. Hepatic dysfunction is common and involves synthetic and detoxification abnormalities. Ileus and pancreatitis are also commonly seen.

N. Hypothermia directly suppresses the release of insulin and increases resistance to insulin's action in the periphery. Elevations in blood glucose, however, are usually mild.

IV. DIAGNOSIS

A. The diagnosis of hypothermia may be suggested by a history of exposure (both intentional, as seen in an operating room, and unintentional, as in cold water immersion), a high-risk patient profile (elderly, alcoholic, diabetic, quadriplegic, or severely debilitated), clinical examination, and laboratory abnormalities.

B. Cool skin, muscle rigidity, some degree of shivering or muscle tremor, and acrocyanosis are present in most noncomatose patients.

C. Between 35°C and 32°C, the patient may be stuporous or confused; between 32°C and 27°C, the patient may be verbally responsive but incoherent; and at temperatures <27°C, most patients are comatose but able to respond purposefully to noxious stimuli. Deep coma is uncommon, but when present it may be difficult to distinguish from death. The criteria for death cannot be applied until core temperature is back near 37°C.

D. Thermometers calibrated to record temperatures lower than 35°C are necessary, and sites that reflect core temperature must be used (bladder, rectal, tympanic, esophageal, or great vessel sites are preferable).

V. TREATMENT

A. Treatment of hypothermia should be aggressive. Wet clothes should be removed and replaced with dry ones if available. The victim should be insulated from cold and wind. Rough handling must be avoided; even minor manipulations can induce VF.

B. Fluid resuscitation, preferably through a central vein, should be attempted in all patients in hypothermic shock. Slightly hypotonic crystalloid fluids should be given after warming to at least room temperature. Pressor agents and procedures (intubation or catheter placement) should not be withheld because of a fear of dysrhythmia.

C. Management of dysrhythmias must be approached in a nontraditional manner because many pharmacologic agents, pacing efforts, and defibrillation attempts do not work in the hypothermic patient. Because atrial dysrhythmias and heart block generally resolve spontaneously on rewarming, therapy is usually unnecessary. Digitalis should be avoided (efficacy is unclear and toxicity increases with rewarming); calcium channel blockers have not been shown to be efficacious. Both procainamide and lidocaine have been of little benefit. Bretylium appears to be the drug of choice and has been shown to both decrease the incidence of VF and increase the likelihood of successful cardioversion. Electrical defibrillation should probably be attempted at least once, but it is unlikely to succeed until the patient's core temperature surpasses 30°C.

D. P_{CO_2} and pH values uncorrected for temperature may be used accurately to assess these patients. However, because of a decrease in oxygen solubility on warming the arterial blood sample to 37°C, P_{O_2} values must be corrected for temperature or the presence of hypoxemia may be overlooked. The following formula may be used: decrease the P_{O_2} measured at 37°C by 7.2% for each degree that body temperature is <37°C.

E. If hypoglycemia is documented, the patient should be given 25 to 50 g of glucose as a 50% dextrose solution. Because of the ineffective action of insulin and the relatively high serum osmolarity from cold diuresis in hypothermia, treatment with highly concentrated glucose solutions should be delayed until the blood glucose level is measured.

F. Rewarming methods may be divided into three categories: passive external rewarming, active external rewarming, and active central rewarming. Passive external rewarming is the least invasive and slowest rewarming technique. It requires only that the patient be dry, sheltered from wind, and covered with blankets to decrease heat loss, thereby allowing thermogenesis to restore normal temperature. Temperature increase varies inversely with the patient's age; the average rate of temperature increase with this method is only 0.38°C/hour.

G. Active external rewarming by use of warmed air circulated through a plastic blanket surrounding the patient (Bair Hugger) has proved safe and effective in rewarming postoperative patients and appears to work well with other types of hypothermia. This may prove an excellent primary therapy or a useful temporary therapy while interventions for active central rewarming are prepared.

H. Active central rewarming is the fastest and the most invasive warming technique available. Safe and effective methods include the following: oxygen that has been humidified and heated to 40°C to 46°C delivered by face mask or endotracheal tube (raises temperature slightly <1°C/hour); peritoneal lavage with saline or dialysate fluid heated to 38°C to 43°C and exchanged every 15 to 20 minutes (raises temperature by 2°C to 4°C/hour); and hemodialysis or cardiopulmonary bypass (raises temperature by 1°C to 2°C/hour). The desired rate of rewarming varies according to the patient's cardiopulmonary status and underlying disease. The rewarming methods selected must be appropriate for the individual patient.

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58 DISORDERS OF TEMPERATURE CONTROL: HYPERTHERMIA

Mark M. Wilson

I. HEAT STROKE

A. General principles

1. Heat stroke is a syndrome of acute thermoregulatory failure in warm environments characterized by central nervous system depression, core temperatures usually above 40°C, and typical biochemical and physiologic abnormalities.
2. Mortality may reach 70%. Approximately 4,000 deaths occur annually in the United States.

B. Etiology

1. Causes of heat stroke involve increased heat production and/or impaired heat loss.
2. Exertional heat stroke is typically seen in younger persons who exercise at higher than normal ambient temperatures. Although thermoregulatory mechanisms are typically intact, they are overwhelmed by the thermal challenge of the environment and the great increase in endogenous heat production.
3. Nonexertional ("classic") heat stroke affects predominantly elderly or sick persons and occurs almost exclusively during a heat wave. These patients frequently have some impairment of thermoregulatory control and are more likely to have a compromised cardiovascular response to heat exposure, deficient voluntary control and poor acclimatization, and take drugs that may adversely affect thermoregulation (anticholinergics, diuretics, alcohol).
4. Impaired voluntary control (schizophrenia, coma, senility) increases the risk of heat stroke when ambient temperatures are high. These patients may fail to perceive a temperature rise or move to a cooler location or change their clothes.
5. Dehydration and impaired cardiovascular status predispose to heat stroke by decreasing skin or muscle blood flow, thereby limiting transfer of heat from the core to the environment.
6. Acclimatization to higher ambient temperatures can greatly increase heat tolerance by increasing cardiac output, decreasing peak heart rate, and lowering the threshold necessary to induce sweating and increase the volume of sweating.
7. Sweat gland malfunction is *not* inherent to the pathogenesis of this syndrome.

C. Pathophysiology

1. Direct cellular toxicity results from temperatures higher than 42°C (the *critical thermal maximum*); mitochondrial activity ceases, enzymatic reactions become dysfunctional, and cell membrane integrity becomes unstable.
2. Dehydration, metabolic acidosis, and local hypoxia potentiate the damage from severe heat stress.
3. Significant muscle enzyme elevation and severe rhabdomyolysis occur commonly in exertional heat stroke, but rarely in classic heat stroke.

4. Direct thermal toxicity to the brain and spinal cord rapidly produces cell death, cerebral edema, and local hemorrhage. Stupor or coma is almost a universal feature and seizures are not uncommon.
5. Hypotension occurs commonly from high output cardiac failure or temperature-induced myocardial hemorrhage and necrosis.
6. Renal damage occurs in nearly all hyperthermic patients; it is potentiated by dehydration, cardiovascular collapse, and rhabdomyolysis. Acute renal failure occurs in 5% of patients with classic heat stroke and in up to 35% of cases of exertional heat stroke. Urine findings include a characteristic "machine oil" appearance.
7. The liver appears to be particularly sensitive to temperature damage; hepatic necrosis and cholestasis occur in nearly every case and cause death in 5% to 10% of cases.
8. White blood cell counts are typically elevated. Anemia and bleeding diathesis are frequently present. Disseminated intravascular coagulation is present in most cases of fatal hyperthermia and usually appears on the second or third day after the insult.
9. Hyperglycemia and elevated serum cortisol levels have been reported in mild heat stroke. Hypoglycemia occurs in severe exertional heat stroke due to metabolic exhaustion.
10. Potassium levels may be extremely elevated from cell lysis. Hypophosphatemia and hypocalcemia also occur commonly.
11. Direct thermal injury to the pulmonary vascular endothelium may lead to cor pulmonale or the acute respiratory distress syndrome. This and the tendency for myocardial dysfunction make pulmonary edema common.

D. Diagnosis

1. Heat stroke should be expected in any patient exercising in ambient temperatures generally >25°C or in susceptible persons during heat waves (ambient peak temperatures exceed 32°C and minimum temperatures do not fall below 27°C).
2. Diagnostic criteria for heat stroke includes a core temperature higher than 40°C, severely depressed mental status or coma, elevated serum creatine kinase levels, and a compatible history. Profuse sweating is typical in exertional heat stroke. Lack of sweating is typical in classic heat stroke, but is *not* a requirement of diagnosis.
3. Arterial blood gas analysis should be done early in treatment and values should be corrected for temperature due to altered solubilities of oxygen and carbon dioxide. The net effect is that the patient is more acidotic and less hypoxemic than uncorrected values imply. For clinical purposes: for each 1°C the patient's temperature exceeds 37°C, one should increase the oxygen tension 7.2%, increase the carbon dioxide tension 4.4%, and lower the pH 0.015 units.

E. Treatment

1. Primary therapy includes cooling and decreasing thermogenesis. Cooling by either evaporative (placing a nude patient in a cool room, wetting the skin with water, and encouraging evaporation with fans) or direct external methods (immersing the patient in ice water or packing the patient in ice) has proved effective.
2. External methods suffer from inconvenience and the possibility that cold skin may vasoconstrict, thereby limiting heat exchange from the core. Cooling blankets, although in common use, are extremely ineffective and are not recommended.
3. Dysrhythmias, metabolic acidosis, and cardiogenic failure complicate the early management of hyperthermic crises. Hypotension should be treated initially with normal saline. Dopamine and α-adrenergic agonists should be

avoided because of their tendency for peripheral vasoconstriction. Volume expansion with dextran is contraindicated due to its anticoagulant effects.

4. Urine output should be closely followed. Patients should routinely receive mannitol 1 to 2 mg/kg intravenously over 15 to 20 minutes to promote urine output and potentially decrease cerebral edema.
5. Morbidity and mortality are directly related to the peak temperature reached and the time spent at an elevated temperature. Delays in treatment of as little as 2 hours may increase the risk of death up to 70%.

II. MALIGNANT HYPERTHERMIA

A. General principles

1. Malignant hyperthermia is a drug- or stress-induced hypermetabolic syndrome characterized by vigorous muscle contractions, an abrupt increase in temperature, and cardiovascular collapse.
2. Occurs in approximately 1 of every 50,000 to 150,000 patients receiving anesthesia and has a mortality between 10% and 30%.

B. Etiology

1. Increased thermogenesis from a defect of calcium metabolism in skeletal muscles causes repeated or sustained contractions after specific exposures. This reaction is *not* allergic in nature.
2. The metabolic predisposition to malignant hyperthermia appears to be inherited in an autosomal dominant manner with variable penetrance and expressivity.
3. Halothane or succinylcholine is involved in >80% of cases.
4. Other agents have also been implicated (enflurane, decamethonium, gallamine, diethyl ether, ketamine, phencyclidine, cyclopropane).
5. Stress, anoxia, viral infections, and lymphoma have also been reported triggers.

C. Pathophysiology

1. Direct thermal injury is the predominant cause of toxicity. Pathophysiologic changes parallel those of exertional heat stroke.
2. Vigorous muscle contractions almost immediately precipitate severe metabolic acidosis; increased carbon dioxide production; and elevations of creatine kinase, aldolase, and lactate dehydrogenase (due to ongoing rhabdomyolysis).
3. Hyperkalemia occurs in minutes to hours and, in combination with tissue hypoxia and acidosis, makes ventricular dysrhythmias more common.
4. Higher maximal temperatures are usually seen in malignant hyperthermia.

D. Diagnosis

1. There is no suitable noninvasive screening test to identify susceptible persons.
2. Early signs of hyperthermic crisis vary with the agent administered, but may include muscle rigidity (masseter contractures after succinylcholine), sinus tachycardia, mottling or cyanosis of the skin, supraventricular tachydysrhythmias, and hypertension.
3. Hyperthermia is typically a late sign in an acute crisis and is rapidly followed by hypotension, acidosis, peaked-T waves on the electrocardiogram (from hyperkalemia), and malignant ventricular dysrhythmias.

E. Treatment

1. Direct pharmacologic intervention to decrease thermogenesis is mandatory.
2. Dantrolene acts by uncoupling the excitation–contraction mechanism in skeletal muscle and by lowering myoplasmic calcium: 1 to 2.5 mg/kg of dantrolene should be given intravenously every 5 to 10 minutes; not to exceed 10 mg/kg. Oral or intravenous dosages of 1 to 2 mg/kg every 6 hours should continue for 24 to 48 hours.

3. Evaporative cooling, iced saline lavage (gastric, peritoneal), and infusion of chilled solutions may be helpful. Direct external cooling methods are not advised.
4. Ventricular fibrillation is the most common cause of early death. Procainamide increases uptake of myoplasmic calcium and should be given prophylactically as soon as feasible.
5. Prophylactic phenobarbital is strongly recommended for seizure prevention.
6. With current management techniques, mortality should be below 30%.

III. NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A. General principles

1. NMS results from an imbalance of central neurotransmitters and is characterized by hyperthermia, muscular rigidity, extrapyramidal signs, and recent neuroleptic drug use.
2. Mental status changes, coma, and catatonia are common.
3. Incidence rates for NMS range from 0.07% to 2.2% and appear to be declining.

B. Etiology

1. In all reports of NMS, patients were receiving agents that decrease dopaminergic hypothalamic tone or the syndrome appeared after withdrawal of dopaminergic agents.
2. Butyrophenones (haloperidol), phenothiazines, thioxanthenes, and dibenzoxazepines are believed to act as dopamine receptor-blocking agents.
3. Atypical antipsychotic drugs (risperidone, molindone, clozapine, fluoxetine) and metoclopramide and domperidone have also caused NMS.
4. Drugs acting at the D_2 dopamine-binding sites appear to have the greatest potential for causing the syndrome.

C. Pathophysiology

1. Increased muscular rigidity, akinesia, mutism, and tremor occur due to hypothalamic dopaminergic imbalance.
2. Motor abnormalities vary but are typically of the parkinsonian type of extrapyramidal reactions. Muscle spasms resolve with the use of centrally acting dopaminergic agents (bromocriptine, amantadine, L-3,4-dihydroxyphenylalanine [L-DOPA]).
3. Because of the relatively low maximal temperatures in NMS compared with the other hyperthermic syndromes, direct thermal injury occurs less often. Rhabdomyolysis and renal failure are usually mild and may occur in up to one third of patients.
4. Pulmonary complications are the most serious frequent sequelae of NMS, including copious sialorrhea leading to aspiration pneumonia and mechanical ventilation.

D. Diagnosis

1. Onset of symptoms occurs within hours of the initial dose of the triggering agent and up to 2 to 4 weeks thereafter.
2. Early symptoms include dysphagia, dysarthria, pseudoparkinsonism, dystonia, and catatonia. Muscle rigidity generally precedes or is concurrent with hyperthermia. Peak temperatures are usually reached within 48 hours of onset of symptoms.

E. Treatment

1. Specific agents (dantrolene, pancuronium, amantadine, bromocriptine, L-DOPA) are used to decrease thermogenesis by reducing muscle contractures.
2. Bromocriptine (2.5 mg three times daily), amantadine (100 to 200 mg twice daily) and carbidopa/L-DOPA (10 to 100 mg three times daily) increase central dopaminergic tone, thereby decreasing the central drive for

muscular rigidity and thermogenesis (and directly reducing extrapyramidal side effects). Duration of treatment is usually 1 to 2 weeks.

3. Prophylactic intubation should be strongly considered for patients with excessive sialorrhea, swallowing dysfunction, or coma.
4. Mortality rates <10% are possible with appropriate support.

IV. DRUG-INDUCED HYPERTHERMIA

Multiple drugs have been reported to produce hyperthermia. Drug-induced hyperthermia (e.g., serotonin reuptake inhibitors) must be added to the differential diagnosis in any hyperthermic patient. Treatment, in general, parallels that for exertional heat stroke. Death or serious morbidity due to the serotonin syndrome appear to be rare.

Suggested Reading

Ali SZ, Taguchi A, Rosenberg H. Malignant hyperthermia. *Best Pract Res Clin Anesthesiol* 2003;17:519.
Nice recent review of this serious complication.

Banushali MJ, Tuite PJ. The evaluation and management of patients with the neuroleptic malignant syndrome. *Neurol Clin North Am* 2004;23:389.
A well-written general overview of NMS.

Bouchama A, Knockel J. Heat stroke. *N Engl J Med* 2002;346:1978.
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Haddad E, Moran DS, Epstein Y. Cooling heat stroke patients by available field measures. *Intensive Care Med* 2004;30:338.
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One of the first reports documenting the ineffectiveness of cooling blankets in the ICU.

SEVERE UPPER AIRWAY INFECTIONS

Oren P. Schaefer and Richard S. Irwin

59

I. GENERAL PRINCIPLES

A. Upper airway anatomy: nose, mouth, nasopharynx, oropharynx, hypopharynx, paranasal sinuses. Minor infections in these areas are common; deep neck infections can be fatal.

II. PATHOPHYSIOLOGY

A. Supraglottitis (epiglottitis). Acute inflammation, usually bacterial, of the supraglottic structures (epiglottis, aryepiglottic folds, arytenoids).

B. Deep space neck infections. Knowledge of anatomy required to understand manifestations, complications, and treatment.

1. **Submandibular space.** Odontogenic infection in up to 90%. Exemplified by Ludwig's angina.
2. **Lateral pharyngeal space (LPS).** Two compartments: anterior and posterior.
3. **Retropharyngeal space (RPS).** Uncommon; most often are seen in children younger than 6 years.
4. **Descending infections.** Any deep neck infection has access to the posterior mediastinum. Descending, necrotizing mediastinitis carries a mortality rate of >40%.

C. Sinusitis. Inflammation/infection of the sinus cavities. Community acquired versus hospital acquired.

III. ETIOLOGY

A. Supraglottitis. *Haemophilus influenzae* type B (Hib) and streptococcal species are the most common pathogen in children and adults. The incidence of Hib in children has significantly declined since introduction of vaccine. Blood cultures in adults are positive in 15%.

B. Deep space neck infections. Microbiology: mix of anaerobic and aerobic organisms; the former predominate. *Peptostreptococcus, Fusobacterium*, and *Bacteroides* most frequent. Gram-negative bacilli less common. *Staphylococcus aureus* in retropharyngeal abscess.

C. Sinusitis. Community acquired: *H. influenzae, Streptococcus pneumoniae,* viruses, and in children, *Moraxella catarrhalis*. Hospital acquired: >50% of polymicrobial origin. Invasive rhinocerebral mucormycosis in association with diabetes mellitus and acidosis, burns, chronic renal disease, cirrhosis, and immunosuppression. *Aspergillus* in immunocompromised patients.

IV. DIAGNOSIS

A. Supraglottitis

1. **History and physical examination — children**
   - **a.** Sore throat, dysphagia, followed by stridor. Child leans forward, usually pale and frightened, breathing is slow, and drooling.
   - **b.** Presentation and course are usually fulminant.
   - **c.** Progression to respiratory arrest may be sudden.

d. In children with classic presentation, do not attempt pharyngeal examination. Artificial airway may be needed; the examination can be done in the controlled setting of an operating room.

2. History and physical examination—adults

a. Sore throat, with or without dysphagia; respiratory difficulty less common, muffled voice, drooling, fever, and stridor. Presentation often indolent.

b. Preceding upper respiratory infection common. Duration of symptoms: hours up to a week.

c. Consider supraglottitis when sore throat and dysphagia are out of proportion to visible signs of pharyngitis.

d. Higher mortality due to unexpected airway obstruction.

e. In older patients without distress, initial examination of the pharyngeal structures is recommended.

3. Radiology

a. Lateral soft tissue radiograph of the neck: epiglottic thickening (thumb sign), swelling of the aryepiglottic folds, ballooning of the hypopharynx, narrowing of the vallecula.

b. Perform radiograph only if the child is clearly stable.

4. Other

a. Direct visualization required when suspicion is high and radiograph normal.

b. Blood cultures are required.

c. Throat culture is of no value.

B. Deep space neck infections. Important to distinguish the space or spaces involved to prevent potentially devastating complications and to perform early surgical therapy if necessary.

1. Submandibular space

a. Young, otherwise healthy adults with neck pain and swelling, tooth pain, and dysphagia, dyspnea, tachypnea, stridor, muffled voice, drooling, and tongue swelling.

b. Bilateral, woody submandibular swelling, mouth distortion, and fever. Trismus not uncommon and indicates spread to the LPS.

c. Airway obstruction can result from swollen tongue, neck and glottic edema, extension to the epiglottis, and poor control of pharyngeal secretions.

2. Lateral pharyngeal space

a. Anterior compartment: unilateral trismus (irritation of internal pterygoid muscle), induration, swelling along angle of jaw, high fever, medial bulging of the lateral pharyngeal wall. History of recent upper respiratory infection, pharyngitis, or tonsillitis often present.

b. Posterior compartment: signs of sepsis, dyspnea. Trismus and tonsillar prolapse are absent. Most patients have no localizing signs.

c. Complications: suppurative jugular venous thrombosis; bacteremia; septic emboli; involvement of the carotid artery. Signs of carotid sheath involvement: persistent tonsillar swelling, ipsilateral Horner syndrome, cranial nerve palsies. Impending rupture may be signaled by "herald bleeds" from the nose, mouth, or ears.

3. Retropharyngeal space

a. Children

i. Fever, irritability, refusal to eat, neck often held stiffly (tilted away from the involved side), dyspnea, dysphagia.

ii. Respiratory compromise can occur as abscess protrudes anteriorly or ruptures into the airway; aspiration and asphyxiation possible.

b. Adults

i. Fever, sore throat, dysphagia, nasal obstruction, noisy breathing, stiff neck, and dyspnea are most common.

ii. Pain in or radiating to the posterior neck that increases with swallowing suggests diagnosis.
iii. Respiratory distress and chest pain suggest mediastinal extension.

4. Descending infections
- **a.** Develops 12 hours to 2 weeks from the onset of primary infection.
- **b.** Severe dyspnea and pleuritic or retrosternal chest pain are suggestive of mediastinal abscess; rupture may result in purulent pleural and pericardial effusions.
- **c.** Cervical necrotizing fasciitis progresses superficially along neck and chest wall; early in course, physical appearance may be deceptively benign. Erythema occurs initially and progresses to dusky skin discoloration, blisters or bullae, skin necrosis.
- **d.** Gas in the tissues can be readily seen on computed tomography (CT) scan.

5. Lemierre's syndrome
- **a.** Acute oropharyngeal infection with invasion into the LPS and secondary septic thrombophlebitis of the internal jugular vein and frequent metastatic infections (in 90% at diagnosis; most commonly to lungs).
- **b.** Can be seen in wake of infectious mononucleosis.
- **c.** High clinical suspicion is necessary for diagnosis to minimize morbidity and mortality.
- **d.** Usual etiologic agent is *Fusobacterium necrophorum.*
- **e.** Swollen and/or tender neck is most common sign; should be a red flag with current or recent pharyngitis.

6. Radiology
- **a.** Lateral neck radiograph. Prevertebral soft tissue swelling and loss or reversal of normal cervical lordosis suggests RPS infection.
- **b.** CT scan. Can define neck masses with excellent results and is indicated in all cases.
- **c.** Ultrasonography. May identify fluid-filled masses and guide needle aspiration for culture and surgical drainage (however, CT is preferable).
- **d.** Carotid angiography. Recommended if carotid arterial involvement suspected.
- **e.** Magnetic resonance imaging. Offers little advantage over CT.

C. Sinusitis

1. History and examination
- **a.** Failure of symptom resolution after a typical cold, facial pain, purulent nasal discharge, postnasal drip, nasal obstruction, cough, and hyposmia. Maxillary toothache, poor response to decongestants, abnormal transillumination, and purulent nasal discharge are independent predictors of sinusitis.
- **b.** Sphenoid sinusitis is uncommon. Delay in diagnosis associated with increased morbidity and mortality. Presentation includes severe headache, often with fever and nasal discharge. Trigeminal hyperesthesia or hypesthesia occurs in 30%.
- **c.** Nosocomial sinusitis occurs in 5% to 8% of intensive care unit (ICU) admissions. Risks: orotracheal and nasotracheal airways, nasogastric tubes, nasal packing. Other factors: corticosteroid use, obtundation, immobility, supine positioning, and blood in the sinuses on admission.

2. Radiology
- **a.** Plain radiographs. Predict culture-positive antral aspirates in 70% to 80% of acute cases. Findings include air-fluid level, opacification, mucosal thickening of >5 mm in adults.
- **b.** CT scans. Useful to evaluate bony or soft tissue complications. May be overly sensitive in intubated patients.

3. Antral aspirate
- **a.** Aspiration of the maxillary antrum is the standard technique to diagnose infectious maxillary sinusitis.

b. Aspiration in critically ill patients may help distinguish between infectious and noninfectious sinus involvement as well as direct appropriate antibiotic therapy.
c. Consider in the septic patient and/or immunocompromised patient.

4. Complications
a. Orbital: cellulitis and abscess, cavernous sinus thrombosis
b. Intracranial: osteomyelitis, meningitis, epidural abscess, subdural empyema, and brain abscess

V. TREATMENT

A. Supraglottitis

1. Airway management
a. Children. Early placement of an artificial airway reduces mortality.
b. Adults. Intubation is reserved for signs of airway obstruction.

2. ICU observation with equipment and personnel for emergency intubation is required. Humidification and mild sedation can be valuable.

3. Antimicrobial therapy
a. Include agents active against *H. influenzae, S. aureus, S. pneumoniae*, and other streptococcal species.
b. Initial antibiotics are given intravenously and continued by mouth for a 10- or 14-day course.

4. Adjunct therapies
a. Helium–oxygen mixture (heliox). May reduce work of breathing due to lower density of helium gas.
b. Corticosteroids. Use in supraglottitis is controversial. May be of value in children with severe croup.
c. Racemic epinephrine. Likely of little, if any value, in supraglottitis.

B. Deep space neck infections

1. Airway management
a. Upper airway obstruction most often complicates submandibular space infections.
b. Endotracheal intubation can be difficult to perform because of trismus and intraoral swelling. Blind intubation is unsafe because of the risk of trauma to the posterior pharyngeal wall or rupture of an LPS or RPS abscess.
c. Intubation with a flexible laryngoscope is recommended.

2. Antimicrobial therapy
a. Combination of high-dose intravenous (IV) penicillin G and metronidazole recommended.
b. Add agents active against gram-negative bacilli in patients at risk for colonization or if pathogens are identified in culture.
c. With history of penetrating trauma, vertebral disc disease, retropharyngeal abscess, or IV drug use, include coverage for *S. aureus*.

3. Surgery
a. May be necessary despite therapy with antibiotics and needle aspiration
b. Most important with infection of the RPS and LPS
c. When indicated, more rather than less aggressive approaches associated with improved outcome

C. Sinusitis

1. Antimicrobial therapy
a. Acute: cover *H. influenzae*, streptococcal species, *M. catarrhalis* in children. Treat 7 to 14 days.
b. Chronic: additionally consider anaerobes and β-lactamase–producing organisms. Duration of therapy unclear; 3-plus weeks preferred.
c. Nosocomial: additionally consider facultative gram-negative rods and *S. aureus*.

2. Other intervention
a. Topical vasoconstrictors and oral decongestants to facilitate drainage

b. Topical/oral steroids to decrease inflammation
c. Remove nasopharyngeal/nasotracheal tubes
d. Surgical drainage for nonresponders or with neurologic signs in sphenoid sinusitis, immunocompromised patient with mucormycosis.

Suggested Reading

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Clinical presentation, diagnostic procedures, treatment, airway management, and complications of 116 consecutive adults with acute epiglottitis are presented. A rise in the incidence of acute epiglottitis and in the number of epiglottic abscesses was established.

Bert F, Lambert-Zechovsky N. Microbiology of nosocomial sinusitis in intensive care unit patients. *J Infect* 1995;31:5–8.
Infections were often polymicrobial and the common pathogens S. aureus, Pseudomonas aeruginosa, Acinetobacter baumannii, and Enterobacteriaceae often drug resistant.

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Huang TT, Liu TC, Chen PR, et al. Deep neck infection: analysis of 185 cases. *Head Neck* 2004;26:854–860.
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Larawin V, Naipao J, Dubey SP. Head and neck space infections. *Otolaryngol Head Neck Surg* 2006;135:889–893.
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Misthos P, Katsaragakis S, Kakaris S, et al. Descending necrotizing anterior mediastinitis: analysis of survival and surgical treatment modalities. *J Oral Maxillofac Surg* 2007;65:635–639.
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Pinto A, Scaglione M, Scudereri MG, et al. Infections of the neck leading to descending necrotizing mediastinitis: role of multi-detector row computed tomography. *Eur J Radiol* 2008;65:389–394.
The authors discuss the current role of radiology in diagnosing descending necrotizing mediastinitis, in determining the level of infection, and in planning a successful treatment.

Potter JK, Herford AS, Ellis E III. Tracheotomy versus endotracheal intubation for airway management in deep neck space infections. *J Oral Maxillofac Surg* 2002;60:349–354.
Both methods of airway control have a unique set of complications. Use of tracheotomy allowed earlier movement to a noncritical care unit and was associated with fewer intensive care costs and less overall cost of hospitalization.

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Various measurements on the soft tissue lateral neck radiograph are described in adults and children and are found to have excellent sensitivity for the radiologic diagnosis of epiglottitis.

Sichel JY, Attal P, Hocwald E, et al. Redefining parapharyngeal space infections. *Ann Otol Rhinol Laryngol* 2006;115:117–123.
The authors review the clinical signs, computed tomography scans, treatment, and outcome of parapharyngeal space infections (PPIs), and define two types of infections of the parapharyngeal space: Posterior parapharyngeal infection or parapharyngeal lymphadenitis, a relatively benign condition, for which nonsurgical treatment is considered and infection involving the parapharyngeal fat (parapharyngeal abscess or deep neck abscess). Dissemination into the mediastinum and other severe complications are frequent; surgical drainage is mandatory.

Solomon P, Weisbrod M, Irish JC, et al. Adult epiglottitis: the Toronto Hospital experience. *J Otolaryngol* 1998;27:332–336.
Soft tissue lateral neck radiographs were abnormal in 88%, but they had a 12% false-negative rate. A rapid clinical course (<12 hours), tachycardia, and positive pharyngeal or blood cultures were factors that selected for a group of patients requiring formal airway intervention.

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Along with Huang, Larawin, and Parahiscar, one of four retrospective reviews of almost 700 subjects reviews the demographics, etiology, associated systemic diseases, bacteriology, radiology, treatment, duration of hospitalization, complications, and outcomes in patients with deep neck infection.

ACUTE INFECTIOUS PNEUMONIA

Andres F. Sosa and Oren P. Schaefer

60

I. GENERAL PRINCIPLES—Pneumonia in the immunocompetent patient

A. Pneumonia in the intensive care unit (ICU)

1. Severe community-acquired pneumonia (CAP)
   - **a.** Mortality rates for patients admitted to the ICU with CAP range from 21% to 54%.
   - **b.** There is no uniform definition for severe CAP. Multiple criteria have been published.
   - **c.** Early and effective empiric therapy and ICU admission may improve survival.
   - **d.** Underlying comorbidity and certain medical interventions increase the risk for pneumonia and increase morbidity and mortality (Table 60-1).
2. Nosocomial pneumonia: hospital-acquired pneumonia; ventilator-associated pneumonia (VAP); health care–associated pneumonia. Definition: pneumonia occurring ≥48 hours after hospital admission and excluding any infection that is incubating at the time of hospital admission.
   - **a.** The infection most likely to contribute to death of hospitalized patients
   - **b.** Risk factors for nosocomial pneumonia
     - **i.** Underlying acute illness: predisposes to secondary pneumonia
     - **ii.** Coexisting medical illness
     - **iii.** Malnutrition
     - **iv.** Other risks: general surgery, acute respiratory distress syndrome (ARDS), head injury, advanced age, obesity, cardiopulmonary disease, renal failure, malignancy, diabetes mellitus, endotracheal intubation, and mechanical ventilation (VAP), tracheostomy, nasogastric tube, and use of corticosteroids, antibiotics, or H_2 antagonists
   - **c.** Additional risk factors for VAP: intubation and mechanical ventilation, reintubation, nasotracheal and nasogastric tubes, antibiotic use, colonization with virulent pathogens, aspiration (supine position), parenteral nutrition

II. PATHOGENESIS.

Understanding normal host defenses (e.g., humoral immunity, cough) and their potential impairments is valuable in assessing those at risk for pneumonia in general and select pathogens in specific (e.g., *Pneumocystis jiroveci* [formerly *carinii*] with impaired cellular immunity). A more thorough discussion of this topic is referenced.

III. ETIOLOGY

A. CAP

1. Organism causing pneumonia identified in approximately 50%.
2. More common organisms: *Streptococcus pneumoniae, Legionella pneumophila, Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae*, respiratory viruses.
3. Less common organisms: *Staphylococcus aureus*, anaerobes, gram-negative enteric bacilli.

TABLE 60-1 Conditions and Interventions that Increase Risk, Morbidity, and Mortality of Pneumonia[a]

Condition	Intervention
Age older than 65 yr	Antibiotic therapy
Cardiac disease	Gastric acid suppression
Chronic obstructive pulmonary disease	Endotracheal intubation
Diabetes mellitus	Medications
Renal disease	Corticosteroids
Hepatic disease	Immunosuppressants
Malnutrition	Central nervous system depressants
Bronchiectasis	
Malignancy	
Splenic dysfunction	
Immunosuppressive illness	

[a] Underlying comorbidities and certain medical interventions noted in the table not only increase the risk for pneumonia but also increase the morbidity and mortality from it.

4. With severe CAP, *S. pneumoniae* and *L. pneumophila* are most common. Also consider community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA).
5. Frequency of viral infection not known, but likely as high as one third of all cases.
6. In specific clinical settings, certain pathogens may be more common (e.g., injection drug use, *S. aureus*; neutropenia, *Pseudomonas aeruginosa*).

B. Nosocomial pneumonia

1. Early onset (before day 5) pathogens to consider include: methicillin-sensitive *Staphylococcus aureus, S. pneumoniae*, and *H. influenzae.*
2. Early onset (on or after day 5) pathogens to consider include: enteric gram-negative bacilli (likely drug resistant), *S. aureus* (likely methicillin resistant).
3. *P. aeruginosa*: more common, especially with steroid use, structural lung disease, neutropenia.
4. Polymicrobial infections seen in intubated, mechanically ventilated patients.
5. *S. aureus*: a common pathogen in ICU patients, especially post trauma.
6. Other gram-negative bacilli: *Enterobacter, Klebsiella, Acinetobacter, Escherichia coli.*

IV. CLINICAL PRESENTATION

A. CAP

1. Signs and symptoms depend on host and bacterial factors. Patients with altered immune function have a more subtle clinical presentation.
2. Classic symptoms: fever and chills, pleuritic chest pain, productive cough. Elderly patients may have more indolent presentation (fever without chills, nonproductive cough, headache, myalgias, or just mental status change).

B. Nosocomial pneumonia

1. Clinical diagnosis is poor.
2. Weighted scoring system using six clinical variables—fever, white blood cell count and differential, presence of pathogens in sputum, purulence of sputum, radiographic changes, and changes in oxygenation—may be helpful.

V. DIAGNOSIS

A. History

1. In addition to usual symptoms, consider comorbid illness, medication use, history of immunosuppression, recent diagnosis/history of influenza,

geographic and travel history, and exposure to animals. This information does not help in diagnosis but broadens the list of initial diagnostic possibilities with respect to specific pathogens.

2. Pneumonia should be classified as to site of origin: community, hospital, or nursing home.

B. Physical examination. Not specific for diagnosis of pneumonia. Findings may help predict severity of disease. Consider presence of pleural effusion or metastatic infection. Dermatologic findings may suggest a pathogen (e.g., large crusted lesion in blastomycosis). Hemorrhagic bullous myringitis is consistent with mycoplasma infection.

C. Diagnostic testing

1. Routine laboratory tests: complete blood count, routine chemistry studies, blood cultures, assess oxygenation.
2. Chest radiography: may suggest a specific pathogen but not diagnostic. Multilobar involvement carries worse prognosis. Look for pleural effusion and cavitation.
   a. Limitation of chest radiograph (CXR) in the ICU must be recognized. Consider noninfectious pneumonia mimics.
3. Sputum examination: routine sputum Gram stain and culture remain controversial—approximately 30% do not produce sputum; approximately 25% may have received prior antibiotics that may be the reason why cultures are negative; results often do not affect empiric therapy. Consider sputum evaluation for atypical, opportunistic, or resistant organisms or tuberculosis in proper setting.
4. Culture: Definitive diagnosis only if cultures of blood, pleural, or spinal fluid are positive.
   a. Bacteremia is uncommon: 15% or less with CAP, 8% to 15% with nosocomial pneumonia.
   b. Expectorated sputum: difficult to interpret (infection vs. colonization).
5. Serology: Routine testing not recommended. Urinary *Legionella* antigen possible value in severe CAP (yield of ~50%); urinary pneumococcal antigen is recommended by Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines in pneumonia requiring the ICU.
6. Invasive diagnostic culture: Techniques that avoid overgrowth by colonizing rather than pathogenic organisms.
   a. Transtracheal aspiration: limited value and is no longer practiced.
   b. Transthoracic needle aspiration: diagnostic in 50% to 80%; risk of pneumothorax (30%), hemoptysis (10%).
   c. Flexible bronchoscopy:
      i. Bronchoscopy for diagnosis of VAP is controversial. In intubated and ventilated patients, similar clinical outcomes occur with endotracheal cultures and protected specimen brush (PSB) cultures. Purulent secretions seen surging from distal bronchi during exhalation may be predictive of VAP.
      ii. PSB with quantitative culture: accurate estimates of the numbers and types of bacteria present when $> 10^3$ organisms/mL are isolated before antibiotics are given.
      iii. Bronchoalveolar lavage (BAL): valuable in establishing nonbacterial causes of infection, especially in the immunocompromised patient.
   d. Open lung biopsy: standard for the diagnosis of infection; most often used in the immunocompromised host.

D. Differential diagnosis. In the critically ill, diseases that mimic pneumonia such as congestive heart failure, pulmonary embolism, and malignancy may be more common.

VI. TREATMENT

A. Supportive therapy

1. Nutritional therapy: Evaluation and support early in the course
   a. Enteral nutrition preferred; data suggest better preservation of immune function.
   b. Gastric (vs. postpyloric) feeding tubes with continuous feeds are equivalent with respect to aspiration. Exception may be in those with gastric ileus.
   c. Large-bore gastric feeding tubes increase reflux and may worsen aspiration risk.
2. Chest physical therapy (CPT): CPT reserved for patients with pneumonia plus bronchiectasis, cystic fibrosis, and diseases associated with bronchorrhea. Lobar aelectasis.
3. Aerosols and humidity: Have little impact. May provoke cough. Mucolytics (e.g., *N*-acetylcysteine) can precipitate bronchospasm. β_2-Adrenergic bronchodilators may enhance mucociliary clearance, though are best reserved for patients with chronic obstructive pulmonary disease or asthma.

B. Antibiotic therapy.

Early (within 4 hours of arrival) and effective antibiotic therapy improves survival in severe CAP.

1. Severe CAP
   a. Initial therapy: third-generation cephalosporin, plus a macrolide, given intravenously. Alternative is fluoroquinolone plus third-generation cephalosporin. Vancomycin until CA-MRSA excluded.
   b. When *P. aeruginosa* considered: antipseudomonal penicillin or ceftazidime plus aminoglycoside.
   c. With clinically severe pneumonia or in the immunosuppressed host with *L. pneumophila* add rifampin, 600 mg four times a day.
   d. Fluoroquinolone monotherapy should not be used for severe CAP.
2. Nosocomial pneumonia
   a. Treat common pathogens; consider local patterns of infection, resistance, and antibiotic use. Broad initial coverage, narrowed on culture result most effective.
   b. Consider disease severity, risk factors for multidrug resistant pathogens, time of onset (Table 60-2).
   c. With risk for *Pseudomonas* or highly resistant gram-negative bacillary pathogen, use combination therapy until cultures demonstrate the absence of such organisms.
   d. Treatment of VAP for 8 days showed same outcome as 15 days (nonlactose fermenting gram negatives had lower relapse rates with 15-day regime).
   e. Aerosolized aminoglycosides, polymixin or colistin may be helpful for VAP due to *Pseudomonas* or *Acinetobacter* as adjunctive therapy.
   f. Linezolid is equally or more effective than vancomycin for methicillin-resistant *Staphylococcus aureus* (MRSA) VAP.
   g. De-escalation strategy is recommended. Reassess cultures, clinical response, and antibiotics every 3 days. Adjust antibiotics as indicated. If low suspicion and negative cultures, stop antibiotics after 3 days.
3. Antibiotic resistance: The frequency of resistance among community-acquired organisms and nosocomial pathogens is increasing. An understanding of local resistance patterns is required.
4. Prevention of VAP: Evidence-based strategies include orotracheal intubation; orogastric tubes; changes of ventilator circuits only for new patient and if circuits soiled; use of closed endotracheal suction systems; heat and moisture exchangers (with weekly change); semirecumbent positioning no lower than 30 degrees. Also consider aspiration of subglottic secretions, kinetic beds, restricted blood transfusion, aggressive control of

TABLE 60-2 Antibiotic Therapy in Nosocomial Pneumonia

Severity of illness	Likely organisms	Therapy[a]
Mild to moderate, no risk factors[b]; severe, early onset, no risk factors	Core organisms[c]	Second- or third-generation cephalosporin, β-lactam/β-lactamase inhibitor
Mild to moderate, specific risk factors[b]	Core + specific pathogens	Above antibiotics modified for consideration of specific pathogen
Severe, early onset, specific risk factors	Core + *P. aeruginosa*, MRSA, resistant Gram-negative bacilli, *Acinetobacter* sp.	Combination antipseudomonal therapy[d] Consider vancomycin
Severe, late onset, risk factors	Same	Same

[a] Suggested therapy for hospital-acquired pneumonia based on severity, timing, and risk factors for specific pathogens.
[b] Risk factors for specific pathogens (e.g., anaerobes after recent abdominal surgery).
[c] Core pathogens: *Streptococcus pneumoniae*, methicillin-sensitive *Staphylococcus aureus*, nonresistant gram-negative bacilli.
[d] Aminoglycoside or ciprofloxacin with an antipseudomonal β-lactam.
MRSA, methicillin-resistant *Staphylococcus aureus*.

hyperglycemia, postpyloric feeding (with significant gastric ileus); avoid reintubation.

5. Drotrecogin alfa (Xigris): Recombinant human activated protein C. Use associated with reduced mortality in patients with septic shock or sepsis-induced ARDS.

Suggested Reading

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Renal Problems in the Intensive Care Unit

IV

METABOLIC ACIDOSIS AND METABOLIC ALKALOSIS

61

Jahan Montague and David Clive

I. METABOLIC ACIDOSIS

A. General principles

1. Background information

- **a.** The pH of extracellular fluid, normally between 7.36 and 7.44, is tightly regulated, largely by the bicarbonate buffer system. Preservation of this buffer system depends on:
  - **i.** Reclamation of filtered bicarbonate, principally in the proximal tubule.
  - **ii.** Disposal of 50 to 100 mEq of metabolically generated hydrogen ion each day. These hydrogen ions are actively secreted by the nephron and buffered in the urine either by filtered buffers, such as phosphate anion, or by ammonia.

2. Definition

- **a.** A metabolic acidosis is characterized by a low arterial pH and reduced plasma bicarbonate. However, the actual pH and bicarbonate depends on the balance of all acid/base abnormalities.

3. Classification

- **a.** Metabolic acidosis is classified as either normal or expanded anion gap (AG). The normal AG is between 6 and 12 mmol/L.

TABLE 61-1 Causes of Metabolic Acidosis with a Normal Anion Gap

Cause of metabolic acidosis with a normal anion gap	Cause	Mechanism
Bicarbonate loss	Type 2 renal tubular acidosis	Inadequate proximal tubular bicarbonate reabsorption
	Diarrhea	Bicarbonate loss from gut
	Ileostomy	
	Laxative abuse	
	Pancreatic fistula	
	Biliary drain	
	Bladder-drained pancreas transplant	
	Intestinal neobladder	
H ion retention	Type 1 renal tubular acidosis	Failure of distal nephronal proton pumps
	Type 4 renal tubular acidosis (hypoaldosteronism)	Impaired ammonia production
Hydrogen chloride overload	Parenteral alimentation	Exogenous hydrogen ion

b. The AG in the following equation is the difference between the plasma concentrations of the predominant cation (sodium) and anions (chloride and bicarbonate):

$$AG = Na^+ - [Cl^- + HCO_3^-]$$

B. Etiology

1. Acidosis with a normal AG (hyperchloremic acidosis). See Table 61-1.

2. Acidosis with an expanded AG (high AG). See Table 61-2.

C. Pathogenesis

1. Acidosis with a normal AG

a. Decrement in plasma bicarbonate concentration is matched by an increase in chloride.

b. See Table 61-1 for causes and mechanisms

TABLE 61-2 Causes of Metabolic Acidosis with a High Anion Gap

Metabolic acidosis with a high anion gap
Lactic acidosis: lactate, D-lactate
Ketoacids: diabetic, alcoholic, and starvation ketoacidosis
Renal failure: a heterogenous group of organic waste acids that accumulate in the uremic state
Ingestions:
Methanol
Paraldehyde
Ethylene glycol
Salicylates

2. Acidosis with an expanded AG
   a. Accumulation of organic acid reduces plasma bicarbonate concentration. For example, lactic acid is composed of a hydrogen cation and lactate anion. In lactic acidosis, excess hydrogen ions are buffered and each bicarbonate molecule consumed is then replaced by a lactate molecule. Since lactate is an unmeasured anion (and therefore is not used in the AG calculation), its retention results in an apparent increase in the AG.

D. Diagnosis

1. Clinical presentation

a. Physical examination often reveals Kussmaul respirations (deep, rapid). Hypotension and hypovolemia are often present, particularly in severe acidosis.

2. Laboratory studies

a. Diagnosis of metabolic acidosis
   i. The diagnosis of metabolic acidosis is a simple laboratory diagnosis made on the basis of a low blood pH in association with a reduced plasma bicarbonate concentration. Note: when multiple acid base abnormalities are present, pH and/or bicarbonate concentration may be normal despite the presence of an acidosis (see below).

b. Hyperkalemia
   i. Hyperkalemia, when present, probably reflects egress of potassium from cells as hydrogen ions enter.

3. Respiratory compensation

a. Respiratory compensation for metabolic acidosis is caused by chemical stimulation of the brainstem respiratory centers.

b. To assess respiratory compensation, the following formula may be used:

$$\text{Expected } PCO_2 \text{ (mm Hg)} = |(1.5 \times HCO_3) + 8| \pm 2$$

c. A quicker method is to compare the last two digits of the pH (i.e., those to the right of the decimal point) with the carbon dioxide pressure (P_{CO_2}); by mathematical coincidence for metabolic acidosis, these numbers should be approximately equal. If the P_{CO_2} is higher than expected, the patient has a concomitant respiratory acidosis. If the P_{CO_2} is lower than expected, the patient has a concomitant respiratory alkalosis.

4. Multiple acid–base disturbances

a. Calculation of the Δ/Δ ratio (the ratio of AG increase to bicarbonate decrease) is used to screen for multiple acid–base disturbances.

$$\Delta/\Delta \text{ ratio} = \Delta \text{ anion gap}/\Delta HCO_3$$

b. or

$$\Delta/\Delta \text{ ratio} = (\text{Measured anion gap} - \text{normal anion gap}) / (\text{Normal } HCO_3 - \text{measured } HCO_3)$$

   i. Metabolic alkalosis and metabolic acidosis can occur simultaneously. For example, a patient who has been vomiting copiously may then develop ketoacidosis. These two acid–base disturbances offset each other so that the pH and bicarbonate concentration may be normal. The acidosis can be detected by the expanded AG. The alkalosis can be detected by a normal bicarbonate concentration in the setting of an elevated AG. In contrast, with a simple AG metabolic acidosis, the bicarbonate level should drop commensurate with the increase with the AG as bicarbonate is consumed to buffer organic acid. Note

that the Δ/Δ ratio is usually >1.0, even in simple metabolic acidosis. A ratio >1.6 suggests concomitant metabolic alkalosis.

ii. Multiple superimposed metabolic acidoses. For example, a patient with diarrhea develops diabetic ketoacidosis (DKA), the simultaneous hyperchloremic normal AG acidosis (from the diarrhea) and expanded AG acidosis (from the ketoacidosis) result in a drop in bicarbonate far exceeding the increase in the AG. The Δ/Δ ratio <1 suggests concomitant normal and expanded A G metabolic acidoses.

iii. In summary, the recognition of complex acid–base disturbances necessitates attention to AG, pH, bicarbonate level, and P_{CO_2}.

5. Treatment

a. Invariably, the best approach to therapy of metabolic acidosis is to treat its underlying cause rather than giving bicarbonate.

b. Bicarbonate supplementation can be used in individuals with non-anion metabolic acidosis in order to raise the bicarbonate. In patients with a high anion gap acidosis, bicarbonate supplementation can be considered in patients with a systemic pH below 7.15 or bicarbonates below 10 but there is little data to support this approach.

c. The therapeutic goal is to raise the pH to approximately 7.20. Rapid normalization of pH with bicarbonate therapy should be avoided.

d. Bicarbonate is typically given in an isotonic solution such as 5% dextrose in water (D5 W) with 150 mEq/L sodium bicarbonate.

e. Specific approaches to the therapy of DKA, lactic acidosis, the acidoses associated with toxic ingestions, and the acidosis of renal failure are found elsewhere in this book (see Chapters 63, 88, and 107).

II. METABOLIC ALKALOSIS

A. General principles

1. Definition

a. The findings of an elevated plasma pH and bicarbonate concentration establish the diagnosis of metabolic alkalosis.

2. Classification

a. Metabolic alkalosis is classified into two categories: Chloride-responsive and chloride-resistant alkalosis. See Table 61-3.

B. Etiology

1. See Table 61-3.

C. Pathogenesis

1. Generative phase. Metabolic alkalosis can be generated in three ways:

a. Loss of hydrogen ion:

i. Vomiting and nasogastric suction result in the loss of gastric secretions rich in hydrogen and chloride ions.

TABLE 61-3 Etiologies of Metabolic Alkalosis

Chloride-responsive alkalosis (urine chloride <15 mEq/L)	Chloride-resistant alkalosis (urine chloride >20 mEq/L)
Vomiting	Mineralocorticoid excess
Nasogastric suction	Exogenous alkali loading
Recent diuretic use	Ongoing diuretic use
Posthypercapnia	Severe hypokalemia
Exogenous alkali loading[a]	Bartter's syndrome and related disorders

[a] Urine chloride level indicates if metabolic alkalosis is related to hypovolemia (low urine chloride) or other factors such as mineralocorticoid excess or intrinsic renal tubular damage (high urine chloride).

ii. Mineralocorticoid excess states, such as hyperaldosteronism, Cushing's syndrome, and Bartter's syndrome, are characterized by enhanced distal tubular sodium reabsorption and hydrogen ion secretion.

b. Exogenous bicarbonate loading.

c. Loss of fluid with a higher chloride-to-bicarbonate ratio than that of normal extracellular fluid (contraction alkalosis). This can be seen with both loop and thiazide diuretics.

2. Maintenance phase. Excess bicarbonate is normally rapidly excreted. This process is impaired if hypovolemia, chloride depletion, and hypokalemia are present. These abnormalities result in enhanced renal bicarbonate absorption and increased H excretion which perpetuates the metabolic alkalosis.

D. Diagnosis

1. Clinical presentation

a. Alkalemia itself is relatively free of adverse clinical effects. Most of the symptoms, such as muscle spasm, paresthesias, and weakness, are more directly attributable to the commonly associated electrolyte imbalances such as hypokalemia, reduced ionized calcium level, and sodium depletion (hypovolemia).

b. Patients should be questioned for vomiting and diuretic use. Bulimic patients and persons who abuse diuretics may not yield this information willingly.

c. The presence of hypertension in a patient with hypokalemic alkalosis should raise suspicion of a mineralocorticoid excess state such as primary hyperaldosteronism or Cushing's disease.

d. Physical examination should include volume assessment, blood pressure, careful assessment of body habitus, and evidence for vomiting (loss of tooth enamel, parotid gland enlargement, and excoriations of the fingers).

2. Laboratory studies

a. The *sine qua non* of laboratory diagnosis is the presence of both an elevated serum bicarbonate concentration and plasma pH.

b. When a metabolic alkalosis coexists with metabolic acidosis, however, the bicarbonate level may not be raised.

c. The urine chloride concentration may be useful in differentiating among the causes of alkalosis. Urine chloride of <15 mEq/L is typical of chloride-responsive alkalosis, >20 mEq/L of chloride-resistant alkalosis (Table 61-3).

E. Treatment

1. Principles

a. Emergency treatment of metabolic alkalosis is rarely necessary because of the relative paucity of adverse effects associated with this disorder. When blood pH is extremely high >7.55, urgent therapy should be contemplated.

b. Chloride-responsive alkalosis:

i. Chloride-responsive alkalosis, typically associated with volume depletion, responds rapidly to chloride replacement. Volume repletion with normal saline is usually effective.

ii. Hypokalemia should be repleted aggressively.

iii. For patients with persistent vomiting or those receiving continuous nasogastric suctioning, ongoing loss of hydrogen chloride may be attenuated by medications such as H_2 blockers that reduce gastric acid output.

iv. Acetazolamide (250 mg intravenously or orally one to four times daily) may be given to enhance renal bicarbonate wasting.

v. In rare cases of severe metabolic alkalosis resistant to conventional therapies, 0.1 N hydrochloric acid can be used.

c. Chloride-resistant alkalosis. Therapy of chloride-resistant metabolic alkalosis should be directed at the underlying cause. For example,

patients diagnosed with primary aldosteronism should be treated with aldosterone-receptor antagonist or, in the case of aldosterone-producing adenoma, the adenoma should be resected. Associated electrolyte abnormalities such as hypokalemia should be corrected.

Suggested Reading

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DISORDERS OF PLASMA SODIUM AND POTASSIUM

62

Eric Iida and Pang-Yen Fan

I. DISORDERS OF PLASMA SODIUM

A. General principles

1. Plasma sodium (PNa) reflects the relative amount of sodium to water.
2. PNa does not correlate with total body sodium or volume status.
3. PNa is the major determinant of plasma osmolality (Posm) which can be estimated:

$$\text{Posm} = 2 \times (\text{Na}^+ \text{ mEq/L}) + (\text{glucose mg/dL})/18 + (\text{BUN mg/dL})/2.8$$

4. PNa disorders generally indicate abnormal water metabolism, rather than abnormal sodium metabolism.
5. Posm is tightly regulated by antidiuretic hormone (ADH).
6. A 1% to 2% rise or fall in Posm, respectively, stimulates or suppresses ADH.
7. Increased ADH leads to water absorption through urinary concentration evidenced by high urine osmolality (Uosm).
8. Decreased ADH leads to water excretion through urinary dilution (low Uosm).
9. Hypotension or intravascular volume depletion stimulates ADH irrespective of Posm.
10. Abnormal Posm results in transcellular water shifts that alter brain volume and neurologic function.

B. Hyponatremia

1. Etiology: Tables 62-1 and 62-2
2. Pathophysiology
   - **a.** Hypovolemic:
     - **i.** Kidney retains Na and water in response to hypoperfusion from volume depletion.
     - **ii.** Urinary indices reflect both sodium avidity with low urine Na and low fractional excretion of Na (FENa) and water avidity (high Uosm).
     - **iii.** Sodium deficit exceeds water deficit.
   - **b.** Hypervolemic
     - **i.** Kidney retains Na and water in response to hypoperfusion despite volume expansion (ineffective circulating volume).
     - **ii.** Urinary indices reflect both sodium avidity (low urine Na and low FENa) and water avidity (high Uosm).
     - **iii.** Water excess exceeds sodium excess.
   - **c.** Euvolemic
     - **i.** With syndrome of inappropriate antidiuretic hormone secretion (SIADH), kidney retains water inappropriately, but handles Na normally.
     - **ii.** Urinary indices typically reflect water avidity (high Uosm) but urine Na and FENa are not low.
     - **iii.** With reset osmostat, water metabolism occurs normally, but maintains an abnormally low PNa.

TABLE 62-1 Causes of Hyponatremia

Hypovolemic
Gastrointestinal fluid losses (vomiting, diarrhea, enterostomy output, nasogastric drainage)
Renal fluid losses (diuretics, hyperglycemia-induced osmotic diuresis)
Transdermal fluid losses (excessive sweating, fever)
Hypervolemic
Ineffective circulating volume (cardiomyopathy, cirrhosis, nephrotic syndrome, third spacing)
Euvolemic
SIADH
Reset osmostat
Endocrine disorders (adrenal insufficiency, hypothyroidism)
Psychogenic polydipsia
Reduced solute intake
Renal failure

SIADH, syndrome of inappropriate antidiuretic hormone secretion.

iv. With psychogenic polydipsia and inadequate solute intake, water intake exceeds renal water excretory capacity and Uosm will be low.

v. With renal failure, water excretion is limited by low urine output.

3. Diagnosis

a. Clinical presentation

i. Symptoms principally neurologic, but rarely focal.

ii. Range from no symptoms to fatigue, lethargy, gait disturbances, confusion, nausea, vomiting, and, in severe cases, seizures and coma.

iii. Severity of symptoms relates to both level of hyponatremia and the rapidity of its development.

b. History and physical examination

i. Assessment of volume and neurologic status.

ii. Estimation of acuity of hyponatremia.

iii. Review of medications.

iv. Evaluation of solute and water intake and losses.

TABLE 62-2 Causes of Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

Pulmonary disease
Central nervous system disease
Ectopic production (carcinoma, especially small cell lung)
Medications (cyclophosphamide, carbamezapine, chlorpropamide, NSAIDs, cisplatin, etc.)
Exogenous antidiuretic hormone or oxytocin
HIV infection (from central nervous system, pulmonary, and malignant causes)
Pain (often postoperative)
Idiopathic

NSAIDs, nonsteroidal anti-inflammatory drugs; HIV, human immune deficiency virus.

- **c.** Laboratory studies
  - **i.** Measured Posm: normal value with a low calculated Posm indicates pseudohyponatremia (hyperlipidemia, hyperproteinemia).
  - **ii.** Uosm: maximally dilute Uosm (50 to 100 mOsm/kg) suggest primary polydipsia.
  - **iii.** Urine sodium
    - **(a)** Typically <20 mEq/L with volume depletion or ineffective circulating volume.
    - **(b)** >20 mEq/L with SIADH.
  - **iv.** For euvolemic hyponatremia, assess renal, adrenal, thyroid function, and obtain chest radiograph (CXR) and head computed tomography (CT).
  - **v.** Uric acid: Levels <4 mg/dL suggest SIADH.

4. Treatment
- **a.** Rate of correction over the first 24 to 48 hours may be more important than rate over a single or first few hours.
  - **i.** Avoid rapid correction due to risk of osmotic demyelination.
- **b.** Asymptomatic patients: increase PNa ≥0.5 mEq/hour and ≥10 mEq/24 hours.
  - **i.** If mildly symptomatic, increase Na up to 1.0 mEq/L/hour for 3 to 4 hours then slow the rate of correction to raise PNa ≥10 mEq/L over the initial 24 hours.
  - **ii.** If severely symptomatic (seizures, coma), increase PNa 1.5 to 2 mEq/L/hour × 3 to 4 hours then slow rate of correction to total of 12 mEq/L over 24 hours.
- **c.** Monitor PNa every 2 hours for rapid correction.
- **d.** Do not correct to normal PNa; target PNa should be 120 to 130 mEq/L.
- **e.** Rapid correction requires hypertonic saline (512 Na mEq/L) infusion.
- **f.** Calculate Na deficit (amount of Na to raise PNa to target):
  - Weight × 0.6 (target PNa−current PNa) = Na deficit
  - Volume (mL) of hypertonic saline needed to correct Na deficit = (Na deficit/512) × 1,000
  - Infusion rate (L/hour) = volume of hypertonic saline needed/(target PNa − current PNa)/desired correction rate
- **g.** Hypovolemic
  - **i.** Saline to correct volume deficit
  - **ii.** In the setting of hypovolemia, each liter of saline will increase PNa ~1 mEq/L.
  - **iii.** Correction of hypovolemia will suppress ADH and subsequently lead to rapid water excretion.
- **h.** Hypervolemic
  - **i.** Water restriction
  - **ii.** Loop diuretics (avoid thiazides which may exacerbate hyponatremia)
  - **iii.** Vasopressin antagonists (role yet to be defined)
- **i.** Euvolemic
  - **i.** Water restriction
  - **ii.** Hypertonic salin
  - **iii.** Vasopressin antagonists (role yet to be defined)
  - **iv.** Correction/treatment of precipitating disorder

5. Complications
- **a.** Osmotic demyelination (aka central pontine myelinolysis) can occur when hyponatremia is corrected too rapidly.
- **b.** Likely due to intracerebral neuronal dehydration from transcellular water shift as extracellular osmolality increases more rapidly than intracellular osmolality.

TABLE 62-3 Causes of Hypernatremia

Water loss
Gastrointestinal losses
Renal losses
Diuretics
Hyperglycemia-induced osmotic diuresis
Central or nephrogenic diabetes insipidus
Insensible and transdermal losses (excessive sweating, fever, burns)
Inadequate intake
Limited access to water
Primary hypodipsia
Hypothalamic lesions affecting osmoreceptor function
Sodium overload
Intravenous (IV) sodium bicarbonate administration
Hypertonic saline
Salt tablets

c. May be related more to degree of correction over first 24 to 48 hours than rate for 1 or several hours.

C. Hypernatremia

1. Etiology: see Table 62-3

2. Pathophysiology:

a. Defect in ADH production, release, or effect with subsequent renal water losses

b. Inadequate replacement of water losses

c. Sodium overload

3. Diagnosis

a. Clinical presentation

i. Symptoms principally neurologic, but rarely focal.

ii. Range from no symptoms (chronic hypernatremia) to thirst, lethargy, weakness, irritability; with severe cases, neuromuscular irritability, seizures, and coma.

iii. Brain volume loss from acute hypernatremia can also cause structural tearing of small blood vessels and venous sinus thrombosis.

b. History and physical examination

i. Assessment of volume and neurologic status

ii. Estimation of acuity of hypernatremia

iii. Review of medications

iv. Evaluation of solute and water intake and losses (especially urine output)

v. Evaluation of thirst

c. Studies

i. Uosm

(a) Near maximal (800 mosmol/kg) suggests inadequate water intake or sodium overload.

(b) Low Uosm suggests either central (ADH-deficient) or nephrogenic (ADH-resistant) diabetes insipidus. Near isotonic Uosm may suggest osmotic diuresis.

ii. Urine sodium: Low (<20 mEq/L) suggests concomitant volume depletion.

iii. ADH challenge
(a) In setting of Posm >295, high urine output, and low Uosm, consider test dose of 1-deamino 8-D-arginine vasopressin (DDAVP) (4 μg subcutaneously).
(b) Immediate significant decrease in urine output and increase in Uosm suggest central diabetes insipidus.
(c) Lack of response suggests nephrogenic diabetes insipidus.
(d) Results may be inconclusive due to incomplete defects in ADH level or response.
(e) ADH level may then be helpful.
iv. Water deprivation test
(a) Useful to assess etiology of hypernatremia in patient whose PNa has already been corrected to normal.

4. Treatment
a. Estimate water deficit:

$$(\text{Weight} \times 0.5)\,(\text{PNa}/140 - 1) = \text{Water deficit in liters}$$

b. Replete deficit with D5 W infusion or enteral water boluses
c. Rate of replacement = water deficit/desired rate of correction
d. Use a rate of correction based on signs and symptoms
i. Symptomatic patients should be corrected rapidly (up to 2 mEq/L/hour), but ≥12 mEq/L in 24 hours.
ii. Asymptomatic patients should be corrected slowly (up to 0.5 mEq/hour) and ≥10 mEq/L in 24 hours.
iii. For hypovolemic patients, correct volume deficit first with saline before correcting water deficit.
iv. For hypervolemic patients, diurese in addition to correcting water deficit.
e. Increase water replacement rate accordingly to replace ongoing water losses as well as prior deficit.
f. If possible, correct the underlying disorder or remove the offending drug.
i. For central diabetes insipidus, DDAVP by nasal spray (5 to 20 μg once or twice a day)
(a) DDAVP treatment risks include water retention and hyponatremia.
ii. For nephrogenic diabetes insipidus, thiazide diuretics diminish polyuria by inducing mild volume depletion and enhancing proximal tubular reabsorption of water.
iii. For patient taking lithium, amiloride decreases tubular lithium reabsorption and may reduce toxicity.
iv. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be helpful by promoting the effect of ADH.
v. Dietary sodium and protein restriction lowers solute excretion and thus urine output.
vi. Some patients with incomplete nephrogenic diabetes insipidus may respond to supraphysiologic doses of DDAVP.

5. Complications
a. With overly rapid correction, cerebral edema may develop.

II. PLASMA POTASSIUM DISORDERS

A. General principles
1. 98% of potassium (K) is intracellular
2. Plasma potassium levels principally reflect shifts between extra- and intracellular compartments and correlate poorly with total body potassium.

TABLE 62-4 Causes of Hypokalemia

Decreased intake
K loss
Gastrointestinal losses
Vomiting
Diarrhea
NGT drainage
Renal losses
Diuretics
Polyuria (hyperglycemia-induced osmotic dieresis, polydipsia)
Mineralocorticoid excess
Severe metabolic alkalosis
Renal tubular acidosis
Hypomagnesemia
Amphotericin B
Salt-wasting nephropathies (e.g., Bartter's syndrome, tubulointerstitial disease, hypercalcemia)
Nonreabsorbable anions (e.g., penicillin derivatives from high-dose therapy)
Transdermal losses
Dialysis
Increased entry into cells
Increased extracellular pH
Increased availability of insulin
Elevated β_2-adrenergic activity (e.g., high catecholamine states)
Hypokalemic periodic paralysis
Marked increase in blood cell production
Hypothermia

NGT, nasogastric tube.

3. Transcellular K shifts are mediated by insulin, β_2-adrenergic stimulation, Posm and pH.
   a. Insulin and β_2-adrenergic stimulation shift K intracellularly.
   b. High Posm shifts K extracellularly (solute drag).
   c. Acidosis can shift K extracellularly and alkalosis shifts K intracellularly.
4. Urinary excretion occurs largely through distal tubule secretion stimulated by high potassium levels, aldosterone, and high distal urine flow.

B. Hypokalemia
1. Etiologies: see Table 62-4
2. Diagnosis
   a. Clinical presentation: muscle weakness, cramps, rhabdomyolysis, paresthesias, ileus, orthostatic hypotension, polyuria, arrhythmias
   b. History and physical examination
      i. Evaluate dietary intake (consider anorexia)
      ii. Assess volume status
      iii. Review medications (consider laxative and diuretic abuse)
      iv. Assess gastrointestinal (GI) losses (consider bulimia)
   c. Studies
      i. Electrocardiogram (ECG): T-wave depression, prominent U waves, arrhythmias.
      ii. Urinary potassium: If <25 to 30 mEq/day, kidney is appropriately conserving K and any ongoing K losses are likely from GI tract.

iii. Magnesium (Mg) level (adequate Mg necessary for correction of low K).

3. Treatment
   a. Plasma levels from 3 to 3.5 mEq/L
      i. Generally do not produce symptoms
      ii. May cause arrhythmias in patients with heart disease (especially if taking digitalis)
   b. Monitor K closely to avoid "overshoot" hyperkalemia, especially in setting of poor renal function.
   c. Consider cardiac monitoring, especially for patients with cardiac disease.
   d. Correct any concomitant Mg deficiency.
   e. For severe hypokalemia, delay (if possible) correction of concomitant metabolic acidosis as increase in pH could aggravate hypokalemia by shifting K intracellularly.
   f. If diuretic-induced hypokalemia, consider adding or converting to potassium-sparing diuretic.
   g. Chloride-based K preparations work fastest.
   h. Consider bicarbonate- or citrate-based supplements when acidosis is present.
   i. For parenteral K repletion, avoid intravenous (IV) fluids with dextrose, which stimulate insulin release and shift K intracellularly.
   j. In diabetic ketoacidosis, begin K repletion early ($K \geq 4.5$mEq/L) as treatment will "unmask" large underlying K deficit.
4. Dosing guidelines
   a. 40 mEq KCl can transiently raise plasma K up to 1 mEq/L, but K will decrease quickly after equilibration.
   b. Give adequate repletion as plasma K of 2 mEq/L may reflect a total K deficit of 400 to 800 mEq.
   c. Rates of IV K repletion >10 to 20 mEq/L/hour require central access and should be used only in extreme circumstances due to the risk of cardiac arrhythmias.

C. Hyperkalemia
1. Etiologies: see Table 62-5
2. Diagnosis
   a. Clinical presentation
      i. Abnormal skeletal and cardiac muscle function including weakness, paralysis, arrhythmias.
      ii. Severe symptoms may occur with levels above 7.5 mEq/L, but substantial interpatient variability exists.
   b. History and physical examination
      i. Dietary assessment
      ii. Review of medications
      iii. Evaluate muscle strength
   c. Studies
      i. ECG: symmetric T-wave peaking; reduced P-wave voltage; widening of QRS complexes and ultimately a sinusoidal pattern.
      ii. ECG may not show changes despite higher levels, especially if the rate of K rise has been slow.
3. Treatment
   a. K >6.5 mEq/L without ECG changes:
      i. Dietary K restriction to >2 g/day.
      ii. Discontinue precipitating medications (NSAIDs, angiotensin-converting enzyme inhibitor [ACEI]).
      iii. Increase K elimination through diuretics or oral cation exchange resins.

TABLE 62-5 Causes of Hyperkalemia

Increased K intake
TPN
K-rich diet
K-based salt substitutes
Transcellular K shift
Pseudohyperkalemia
Metabolic acidosis
Insulin deficiency
Hyperosmolality (hyperglycemia)
Tissue catabolism and necrosis
Hemolysis
β-Adrenergic blockade
Exercise
Digitalis overdose
Hyperkalemic periodic paralysis
Trimethoprim
Reduced urinary potassium excretion
Hypoaldosteronism
Type 4 renal tubular acidosis (RTA)
Medications
ACEIs, ARBs, NSAIDs, trimethoprim, heparin, aldosterone antagonists
Renal failure
Renal tubular disorders
Adrenal insufficiency
Severe renal hypoperfusion
Urinary tract obstruction

TPN, total parenteral nutrition; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs.

b. Severe or symptomatic hyperkalemia (>6.5 mEq/L, or lower level with ECG changes):

c. Implement treatment to rapidly lower plasma K or reduce electrophysiologic effects.

i. Calcium (10 mL of 10% calcium gluconate IV) stabilizes cell membranes rapidly but only for 15 to 30 minutes. Use for significant ECG changes (widened QRS complex or loss of P waves). Can induce digitalis toxicity.

ii. IV Insulin (10 units of regular) and glucose (50 mL of D50) induces intracellular K shift and can decrease K by 0.5 to 1.5 mEq/L. Acts in 15 to 30 minutes and lasts for several hours.

iii. Sodium bicarbonate: 50 mEq IV induces intracellular K shift in patients with metabolic acidosis. Acts within 30 to 60 minutes and lasts for several hours.

d. Increase K excretion.

i. Loop or thiazide diuretics: Need to ensure adequate Na intake for response.

ii. Cation exchange resins: Sodium polystyrene sulfonate 15 to 30 g PO or by retention enema exchanges potassium for sodium in the stool and induces osmotic diarrhea if given with sorbitol. May repeat every 4 to 6 hours as needed. Use cautiously in patient with impaired bowel motility (risk of colonic necrosis).

iii. Hemodialysis: Consider for severe hyperkalemia, especially in setting of renal failure. Can induce transient hypokalemia with risk of cardiac arrhythmia.

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63 ACUTE KIDNEY INJURY IN THE INTENSIVE CARE UNIT

Namrata Krishnan and Konstantin Abramov

I. GENERAL PRINCIPLES

A. Definition

1. Acute kidney injury (AKI), also known as *acute renal failure* (ARF) is characterized by a sudden decline in kidney function. Most important features are azotemia (accumulation of nitrogenous waste products, e.g., urea and creatinine) and oliguria (decrease in urine output to <500 mL/day). New definitions of AKI, based on either reduction of glomerular filtration rate (GFR) or oliguria, are being developed (e.g. RIFLE criteria, see reference Bagshaw et al., 2008).

B. Classification

1. Categorized according to pathophysiologic mechanism:

a. Prerenal azotemia: impaired renal perfusion

b. Intrinsic or parenchymal AKI: injury to the renal parenchyma

c. Postrenal AKI: obstruction of the urinary tract

C. Epidemiology

1. AKI in the intensive care unit (ICU) setting affects up to 25% of patients with a mortality rate of up to 64%. Mortality reaches 70% for AKI combined with sepsis.

2. AKI often develops as a consequence of the course or treatment of other disorders.

3. Ischemia is the most common cause of AKI in the ICU.

4. AKI is often etiologically multifactorial.

II. ETIOLOGY

A. Prerenal azotemia

See Table 63-1

B. Intrinsic AKI

See Table 63-2

C. Postrenal AKI

See Table 63-3

For discussion of selected syndromes, see Table 63-6

III. PATHOGENESIS

For pathogenesis of selected syndromes, see Table 63-6.

A. Prerenal azotemia

1. Arises from a reduction in renal blood flow from hypovolemia, reduced effective circulating volume, renal artery stenosis, or autoregulatory failure.

2. Reduced renal perfusion leads to intense conservation of solute and water.

3. With reduced effective circulating volume or autoregulatory failure, renal perfusion is compromised despite a euvolemic or hypervolemic state. This may be due to loss of vascular resistance, low cardiac output, or dysregulation of intrarenal hemodynamics.

4. It is a functional condition that is rapidly reversible with correction of renal perfusion.

TABLE 63-1 Causes of Prerenal Azotemia

Hypovolemia
Gastrointestinal losses
Vomiting or NG tube drainage
Diarrhea
Renal losses
Osmotic diuresis (hyperglycemia)
Diuretics
Skin losses
Burns
Excessive insensible losses (fever)
Hemorrhage
Translocation of fluid ("third-spacing")
Postoperative
Pancreatitis
Reduced effective circulating volume
Hypoalbuminemia
Hepatic cirrhosis
Cardiomyopathy (cardiorenal syndrome)
Peripheral blood pooling (vasodilator therapy, anesthetics, anaphylaxis, sepsis, toxic shock syndrome)
Renal artery stenosis
Autoregulatory failure
Medications (NSAIDs, ARBs, ACEIs, pressor agents, etc.)

NG, nasogastric; NSAIDs, nonsteroidal anti-inflammatory drugs; ARB, angiotensin receptor blocker, ACEI, angiotensin-converting enzyme inhibitor

B. Intrinsic AKI

1. Acute injury to renal parenchyma from nephrotoxic insult, most commonly ischemia.
2. Not immediately reversible due to damage to nephrons.
3. Acute tubular necrosis (ATN) is very common as renal medulla is extremely susceptible to injury due to relatively poor oxygenation. Ischemia is most common cause, but may result from nephrotoxins or inflammation of the renal tubular epithelium/interstitium.
4. Intratubular obstruction—drugs (acyclovir, methotrexate, oral sodium phosphate bowel preparation) or toxins (ethylene glycol, myoglobin) can precipitate in and obstruct the tubules.
5. Glomerular injury can cause predominantly proteinuria/nephrotic syndrome or hematuria/nephritic syndrome. Nephrotic and nephritic syndromes may overlap.
6. Vascular disease may present as thrombosis, thromboembolic occlusion, or inflammation.

C. Postrenal AKI

1. Caused by any obstruction to urine flow including functional obstruction as with a neurogenic bladder.
2. For obstruction to cause azotemia, both kidneys must be involved or unilateral obstruction of a single functioning kidney must occur. Unilateral

TABLE 63-2 Causes of Intrinsic (Parenchymal) Acute Kidney Injury

- Tubulointerstitial disease
- Acute tubular injury (acute tubular necrosis)
- Ischemic
- Nephrotoxins:
  - Radiocontrast
  - Medications — aminoglycosides, cisplatin, amphotericin B, foscarnet
  - Pigment — myoglobin (rhabodmyloysis), hemoglobin
- Tumor lysis syndrome — direct toxicity from uric acid, phosphates causing diffuse nephronal microobstruction and tubular damage
- Acute interstitial nephritis (AIN)
  - Drug induced — NSAIDs; antibiotics, most commonly penicillins, cephalosporins, sulfas; allopurinol, thiazides
  - Infections — legionella, Epstein–Barr virus, cytomegalovirus, etc.
  - Autoimmune diseases — sarcoidosis, Sjögren's syndrome
- Glomerular disease
  - Nephrotic syndrome — minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy
  - Nephritic syndrome — membranoproliferative glomerulonephritis, IgA nephropathy, Wegener's granulomatosis, vasculitis
- Vascular disease
  - Thrombosis
  - Thromboembolism
  - Atheroembolism
  - Vasculitis
  - Microangiopathy
    - Scleroderma
    - Malignant hypertension,
    - Toxemia of pregnancy
    - TTP/HUS
    - Medications (cyclosporine, mitomycin)

NSAID, nonsteroidal anti-inflammatory drug; IgA, immunoglobulin A; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome

TABLE 63-3 Causes of Postrenal (Obstructive) Acute Kidney Injury

- Prostatic hypertrophy or tumor
- Neurogenic bladder
  - Diabetes mellitus
  - Multiple sclerosis
  - Paraplegia
- Neoplasms involving the urinary tract, particularly bladder
- Nephrolithiasis (if solitary functioning kidney)
- Retroperitoneal fibrosis

obstruction may go undetected due to compensatory hyperfiltration by the nonobstructed kidney.

3. Complete urinary tract obstruction will cause anuria. However, partial obstruction, even if severe, may not affect urine output.

IV. DIAGNOSIS

A. Clinical presentation:

1. AKI in the ICU setting often presents with azotemia and/or oliguria. Oliguria may precede azotemia.

B. Differential diagnosis:

1. See Tables 63-1, 63-2, and 63-3 for differential diagnosis of AKI.

C. History and physical examination

1. Identify nephrotoxic exposures or events.
2. Associated symptoms and signs (rash, arthritis, hemoptysis, fever, liver disease, bladder distention, prostatic enlargement, etc.).
3. Symptoms and signs of uremia (lethargy, nausea, anorexia, asterixis, myoclonus).
4. Establish acuity and chronicity of renal disease.
5. Assess volume status.

D. Laboratory studies:

1. Urinalysis
   - **a.** Dipstick test for blood and protein
   - **b.** Urine microscopy
     - **i.** Dysmorphic red blood cell (RBC) or RBC casts (glomerulonephritis)
     - **ii.** White blood cell (WBC) casts (acute interstitial nephritis [AIN], pyelonephritis)
     - **iii.** Eosinophils (AIN)
     - **iv.** Fatty casts (nephrotic syndrome)
     - **v.** Muddy brown or coarse granular casts (ATN)
   - **c.** Urine chemistries
     - **i.** Urine sodium concentration (UNa) <10 mEq/L suggests prerenal azotemia.
     - **ii.** Fractional excretion of sodium (FENa):

$$\text{FENa} = (\text{urine sodium}/\text{plasma sodium})/(\text{urine creatinine}/\text{plasma creatinine}) \times 100\%$$

       - **(a)** Less than 1% suggests prerenal azotemia
       - **(b)** May be falsely elevated in setting of diuretic use
     - **iii.** Fractional excretion of urea (FEUrea):

$$\text{FEUrea} = (\text{urine urea}/\text{plasma urea})/(\text{urine creatinine}/\text{plasma creatinine}) \times 100\%$$

       - **(a)** Unaffected by diuretics and is typically <35% in prerenal azotemia
   - **d.** Blood tests:
     - **i.** Serum chemistry studies: electrolyte and acid–base abnormalities
       - **(a)** Hyponatremia
       - **(b)** Hyperkalemia
       - **(c)** Metabolic acidosis
     - **ii.** Complete blood count (CBC)
       - **(a)** Anemia (multiple myeloma, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome [TTP/HUS], chronic kidney disease)
       - **(b)** Thrombocytopenia (TTP/HUS)
       - **(c)** WBC differential (eosinophilia suggests AIN, atheroemboli)

e. Serologic tests: should be ordered when indicated
   i. Antinuclear antibody (ANA), anti–double-stranded DNA antibodies, (systemic lupus erythematosus [SLE])
   ii. Antineutrophil cytoplasmic antibody (ANCA) (vasculitis)
   iii. Hepatitis serologies (polyarteritis nodosa, glomerulonephritis)
   iv. Antiglomerular basement membrane antibody titer (Goodpasture's syndrome)
   v. Cryoglobulins complement levels (postinfectious glomerulonephritis, SLE)

f. Radiologic studies
   i. Renal ultrasound: noninvasive, rapid, can assess both renal parenchyma and collecting systems. Sensitive for urinary obstruction. Small renal size and increased cortical echogenicity suggest underlying chronic kidney disease.
   ii. Post void bladder ultrasound: assess bladder emptying.
   iii. Renal duplex: screen for renovascular disease, renal vein thrombosis.
   iv. Computed tomography: high resolution, carefully consider risk/benefits before use of radiocontrast in patients with ARF.
   v. Retrograde pyelography: consider if urinary tract obstruction suspected.
   vi. Radionuclide renal scan: assess renal perfusion as well as function.
   vii. Renal arteriogram: consider if renal artery thrombus suspected.
   viii. Magnetic resonance imaging (MRI): high resolution, carefully consider risks/benefits before use of gadolinium due to risk of nephrogenic systemic fibrosis (NSF). NSF risk may be reduced with postexposure hemodialysis.

g. Renal biopsy: consider if other studies do not identify cause of AKI, confirmation of diagnosis needed before initiation of specialized treatment such as immunosuppressive medication, or if prognostic information needed.

V. COMPLICATIONS

A. See Table 63-4

VI. PROGNOSIS AND OUTCOME

A. Overall, the mortality rate from AKI ranges from 25% to 64%. Mortality reaches 70% for AKI combined with sepsis.

B. Nonoliguric AKI is associated with the higher rate of recovery of renal function and approximately half the mortality of oliguric AKI.

TABLE 63-4 Complications of Acute Kidney Injury

Hyperkalemia
Hyponatremia
Metabolic acidosis
Volume overload
Hypocalcemia
Hyperphosphatemia
Uremia
Abnormal drug metabolism
Anemia
Hemorrhage
Platelet dysfunction

TABLE 63-5 General Management of Acute Kidney Injury

Weigh patient daily
Monitor input and output
Maintain mean arterial pressure (MAP) >60–70 mm Hg and central venous pressure (CVP) 8 — 10 mm of water
In normovolemic or edematous patients with oliguria, restrict fluid intake (<1,500 m/d) and sodium intake (<2 g/d)
Consider diuretic challenge (furosemide 120–160 mg IV) for oliguric patients; if no response, discontinue
Restrict potassium intake (<2 g/d)
Consider supplemental bicarbonate for arterial pH <7.2
Use phosphate binders to maintain serum phosphorus <5.0 mg/dL if patient is eating or taking enteral nutrition
Discontinue and avoid nephrotoxins, if possible
Adjust doses of all drugs excreted by the kidneys
Avoid magnesium-containing drugs (antacids, milk of magnesia) due to the risk of hypermagnesemia
Remove indwelling urinary catheter in oliguric, nonobstructed patients
Prerenal azotemia:
  Correct volume depletion
  Optimize hemodynamics
Parenchymal:
  Treat underlying illness
  Maximize supportive care
Postrenal:
  Alleviate obstruction
  Monitor for postobstructive diuresis

In general, dialysis therapy should be reserved for patients in whom fluid and biochemical parameters cannot be controlled through medical means alone or in patients who develop uremic symptoms. The use of dialysis is discussed in depth in Chapter 64.

TABLE 63-6 Pathogenesis and Management of Selected Syndromes

Hepatorenal syndrome
  AKI in advanced liver disease, unresponsive to volume resuscitation
  Often precipitated by gastrointestinal bleeding, infection, diuresis, and large volume paracentesis (especially if done without concomitant albumin infusion)
  May be reversible with improvement in liver function or liver transplantation
  Management: midodrine (5–10 mg tid) in combination with octreotide (up to 250 μg SC bid), consider salt-poor albumin infusions (up to 50 mL of 25% albumin tid) if associated with spontaneous bacterial peritonitis
Cardiorenal syndrome
  Impaired renal perfusion due to low cardiac output
  Management: treat underlying heart failure with ACE inhibitors, diuretics, dobutamine etc. Dialytic support if significant volume overload or poorly responsive to diuretics

(continued)

TABLE 63-6 Continued

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS)
- Characterized by microangiopathic hemolytic anemia, thrombocytopenia and AKI
- TTP, in addition, presents with fluctuating neurologic symptoms and fever
- Causative factors: infection with *Escherichia coli* O157:H7, ADAMTS 13 deficiency, drug induced (quinine, mitomycin, cisplatin, antiplatelet agents, etc.), idiopathic in 40%.
- Management: plasma exchange

Scleroderma renal crisis
- AKI with symptoms of malignant hypertension
- Occurs in 10%–20% of patients with systemic sclerosis
- Pathology: "onion skin hypertrophy" and intimal hyperplasia of interlobular and glomerular vessels. Urine sediment typically bland
- Management: ACE inhibitors; steroids contraindicated

Acute interstitial nephritis (AIN)
- Inflammation of the renal interstitium and tubules; often drug induced, with features of allergy: fever, rash, and eosinophilia (may be absent if NSAID-induced)
- Treatment: if no improvement after drug withdrawal, consider prednisone 1 mg/kg for 4–6 wk, then tapered

Myoglobinuric AKI
- AKI in setting of extensive myoglobin release from skeletal muscle injury (rhabdomyolysis)
- Serum creatine phosphokinase >10,000, urine dipstick strongly positive for blood without RBCs in urine sediment
- Management: High-volume alkaline diuresis if patient maintains adequate urine output; IV bicarbonate infusion (e.g., three ampules of bicarbonate in 1 L of 5% dextrose in water) to keep urinary pH >6.5 and diuretics as needed to maintain urine output 250–300mL/h

Tumor lysis syndrome
- Diffuse nephronal microobstruction by released intracellular contents (phosphates, uric acid, purine metabolites) in setting of rapid cell death
- Diagnosis: high phosphorus, LDH, uric acid
- Common precipitants: chemotherapy induction for hematologic and lymphoproliferative malignancies with large tumor burdens or for tumors with rapid cell turnover
- Management: volume expansion before chemotherapy, diuresis, urinary alkalinization, pretreatment with allopurinol and rasburicase (recombinant urate oxidase enzyme) to prevent acute urate toxicity

Radiocontrast-induced nephropathy
- AKI develops within 24 h of radiocontrast exposure, peaks by 72 h, and improves over 4—7 d
- FENa is <1%, high specific gravity, urinary sediment bland or with muddy brown casts
- Risk factors: preexisting renal insufficiency, volume depletion
- Risk can be reduced by preventive measures:
  1. Isotonic bicarbonate (D5W with 150 mEq of sodium bicarbonate 3 ml/kg/hour 1 hour before the procedure, then 1 ml/kg/hour for 6 hours after) or 1 mL/kg of normal saline starting 2–6 h before the procedure and to continue for 6 h afterward
  2. *N*-acetylcysteine 600–1,200 mg every 12 h orally for two doses, before and after the procedure
  3. Use nonionic, low-osmolality radiocontrast

AKI, acute kidney injury; ACE, angiotensin-converting enzyme; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; ADAMTS, a disintegrin-like and metalloproteinase with thrombospondin; NSAID, nonsteroidal anti-inflammatory drug; RBCs, red blood cells; LDH, lactate dehydrogenase; FENa, fractional excretion of sodium; D5W, dextrose 5% in Water.

C. Eventual recovery of renal function can be expected in most patients without prior chronic kidney disease who survive AKI.

VII. TREATMENT

A. See Table 63-5

B. For treatment related to selected syndromes, see Table 63-6.

Suggested Reading

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64 DIALYTIC THERAPY IN THE INTENSIVE CARE SETTING

Matthew J. Trainor and Dagmar Klinger

I. GENERAL PRINCIPLES

A. Background

1. Dialytic therapy or renal replacement therapy (RRT) is essential for management of patients with end-stage renal disease (ESRD), acute kidney injury (AKI), and toxic ingestions and is a common practice in the modern intensive care unit (ICU).

2. In hemodialysis (HD) and hemofiltration, solute and water pass from blood into a solution (dialysate) across a semipermeable membrane contained in a filter (dialyzer). The dialysis machine continuously pumps blood from a vascular access catheter, arteriovenous fistula (AVF), or arteriovenous graft (AVG) through an extracorporeal dialyzer circuit. The dialyzer membrane permits diffusion of small molecules and water into the dialysate compartment while cells and large molecules are retained in the blood compartment. The dialysis machine also creates a pressure gradient across the dialyzer membrane resulting in ultrafiltration of fluid and increased volume removal. Dialyzed blood is then returned to the patient through the vascular access.

3. To prevent dialyzer thrombosis, anticoagulation may be used for HD and hemofiltration.

4. In peritoneal dialysis (PD), solute and water diffuse from the blood across the peritoneal membrane into dialysate infused into the abdomen through a peritoneal catheter. After a period of equilibration, the initial fluid is exchanged for fresh dialysate.

Optimal modality, timing for initiation, and dosing of RRT for AKI remain controversial. Guidelines are being developed.

5. Dialytic therapies remove solute, toxins, and fluid from blood though three principal mechanisms:

a. Diffusion: solute or water moves from an area of high concentration (blood) to an area of low concentration (dialysate). Factors affecting diffusive transport include concentration gradient, solute characteristics (molecular size and charge), dialyzer membrane characteristics (surface area, porosity, and thickness), and flow rate of blood and dialysate.

b. Convection: solutes and water are forced across the dialyzer membrane by hydrostatic pressure. Filtrate has essentially the same chemical composition as plasma. Convection is most important for fluid removal and hemofiltration.

c. Adsorption: some substances (cytokines, antibiotics) may adhere directly to the dialyzer membrane. This process is limited by the binding capacity of the membrane and is of uncertain clinical significance.

II. INDICATIONS

A. Absolute indications

1. Life-threatening fluid and electrolyte imbalances (hyperkalemia, hypervolemia, and metabolic acidosis) that cannot be managed through other means

2. Severe uremic symptoms (pericarditis, encephalopathy)

3. Life-threatening intoxication with a dialyzable substance

B. Relative indications
1. Minor uremic symptoms (nausea and lethargy, bleeding exacerbated by uremic platelet dysfunction)
2. Non–life-threatening chemical imbalances (moderate hypercalcemia)
3. Need for volume removal to allow for maximal medical therapy

III. PROCEDURE

A. Types of RRT
1. Intermittent hemodialysis (IHD): the preferred method of RRT in hemodynamically stable patients with ESRD or acute intoxication with a dialyzable substance.
   - **a.** Typically performed thrice weekly, but done more often if indicated
   - **b.** Treatment duration usually 3 to 4 hours; extended dialysis may be necessary for toxic ingestion (e.g., methanol)
   - **c.** Yields excellent clearances through diffusion and rapid fluid removal through convection
2. Continuous renal replacement therapy (CRRT): Continuous forms of RRT preferred for patients with significant hemodynamic instability, severe volume overload, and/or high obligatory daily fluid requirements and inadequate urine output. Hourly clearances lower than IHD, but total daily solute and fluid removal are typically greater.
   - **a.** Slow continuous ultrafiltration (SCUF): ultrafiltrate removed slowly, but not replaced.
   - **b.** Continuous venovenous hemofiltration (CVVH): large volumes of ultrafiltrate (>1.5 L/hour) removed and largely replaced with a physiologic crystalloid. High-volume hemofiltration generates substantial convective clearance.
   - **c.** Continuous venovenous hemodiafiltration (CVVHD): CVVH with the addition of dialysate pumped through the dialyzer, generating both diffusive and convective clearance.
   - **d.** Slow low efficiency dialysis (SLED): Similar to IHD, but with much slower blood and dialysate flows and conducted over a longer duration, though not always fully continuous.
3. PD: Solute and water diffuse from peritoneal vasculature into dialysate within the abdominal cavity. The high concentration of dialysate dextrose creates an osmotic gradient necessary for water/volume removal. PD is principally used for ESRD, but rarely for AKI because PD catheters are much more difficult to place than HD or CRRT catheters. In addition, peritoneal dialysate can impair pulmonary mechanics and may be contraindicated with recent abdominal surgery.

B. Vascular access
1. Temporary
   - **a.** Dual-lumen venous catheter:
     - **i.** Tunneled: preferred when the expected duration of RRT is >3 weeks. Most commonly placed in right internal jugular vein.
     - **ii.** Nontunneled: preferred for RRT of expected short duration. May be placed in internal jugular, subclavian, and femoral veins. Femoral site associated with increased infection rate when catheter is in place for >5 days. Subclavian approach should be avoided due to risk of central venous stenosis.
2. Permanent
   - **a.** AVF: preferred access for patients with ESRD. Surgical anastamosis of an artery and vein increases venous flow and causes enlargement (maturation) of the fistula over weeks to months. Not useful for AKI (prolonged maturation) or CRRT (risk of AVF rupture with prolonged needle cannulation).

b. AVG: Surgical placement of large-caliber synthetic conduit connecting an artery and vein. Can be used within 2 to 3 weeks. As with AVF, grafts are not used for AKI or CRRT.

C. Peritoneal access
1. Temporary
a. Rigid catheter passed over a stylet. Risk of bladder perforation. Catheters cannot be used >3 days due to risk of infection.
2. Permanent
a. Soft, Dacron-cuffed catheters placed surgically; typically require 2 weeks to mature. Can attempt early use with low dialysate volumes in supine patients, but high incidence of leakage from the catheter tunnel.

D. Anticoagulation
1. Heparin: typically used with IHD. Generally given as a bolus with minimal postdialytic anticoagulant effect. Can be used for CRRT, but may have higher rates of filter thrombosis and bleeding complications than citrate. Complications include hemorrhage and thrombocytopenia.
2. Citrate: used extensively with CRRT. Regional anticoagulation achieved by calcium chelation and arrest of the coagulation cascade. This effect is reversed by postdialyzer calcium infusion. The citrate is hepatically metabolized to bicarbonate. Complications include metabolic alkalosis and hypocalcemia.
3. Other modalities: prostacyclin—a short-acting agent that blocks platelet aggregation through arachidonic metabolite inhibition. Use in CRRT limited due to hypotensive effect and cost.
Hirudin: use limited by long half life.
4. No anticoagulation is used during RRT when the patient is at high risk of life-threatening hemorrhage.

E. Fluids
1. Dialysate solutions
a. The chemical composition of dialysate closely resembles normal plasma, but does not contain metabolic waste products such as urea or creatinine. For hemodialysate:
i. Sodium concentration ranges between 135 and 155 mEq/L and can be varied during the treatment (sodium "modeling" or "profiling") to minimize dialysis-induced reductions in plasma osmolality (which can result in hypotension as water shifts intracellularly).
ii. Potassium concentration is determined based on serum level. Low concentrations (1 to 2 mEq/L) removes potassium while concentrations of 3 to 4 mEq/L may replete potassium).
iii. Bicarbonate concentration is typically 30 to 35 mEq/L to replete buffer.
2. Replacement solutions for CRRT
a. Similar to dialysate.
i. Bicarbonate or citrate based or lactated Ringer's solution are used. The use of citrate-based replacement fluid may be limited by hepatic dysfunction (see IV).
3. Peritoneal dialysate
a. Peritoneal dialysates contain various dextrose concentrations (1.5%, 2.5%, and 4.25%) to generate the osmotic gradient for diffusion of fluid. Higher concentrations increase solute and fluid removal. Diabetic patients undergoing PD must have serum glucose levels monitored.

IV. COMPLICATIONS

A. Hemodialysis
1. Hypotension: common complication which can occur even without volume removal (due to water shifts induced by solute clearance). Can be

partially prevented by cooling of dialysate (which promotes vasoconstriction and improved myocardial contractility), and careful volumetric control of ultrafiltration and solute removal.

2. Dysequilibrium syndrome: neurologic symptoms, most commonly dizziness and headache, caused by transcerebral fluid movement after dialysis. Can be avoided by limiting solute clearance during first few dialysis sessions.
3. Hypoxemia: owing to alveolar hypoventilation and intrapulmonary leukostasis from cytokine release triggered by reaction to dialyzer membrane. Rarely clinically significant, except for occasional patients with severe cardiopulmonary disease.
4. Infection: owing to either dialysis catheter or needle cannulation site infection or bacteremia.
5. Technical errors: air embolism and blood leaks rare when adequate precautions are observed.
6. Hemorrhage: mandates a cautious use of anticoagulation

B. CRRT

1. Same as HD, except no dysequilibrium syndrome. CRRT-specific issues include:
   - **a.** Citrate accumulation—with hepatic failure and reduced citrate metabolism, ionized calcium can drop dramatically despite normal serum levels as calcium chelated by citrate accumulates. This necessitates regular measurement of both ionized and total calcium level.
   - **b.** Hypophosphatemia—phosphate clearance is high with CRRT and intravenous phosphate replacement is usually required.

C. Peritoneal dialysis

1. Infections
   - **a.** Peritonitis may arise from introduction of pathogens into the dialysis system during dialysate exchanges. When a patient is suspected of having peritonitis associated with PD, begin empiric therapy with vancomycin and ceftazidime pending cultures results.
   - **b.** Tunnel infections arise at the catheter exit site and may track subcutaneously into the peritoneum. The most commonly isolated pathogens are *Staphylococcus aureus* and *S. epidermidis*. Gram-negative bacteria and fungi are occasionally culpable.

V. DISCONTINUATION OF DIALYSIS

A. Most patients with AKI become dialysis independent within several weeks. Signs of renal recovery include increased urine output in a previously oliguric patient and declining serum creatinine level or one does not increase between dialysis treatments.

B. Discontinuation of dialysis may also be contemplated under less fortunate circumstances, that is, in patients with persistent renal failure who languish or fail despite intensive medical care. Such decisions should reflect close communication between patients (or their representatives) and physicians.

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Infectious Disease Problems in the Intensive Care Unit

V

APPROACH TO FEVER IN THE INTENSIVE CARE PATIENT

65

Sonia N. Chimienti and Richard H. Glew

I. GENERAL PRINCIPLES

A. Fever is common in the intensive care unit (ICU) setting and its evaluation can be cost- and time-consuming.

1. Rational and efficient utilization of resources in the determination of the cause of fever is imperative.

B. Definition of fever

1. Body temperature may be measured in a variety of ways and each method has advantages and limitations.

a. The most reliable method is through a rectal probe.

i. Rectal thermometers should not be used in neutropenic patients.

b. Axillary temperatures and use of the chemical dot system are less reliable and generally should not be used in ICU patients.

c. Normal average body temperature is 37.0°C (98.6°F), but this may vary by 0.5 to 1.0°C depending on time of day and hormonal factors.

d. Fever in a normal host is a single core temperature >38.3°C (101.0°F).

i. Fever in a neutropenic or otherwise immunosuppressed patient may also be considered to be a temperature elevation of >38.0°C (100.4°F) for >1 hour.

e. Hypothermia may also be a sign of severe systemic infection.

i. New-onset temperature of <36.0°C in the absence of another explanation (cooling blanket, environmental, hypothyroidism).

2. The febrile response may be blunted or absent in certain patient populations:
   a. The elderly
   b. Those with open abdominal wounds
   c. Those with azotemia, congestive heart failure, end-stage liver disease
   d. Those with significant body surface area burns
   e. Those receiving antipyretics or corticosteroids
3. Environmental factors in the ICU also may influence a patient's measured body temperature (specialized mattresses, hot lights, ambient temperature, continuous venovenous hemofiltration/continuous venovenous hemodiafiltration (CVVH/CVVHD) or peritoneal lavage).
4. Central and autonomic nervous system disruption can affect thermoregulatory responses.

II. ETIOLOGY

A. Common infectious causes of fever in the ICU
   1. Intravascular catheter-related bacteremia/fungemia
      a. See Chapter 69 regarding line-associated infections.
      b. Risk of infection varies with a given device (highest risk →lowest risk):
         i. Short-term, noncuffed central venous catheters (CVCs), particularly those used for hemodialysis (2.7/1,000 catheter-days)
         ii. Peripherally inserted CVCs (2.1/1,000 catheter-days)
         iii. Arterial catheters used for hemodynamic monitoring (1.7/1,000 catheter-days)
         iv. Surgically implanted long-term central venous devices (cuffed and tunneled catheters) (1.6/1,000 catheter-days) and central venous ports (0.1/1,000 catheter-days)
         v. Small peripheral intravenous catheters (0.5/1,000 catheter-days)
         vi. Midline catheters (0.2/1,000 catheter-days)
      c. Consider central venous septic phlebitis, other endovascular focus (endocarditis, graft infection, etc.) when fever persists on effective antibiotic treatment and blood cultures remain positive after removal of the implicated intravascular catheter.
   2. Sinopulmonary infections
      a. Pneumonia—see Chapter 60
      b. Isolated tracheobronchitis
      c. Nosocomial sinusitis—consider this diagnosis in patients with
         i. Transnasal intubation (prevalence of 33% after 7 days of intubation)
         ii. Maxillofacial trauma with obstruction of nasal drainage
   3. Antibiotic-associated colitis (*Clostridium difficile* colitis)
      a. See Chapter 81 regarding fulminant colitis and toxic megacolon.
      b. *C. difficile* colitis causes 10% to 25% of all cases of antibiotic-associated diarrhea, and almost all cases of antibiotic-associated pseudomembranous colitis.
         i. May occur following treatment with virtually any antibiotic (most common precipitants are the fluoroquinolones, cephalosporins, and clindamycin)
      c. Fever, diarrhea, and leukocytosis are the most common presenting features.
         i. Some patients may present with an adynamic ileus, toxic megacolon, and no diarrhea; rarely with constipation.
   4. Urinary tract infection
      a. See Chapter 70.
      b. Bacteriuria or candiduria associated with urinary catheters often represents colonization.
      c. Urinary tract infections associated with urinary catheters in the ICU setting are often due to nosocomial, multiple antibiotic resistant, gram-negative aerobic bacteria.

5. Surgical site infections
   a. Higher risk in certain patient populations (diabetic, immunocompromised), with emergent versus elective procedures, and with prolonged surgical procedures).
      i. Most common etiologies are skin flora, including *Staphylococcus aureus*, including MRSA, and coagulase-negative *Staphylococcus* species.
6. Other gastrointestinal infections
   a. Acute cholecystitis—calculous and acalculous
   b. Ascending cholangitis
   c. Diverticulitis, intra-abdominal abscess
   d. Acute appendicitis
   e. Mesenteric infarction
7. Skin and soft tissue infections
   a. Decubitus ulcers
8. Central nervous system infections
   a. Uncommon cause of fever in ICU patients, in the absence of neurosurgical procedures, head trauma, high-grade bacteremia, invasive sinus infection or immunocompromised state.
      i. Patients with intracranial devices (shunt, ventriculostomy catheter, reservoir for chemotherapy) should have cerebrospinal fluid (CSF) sampling to rule out infection and determine the causative organism.

B. Common noninfectious causes of fever
1. Drugs
   a. Reactions to medications ("drug fever") and blood products, malignant hyperthermia
   b. Acute alcohol withdrawal
2. Vascular
   a. Acute vasculitis
   b. Subarachnoid hemorrhage, dissecting aortic aneurysm
   c. Mesenteric ischemia
   d. Deep vein thrombosis (DVT) or pulmonary embolism (PE)
   e. Acute myocardial infarction
   f. Fat emboli
3. Malignancy
   a. Lymphomas
   b. Tumor lysis syndrome
4. Endocrine/metabolic
   a. Heat stroke
   b. Hyperthyroidism/thyroid storm
   c. Adrenal insufficiency
5. Other
   a. Seizures
   b. Pancreatitis
   c. Organ transplant rejection

III. PATHOPHYSIOLOGY

A. Principal mediators of fever are interleukin 1 (IL-1), tumor necrosis factor (TNF), and IL-6.
1. Cytokines interact with receptors in the anterior hypothalamic thermoregulatory area that releases prostaglandins, resetting the thermoregulatory set point.

B. Many aspects of ICU care can lead to impaired host defense and a resultant increase in the risk for infection, including:
1. Mechanical ventilation
2. Indwelling intravascular catheters (arterial and venous) and urinary catheters

C. Expedient discontinuation of invasive monitoring and supports as soon as feasible will prevent many nosocomial infections.

IV. DIAGNOSIS

A. Clinical assessment

1. A thorough history must be obtained; if the patient cannot communicate, careful review of nursing and physician notes may be revealing.
   a. Particular attention should be devoted to recent changes in clinical status.
      i. Decreased or altered urine output (cloudy urine, hematuria)
      ii. Diarrhea or absent bowel movements
      iii. Increased ventilator settings or oxygen requirement
      iv. Increased sputum production, increased endotracheal secretions, change in color/quality of endotracheal secretions
      v. Difficulty drawing or infusing through CVCs
2. A thorough physical examination of all systems is imperative. Particular attention should be devoted to entry sites of indwelling intravascular catheters (inflammation, purulent drainage), duration of catheter cannulation, unusual oral or skin lesions or ulcerations, skin breakdown/pressure ulcers, surgical wound sites, new or changing murmurs, and changes in abdominal examination.
   a. Focus initial assessment on the common infectious and noninfectious causes of fever noted earlier.

B. Laboratory studies

1. Blood cultures
   a. Always obtain blood cultures to evaluate a new fever with suspected infectious or unknown cause on clinical examination.
      i. Always obtain cultures before empiric antibiotics are initiated, as long as this can be done safely and without generating a significant delay in treatment.
      ii. Method of collection is important.
         (a) Clean and prep venipuncture site using 2% alcoholic chlorhexidine. Use 1% to 2% tincture of iodine if there is an allergy to chlorhexidine.
         (b) The prepped area should be allowed to dry for 1 to 2 minutes.
         (c) Bottles should be swiped with 70% to 90% alcohol.
      iii. Volume of blood collected is important.
         (a) Twenty to 30 mL from adults, drawn from a single peripheral site, is needed for a single set (two bottles) of blood cultures.
            (1) If an adequate volume cannot be drawn for the full set, inoculate the anaerobic bottle with all of the blood obtained, up to the maximum volume that can be added to the bottle.
         (b) Optimal yield of culture results to detect bacteremia or fungemia is achieved when 2 to 3 separate sets of blood cultures are obtained in the first 24 hours of a new fever evaluation.
      iv. Sites of collection are important.
         (a) Separate sets of blood cultures should be obtained from different sites, by venipuncture through intact and noninfected skin.
         (b) In patients with indwelling CVCs, all sets of blood cultures can be drawn peripherally, or one blood culture drawn through the CVC can be obtained along with peripheral blood cultures.
            (1) Isolating the same organism from CVC and peripheral blood cultures, and earlier time to positivity from the CVC blood culture, suggest a line-associated infection.
            (2) A single positive culture drawn from a CVC with negative peripheral blood cultures should be interpreted with caution and may not represent true infection.

(c) If blood cultures are collected from a CVC:
(1) It is not necessary to culture different ports; a single port is sufficient.
(2) The distal port of a multiple-port CVC should generally be sampled.
(3) If blood can only be obtained from CVCs and venipuncture cannot be performed, the line placed most recently should be sampled first.

2. Cultures of intravascular catheter tips
a. If a catheter is thought to be a probable or definite source of infection, the device should be removed and the tip sent (in a dry, sterile container) for semi-quantitative culture.
i. If peripheral blood cultures are positive, catheter tip cultures >15 colony-forming units point to the catheter as the source of infection.
ii. The significance of positive catheter tip cultures with negative blood cultures is unknown, may represent false positive results, and should be interpreted with caution.

3. Sputum cultures
a. Most ICU patients will become colonized in the oropharynx with gram-negative bacilli within a few days of hospitalization.
b. Gram stain and culture of sputum/pulmonary secretions should be obtained, preferably before initiation of empiric antibiotics.
i. Expectorated sputum or endotracheal aspirates
(a) Adequacy of sample can be assessed by the presence of <10 epithelial cells and >25 polymorphonuclear cells per high power field (in non-neutropenic patients).
(b) Recognition of a pathogen versus contaminant is suggested by the presence of a dominant organism that is recognized as a recognized pulmonary pathogen versus the presence of multiple organisms in scant amounts on Gram stain and culture.
(c) Semiquantitative culturing of endotracheal secretions appears to yield similarly useful clinical information as quantitative bronchoscopy information.
ii. Fiberoptic bronchoscopy
(a) Quantitative bronchoalveolar lavage or protected specimen brushing cultures may be helpful in determining the presence of a true pathogen.
(b) Bronchoscopy may be particularly useful when unusual pathogens are suspected, or if the patient is immunocompromised.
(c) Additional stains, antigen testing, and cultures of sputum and bronchoscopy samples should be obtained as indicated by the clinical situation.

4. Urine studies
a. Urinalysis (spun sample) and culture should be obtained in all cases of suspected nosocomial urinary tract infections.
b. Collection from catheterized patients:
i. Fluid should not be collected from the drainage bag (high levels of bacteria can develop while urine is retained within the collecting bag).
ii. A fresh specimen should be aspirated from the urinary catheter sampling port.
(a) The port should be cleaned with 70% to 90% alcohol before collection of the specimen.
c. A midstream, clean-catch urine specimen provides adequate sampling from patients without indwelling urinary catheters.

d. Prompt transport and processing is essential to prevent overgrowth of contaminating bacteria.
e. Cultures revealing $>10^3$ cfu/mL in catheterized patients likely represent true bacteriuria or candiduria.
f. Urine for *Legionella* antigen should be sent in selected patients with pneumonia.

5. Cultures of fluid collections
   a. Pleural fluid (bacterial empyema)
      i. Diagnostic thoracentesis for Gram stain, aerobic and anaerobic culture, cytology, measurement of pH, protein, glucose and lactate dehydrogenase (LDH)
      ii. Should be performed in a febrile patient without another obvious source, with an adjacent parenchymal pulmonary process
      iii. Should also be performed in individuals with trauma to the chest, recent thoracic surgery, or concern for a fistula
   b. Surgical wound infections
      i. Intra-abdominal collections must be sampled and drained, either percutaneously via interventional radiology or open laparotomy, depending upon the clinical situation and feasibility of each approach.
      ii. Incisional wound infections should be opened and cultured, irrigated and left open with packing as indicated.
      iii. All collections should be sent for Gram stain and aerobic and anaerobic culture.
6. Stool studies
   a. *C. difficile* colitis must be ruled out in any ICU patient with fever, leukocytosis and diarrhea, particularly in the setting of recent (within 60 days) antibiotic treatment.
      i. Enzyme immunoassay (EIA) is widely employed because of ease of use and rapid turnaround time; EIA is less sensitive than tissue culture assay.
         (a) Two to three tests may be required to improve the sensitivity and make the diagnosis of *C. difficile* colitis. If clinical suspicion is high, a third test may improve diagnostic sensitivity slightly.
         (b) Assays are available for toxin A alone, or toxin A and B; the combined assay is preferred.
         (c) Follow-up assays should not be sent; individuals may shed toxin in stool for prolonged periods, even after clinical resolution of colitis.
   b. Stool cultures for common enteric pathogens should not be obtained routinely, except if a patient was admitted to the ICU with fever and diarrhea, and in immunocompromised patients.
   c. Stool ova and parasite examinations, cultures, or antigen tests for intestinal parasites generally should be obtained in the ICU setting only in selected immunocompromised patients (transplant recipients, human immunodeficiency virus [HIV]-infected patients) or in travelers recently returning from endemic countries.
7. Lumbar puncture (consider computerized scanning of the head before LP, especially if lateralizing neurologic signs are detected)
   a. Should be considered in a patient with fever and any of the following:
      i. Sudden, unexplained change in mental status
      ii. A recent history of head trauma or neurosurgery
      iii. Mental status change that is difficult to evaluate
   b. Basic evaluation: opening pressure, cell count with differential, glucose, total protein, Gram stain and culture.
   c. Additional testing, depending on the clinical scenario (consultation with infectious diseases, neurology, or neurosurgery specialists is advised).

C. Radiologic studies

1. Plain radiography:
   a. Portable upright anteroposterior chest radiography is a reasonable initial test to rule out pneumonia.
   b. Posterior-anterior and lateral upright chest radiography is preferred, if feasible.
   c. Abdominal plain films for patients with abdominal distension, diarrhea.
2. Obtain more dedicated radiologic studies if initial films do not reveal a source.
   a. Chest computed tomography (CT) scan (noncontrast is sufficient to evaluate for parenchymal infiltrates, effusions, focal nodules, and masses).
   b. Immunocompromised patients may warrant earlier and more aggressive radiologic evaluation with CT scanning.
   c. Dedicated CT scan of the sinuses to evaluate for opacification, mucosal thickening, air-fluid levels, and bony destruction is a more sensitive and specific test to rule out sinusitis, compared with plain radiographs.
   d. Abdominal/pelvic CT scan to evaluate for intra-abdominal collections/abscesses, colitis, neutropenic enterocolitis, diverticulitis, appendicitis, etc.

V. TREATMENT

A. Principles

1. Daily reassessment of all indwelling CVCs to determine if they are still necessary.
   a. Avoid the femoral site in favor of other sites for central venous catheterization whenever possible.
2. Prompt initiation of empiric and broad antibiotic treatment in patients with fever and signs suggestive of systemic infection/sepsis.
   a. Delay in therapy may increase morbidity and mortality in patients with sepsis.
   b. Antibiotic selection should be individualized based on clinical assessment and available laboratory and radiographic data.
3. Not all patients require immediate and broad antibiotic treatment.
   a. Patients with stable hemodynamics (no clinical evidence of sepsis) and no apparent source of infection upon initial assessment may in certain circumstances be observed while the diagnostic evaluation proceeds.

B. Definitive care

1. Initial empiric antibiotic choices should be reassessed daily and tailored immediately to target an identified focus of infection and/or infectious pathogen.
2. Infected collections must be drained.
   a. Surgical wound infections must be opened, drained, and irrigated.
3. Whenever feasible, indwelling intravascular catheters should be removed if they are determined to be a probable or definite source of infection.
   a. Removal is strongly advocated in patients with prosthetic heart valves or newly inserted arterial grafts.
   b. Removal of all intravascular devices, with reinsertion at new sites under sterile conditions, should be considered in patients with sepsis or septic shock, evidence of disseminated intravascular infection, or those who are refractory to initial medical and supportive management.

Suggested Reading

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66 THE USE OF ANTIMICROBIALS IN THE TREATMENT OF INFECTION IN THE CRITICALLY ILL PATIENT

David M. Bebinger, Sonia N. Chimienti, and Jennifer S. Daly

I. GENERAL PRINCIPLES

- **A.** Make all reasonable attempts to arrive at a diagnosis for the syndrome encountered.
  - **1.** Outcomes are improved when a diagnosis is obtained and targeted treatment is provided.
  - **2.** Use clinical signs and symptoms to develop a differential diagnosis and predict morbidity.
  - **3.** Pursue diagnostic studies until a diagnosis identified.
- **B.** Develop an empiric antimicrobial regimen based upon the differential diagnosis and predicted morbidity.
  - **1.** Isolated fever usually does not require empiric antimicrobial therapy. Patients with vital sign abnormalities have systemic inflammatory response syndrome (SIRS) until an infection has been identified SIRS can be due to many non-infectious etiologies.
  - **2.** However, immunocompromised patients and those with signs of vascular collapse or organ dysfunction usually require empiric antimicrobial therapy.
  - **3.** In the case of infection, source control is required for optimal care.
    - **a.** Remove infected catheters or other nonessential foreign bodies.
    - **b.** Drain infected collections (ex: empyema).
  - **4.** Empirically treat patients with sepsis and organ dysfunction with broad spectrum antibiotics.
    - **a.** All patients at risk for *Staphylococcus aureus* disease should be treated empirically for methicillin-resistant *Staphylococcus aureus* (MRSA).
    - **b.** Antimicrobials directed against gram-negative organisms depend on the setting where the infection was acquired, the anatomic site of infection, and local susceptibility patterns.
    - **c.** Syndromes with an identified source should prompt antibiotic treatment directed at likely pathogens causing the specific type of infection.
- **C.** Dose antimicrobials properly to ensure adequate levels and minimize toxicity.
  - **1.** The initial dose should be adequate to reach therapeutic levels quickly, rarely requires dose modification for organ dysfunction, and may need to be increased in septic shock.
  - **2.** Modification of subsequent doses may be required in patients with renal or hepatic dysfunction.
  - **3.** Prescribe with caution as many antimicrobials interact with other medications in the intensive care unit (ICU).
- **D.** Address dose/duration of therapy on a daily if not a shift by shift basis.
  - **1.** Discontinue antimicrobials if a noninfectious etiology explains the encountered syndrome.
  - **2.** Narrow antimicrobials when a specific organism is isolated, and when sensitivity test results become available.
  - **3.** Adjust dose as needed if renal or hepatic function changes.
  - **4.** Determine the duration of therapy according to established standards.
  - **5.** Always discontinue nonessential antimicrobials to prevent toxicity and drug resistance.

II. ETIOLOGY/DIAGNOSIS/TREATMENT

A. Table 66-1 lists commonly used antimicrobials in the ICU setting along with some of their important characteristics.

B. Table 66-2 contains many of the commonly encountered infectious agents in the ICU setting and their preferred drug regimen(s).

TABLE 66-1 Important Considerations of Selected Antimicrobials

Broad spectrum[a] agents with activity against *Pseudomonas aeruginosa*	
Ceftazidime (Class: Cephalosporins)	■ Reserved for patients at risk for pseudomonas infections ■ Not active against organisms with extended spectrum β-lactamase (ESBL) and Amp C β-lactamases (*Enterobacter* species) ■ Well tolerated, allergic reactions do occur, good CSF penetration (R)
Imipenem–cilastatin (Class: Carbapenems)	■ Excellent activity against most species including anaerobes (except *Stenotrophomonas, Burkholderia, Aeromonas*) ■ Should be reserved for use in critically ill patients where resistance to other antibiotics has developed ■ As with many β-lactams, bone marrow suppression and hemolytic anemia occur as do seizures; cross-reactivity with penicillin allergic patients is observed (R)
Levofloxacin (Class: Quinolones)	■ Widespread use has led to increased resistance ■ Has *Mycobacterium tuberculosis* (MTB) activity; therefore, use with caution in patients with suspected/untreated MTB (R), (I)
Piperacillin–tazobactam (Class: Penicillins)	■ A preferred empiric agent when broad spectrum antimicrobial activity is needed and in empiric therapy for severe sepsis ■ Species harboring ESBL and AMP-C beta-lactamases (Ex: *Enterobacter* species) are likely resistant (R)
Gram-negative agents with *P. aeruginosa* activity	
Amikacin (Class: Aminoglycosides)	■ Used in combination with β-lactams to treat difficult infections; used empirically in septic shock when resistant gram-negative bacteria are suspected ■ Also active against some mycobacterial species ■ Lack of penetration limits efficacy ■ Renal, ototoxicity limits widespread use (R), (I)
Aztreonam (Class: Monobactams)	■ Active against aerobic gram-negative species. Typically reserved for use in patients with significant allergic reactions to β-lactams (R)
Colistin (Class: Polymyxins)	■ Generally reserved for multidrug resistant gram- negative bacilli against which it is usually has bactericidal activity ■ Use limited by dose dependent nephrotoxicity, neuromuscular blockade (R), (I)

(continued)

TABLE 66-1 Continued

Broad spectrum[a] agents without *P. aeruginosa* activity (MRSA activity as indicated)	
Ampicillin–sulbactam (Class: Penicillins)	■ Preferred drug for human and animal bites; also head and neck infections that arise outside of the ICU setting ■ Retains activity for GI flora including many enterococcal species outside of the ICU (R)
Ceftriaxone (Class: Cephalosporins)	■ Excellent broad spectrum activity, but used in combination with an antianaerobic agent when anaerobes are suspected ■ Often the preferred empiric drug for serious pneumococcal infections (meningitis, pneumonia), other central nervous system, GI, and complicated urinary tract infections that arise outside the ICU ■ May cause biliary sludge/cholecystitis (I)
Tigecycline (Class: Tetracycline)	■ Broad spectrum with activity against some MRSA and vancomycin-resistant enterococci (VRE) species make it attractive for GI and skin and soft tissue infections in which other agents are either not active or contraindicated ■ Limited *Proteus* coverage ■ Active against anaerobes, various aerobic gram-positive organisms (H), (I)
Gram-positive agents	
Cefazolin (Class: Cephalosporin)	■ Excellent drug for many soft tissue infections and methicillin-sensitive *Staphylococcus aureus* (MSSA) endocarditis ■ Has limited gram-negative coverage ■ Seizures and confusion in high doses (R)
Clindamycin (Class: Lincosamide)	■ Excellent anaerobic coverage and activity against MSSA and some MRSA isolates; resistance can occur on therapy ■ Diarrhea and increased incidence of *Clostridium difficile* colitis (H)
Daptomycin (Class: Lipopeptide)	■ Active against gram-positive organisms but resistance has emerged on therapy ■ *Do not* use to treat pneumonia as is inactivated by surfactant ■ Muscle enzyme elevations limit higher doses that may be required to treat multidrug resistant organisms and severe infections (I)
Linezolid (Class: Oxazolidinones)	■ Narrow spectrum gram-positive agent active against both MRSA and VRE with good bioavailability and volume of distribution; resistance can develop on therapy ■ Myelosuppression is significant and limits long-term use Thrombocytopenia in particular develops, often after 2 weeks of therapy ■ Serotonin syndrome has been observed with concomitant use of SSRIs (I)
Oxacillin (Class: Penicillins)	■ Preferred agent to treat serious MSSA infections and active against pen-susceptible streptococcal strains and gram-positive anaerobes but limited efficacy beyond these organisms ■ Side effects: neutropenia and elevated liver enzymes

TABLE 66-1 Continued

Quinupristin–dalfopristin (Class: Streptogramins)	■ Active against gram-positive aerobic organisms but not *Enterococcus faecalis* ■ Peripheral infusions cause phlebitis; commonly causes arthralgia and myalgia (H), (I) ■ Despite reduced efficacy, it remains treatment of choice for MRSA and vancomycin-sensitive, penicillin-resistant enterococci
Vancomycin (Class: Glycopeptides)	■ Oral vancomycin is treatment of choice for severe *C. difficile* colitis ■ Rapid infusion results in histamine release and allergic reactions ■ Bone marrow suppression and nephrotoxicity occur with high doses (R), (I)
Additional antibacterial agents	
Ampicillin (Class: Penicillins)	■ Utility limited by β-lactamase production but widely used as therapy for susceptible enterococci, *Listeria*, gram-negative infections ■ Rash, allergy (R)
Azithromycin (Class: Macrolides)	■ Use in the ICU setting is typically reserved for atypical pulmonary pathogens (*Legionella* species, *Chlamydiophila pneumoniae*, and *Mycoplasma*) ■ It also has activity against non-TB mycobacteria (I)
Metronidazole (Class: Nitroimidazoles)	■ Excellent anaerobic activity; has been the preferred treatment for *C. difficile* colitis but efficacy waning ■ Well tolerated but has neurologic side effects including seizures and peripheral neuropathy (R), (I)
Rifampin (Class: Rifamycins)	■ Never used alone as resistance occurs quickly on monotherapy; used in combination to treat *Staphylococcal* prosthetic valve endocarditis (R), (I-CAUTION), (H)
Trimethoprim–sulfamethoxazole (Class: Folate inhibitors)	■ Active against most MRSA isolates but not advised for severe infections; treatment of choice for *Pneumocystis jirovecii* and *Stenotrophomonas maltophilia;* allergic reactions and GI upset are relatively common and bone marrow suppression rare (R), (I)
Antifungal agents	
Amphotericin B (Class: Polyene antifungals)	■ Treatment of choice for many severe life-threatening fungal infections (cryptococcal meningitis with flucytosine, zygomycosis) ■ Use is limited by significant toxicities which are improved with lipid formulations but remain organ/life threatening (R), (I)
Caspofungin (Class: Echinocandins)	■ Preferred by many as the empiric therapy of choice for suspected deep seated *Candida* infections ■ It is second-line agent against *Aspergillus* species infections ■ Mild side effect profile (H), (I)

(continued)

TABLE 66-1 Continued

Fluconazole (Class: Azole)	■ Remains well tolerated and effective agent against *Candida albicans* and other fungi including *Cryptococcus neoformans;* often given empirically to severely ill patients with sepsis syndrome not responding to broad spectrum antibiotics (R), (I)
Voriconazole (Class: Azole)	■ Treatment of choice for invasive aspergillosis and active against *Candida* species; empiric therapy in patients with fever and neutropenia not responding to broad spectrum antibiotics ■ Well tolerated but with visual side effects (R-IV formulation, vehicle accumulates), (H), (I-CAUTION)
Antiviral agents	
Acyclovir (valacyclovir — oral)	■ Usual agent used to treat *herpes simplex* virus infections; also used for shingles in the immunocompromised host ■ Renal toxicity can occur due to crystal formation which is reduced with adequate hydration
Ganciclovir (valganciclovir — oral)	■ Used for prophylaxis and treatment of cytomegalovirus in immunocompromised patients ■ Many side effects of which neutropenia is most significant; also reversible thrombocytopenia and nephrotoxicity (R), (I-CAUTION)

[a]Broad spectrum refers to having activity against many gram-positive, gram-negative, and anaerobic organisms.
CSF, cerebrospinal fluid; (R); dose adjust with renal dysfunction; (I); significant drug interactions exist with this agent; MRSA, methicillin-resistant *Staphylococcus aureus*; (H), dose adjust with hepatic dysfunction; ICU, intensive care unit; GI, gastrointestinal; SSRI, selective serotonin reuptake inhibitor; TB, tuberculosis.

TABLE 66-2 Evaluation and Treatment of Selected Intensive Care Unit Pathogens

Organism	Therapy
Acinetobacter species	Able to live on inanimate objects under stringent conditions. It is primarily an opportunistic organism in hospitalized patients with the capacity to cause severe disease. Colonization and contamination should be considered with all positive cultures. Treat severe infections with two active agents. Local susceptibilities vary widely. ID consultation recommended
Aspergillus species	Highly prevalent fungus typically causing lung disease of various forms, as well as invasive sinus infections. In the ICU in immunocompromised patients it can produce hemorrhagic pneumonia characterized by vascular invasion. Diagnosis requires biopsy as colonization is more common than infection. Treatment of choice is voriconazole

TABLE 66-2 Continued

Organism	Therapy
Burkholderia cepacia	Hardy, resistant pathogen with ability to adhere to tissues and plastic, it also is invasive. Preferred therapy is TMP–SMX but meropenem and minocycline are active as well. Combination therapy according to susceptibility profile in chronic lung disease patients may be required
Candida species	Candidemia should be suspected in patients with risk factors (abdominal surgery, recent broad spectrum antibiotics, indwelling catheters and fungal colonization) who develop sepsis. Optimal treatment varies by *Candida* species but *C. albicans* usually susceptible to fluconazole
Clostridium difficile	Causes diarrhea/colitis when overgrowth is permitted in the setting of antibiotic therapy due to toxin secretion. Stopping all unnecessary antibiotics can be curative. Severe disease: treat with oral vancomycin. With GI motility disorder, add IV metronidazole. Mild to moderate cases respond to oral metronidazole. Occasionally the disease is recurrent and chronic therapy is required
Enterobacteraciae species (*Citrobacter, Enterobacter, Serratia, Proteus*)	Widespread in environment and in human flora, causes community and nosocomial infections. Resistance develops due to many mechanisms and empiric therapy should be guided by local susceptibility patterns. Inducible β-lactamases are common in some species and expressed with antibiotic treatment. See subsequent text for *Escherichia coli* and *Klebsiella* species
Enterococcus species	Colonizes the GI tract of most humans. A frequent contaminant, it also causes severe disease including endocarditis. Bacteremia is associated with a poor outcome in ICU patients with or without effective treatment. Treatment depends on susceptibility testing; cell wall agent (penicillin or vancomycin) used with aminoglycoside for endocarditis. VRE is often very difficult to treat even with newer active agents such as linezolid, quinupristin/dalfopristin, and daptomycin that are typically active
E. coli, Klebsiella species	Can cause a host of infectious processes and can harbor a wide range of resistance mutations. Resistance to fluoroquinolones exceeds 40% in some ICUs. Empiric therapy depends on clinical factors and local susceptibility profile. Ceftriaxone is most likely adequate but any concern for ESBL production should prompt use of a carbapenem
Legionella species	Thrives in warm water environments such as hot tubs and heating systems. An important albeit uncommon (approximately 5%) cause of both CAP and HCAP, it is important to consider because it can lead to septic shock. Cell wall agents (e.g., penicillins) are not active and levofloxacin or azithromycin are treatments of choice
Listeria monocytogenes	A ubiquitous organism in the environment, disease (bacteremia, meningitis) tends to be limited to those with T-cell impairment (pregnancy, the elderly, neonates, HIV, and transplant patients) Ampicillin is preferred treatment

(continued)

TABLE 66-2 Continued

Organism	Therapy
Neisseria meningitidis	Causes bacterial meningitis that may be fatal especially with even minor complement deficiencies. Penicillin G or ceftriaxone are preferred treatments
Nocardia species	Causes pulmonary infections and brain abscesses, usually in immunocompromised hosts. Most species are susceptible to sulfonamides (sulfamethoxazole)
Pseudomonas aeruginosa	Ubiquitous organism in the environment and therefore a frequent colonizer, it also develops biofilms and is difficult to eradicate from foreign materials and diseased tissues. Treatment considerations begin with defining the isolate as a colonizing or infecting organism. Remove (preferred) or replace foreign bodies. Life-threatening infections require treatment with two agents until susceptibility is known, preferably based on institution antibiogram data, with a β-lactam and aminoglycoside. Development of high-grade resistance in critically ill or immune deficient hosts is common
Staphylococcus aureus (MSSA)	Wide range of infections from impetigo to toxic/septic shock to endocarditis. Continues to cause significant morbidity and should be treated aggressively. Oxacillin is much more active than vancomycin and slightly better than cefazolin
S. aureus (MRSA)	Isolates in the setting of an infection are typically viewed as pathogens and treated aggressively. Vancomycin is the treatment of choice for severe infections despite recognized decrease in efficacy. Necrotizing pneumonias due to MRSA should be treated with linezolid
Stenotrophomonas maltophilia	Able to withstand cleaning products and resistant to many drugs, it can colonize diseased tissue and cause line-related bacteremia. TMP-SMX best agent for treating infections and previous therapy with quinolones and cefepime are risk factors for bacteremia
Streptococcus pneumoniae	Continues to play a major role in both community and hospital acquired pneumonia as well as bacterial meningitis. Pen resistant strains number 40%. Ceftriaxone resistance is uncommon and vancomycin resistance not seen. Empiric therapy depends on severity of infection. Meningitis: vancomycin and ceftriaxone are used. Susceptibility studies direct further care

ID, infectious diseases; ICU, intensive care unit (ICU); TMP, trimethoprim; SMX, sulphamethoxazole; GI, gastrointestinal; IV, intravenous; VRE, vancomycin-resistant enterococci; ESBL; CAP, community acquired pneumonia; HCAP, healthcare-associated pneumonia (HCAP); HIV, human immunodeficiency virus; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

Suggested Reading

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Rello J. Importance of appropriate initial antibiotic therapy and de-escalation in the treatment of nosocomial pneumonia. *Eur Resp Rev* 2007;16(103):33–39.
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67 BACTERIAL MENINGITIS

Alan L. Rothman

I. GENERAL PRINCIPLES

A. Definition—presence of bacteria in the cerebrospinal fluid (CSF), and concomitant meningeal inflammation

B. Epidemiology

1. Incidence (United States) is 2.0 to 2.5 cases per 100,000 population per year.

a. Incidence of meningitis due to *Streptococcus pneumoniae* and *Haemophilus influenzae* has declined substantially since introduction of routine infant immunization.

b. Increasing use of conjugate meningococcal vaccine in adolescents in recent years.

2. Incidence is higher in the very young (younger than 2 years of age) and elderly.

C. Prognosis

1. Mortality 10% to 50%, depending on pathogen; intensive care unit (ICU) admission recommended

2. Independent predictors of outcome: hypotension, alteration in consciousness, seizures

a. None present—favorable outcome in 91%

b. Two or three present—favorable outcome in 43%

II. ETIOLOGY

A. Community-acquired meningitis

1. *S. pneumoniae*—most common in all age groups

2. *Neisseria meningitidis*—especially in older children and young adults, outbreaks

3. *Listeria monocytogenes*—especially in compromised hosts, infants (age younger than 3 months of age), older adults (older than 50 years), alcoholism, immunosuppression, general debility

4. *H. influenzae* type B—most common cause in young children before introduction of vaccine

B. Nosocomial meningitis

1. Skin or hospital flora—*Staphylococci*, aerobic gram-negative bacilli

III. PATHOGENESIS

A. Bacterial entry is through bloodstream, except after head trauma or neurosurgery.

B. Innate immune responses to bacterial components cause leukocyte infiltration, altered cerebral blood flow.

C. Symptoms and signs are related to meningeal irritation.

D. Altered neurologic function is due to metabolic and circulatory disturbances.

IV. DIAGNOSIS

Clinical evaluation should be compressed to avoid treatment delays. The goals are to recognize the diagnosis and define likely pathogen.

A. History
1. Consider meningitis in any patient with altered consciousness.
2. Classical presentation is acute onset fever with headache, photophobia, or stiff neck.
3. Alcohol use, previous head trauma, recent use of antibiotics, ill contacts, and immunosuppression influence risk, etiology, and yield of diagnostic tests.

B. Physical examination
1. Nuchal rigidity and altered consciousness are suggestive.
   a. Absence of these signs does not exclude the diagnosis.
2. Papilledema or focal neurologic deficits—delay lumbar puncture (LP) until mass lesion is excluded.
3. Petechiae—suggests meningococcal meningitis, but can be seen in other infections.

C. Laboratory studies
1. Blood
   a. Most tests of limited value for diagnosis; help to identify complications
   b. Blood cultures positive in 30% to 80% with community-acquired meningitis
      i. Collect before initiation of antibacterial therapy!
2. CSF
   a. LP should be performed promptly except when suggestion of a mass lesion
   b. CSF white blood cell (WBC) count—typically >1,000 cells/mm^3
      i. WBC differential—neutrophil predominance (often >85%) in most patients
   c. CSF glucose—<20 mg/dL highly suggestive; normal in up to 40% of patients
   d. CSF protein—usually >100 mg/dL
   e. CSF Gram stain—positive in ≥75% of community-acquired meningitis (in absence of prior antibiotics)
   f. Routine CSF culture—positive in >90% of community-acquired meningitis
      i. Yield lower when antibiotics given before LP
   g. Stains and cultures for fungi or mycobacteria—do them but low yield
      i. Reserve for immunosuppression, chronic meningitis, or lymphocytic CSF pleocytosis with negative routine culture.

D. Radiologic studies
1. Cranial computed tomography (CT) and magnetic resonance imaging (MRI) normal in 76%
   a. Routine imaging before LP is not supported by literature.
   b. Reserve for patients with focal neurologic deficits or other suspicion of mass lesion.

V. TREATMENT

A. Antibacterial therapy
1. General principles
   a. Start therapy as soon as possible after diagnosis is suspected; optimally within 30 minutes of initial evaluation.
      i. Brief delay for collection of blood cultures and CSF acceptable
      ii. If LP delayed further, start therapy as soon as blood cultures obtained
   b. Continue high-dose therapy for full course.
   c. Check on local patterns of drug resistance.
2. Empiric therapy
   a. Community-acquired meningitis (doses shown for adults with normal renal function)
      i. All patients—ceftriaxone 2 g IV q12 h or cefotaxime 2 g IV q6 h

ii. Add vancomycin 1 g IV q12 h if CSF Gram stain negative or shows gram-positive cocci
iii. Add ampicillin 2 g IV q4 h if age younger than 3 months or older than 50 years, immunosuppression, alcoholism, debilitation, or CSF Gram stain shows gram-positive bacilli

b. Postneurosurgical meningitis
i. Vancomycin 1 g IV q12 h plus ceftazidime 2 g IV q8 h

c. Patients with β-lactam allergies
i. Few good alternatives are available; use standard regimen unless documented serious drug intolerance.
ii. Vancomycin plus (fluoroquinolone or aztreonam).
iii. Add trimethoprim-sulfamethoxazole if there is risk for *L. monocytogenes.*

3. Therapy after results of CSF culture
a. *S. pneumoniae*
i. Ceftriaxone MIC ≤0.5 mg/L—ceftriaxone as single agent
ii. Ceftriaxone MIC >0.5 and ≤2.0 mg/L—ceftriaxone plus (vancomycin or rifampin)
iii. Ceftriaxone MIC >2.0 mg/L—ceftriaxone plus vancomycin plus rifampin
iv. Repeat LP for ceftriaxone MIC >0.5; consult infectious disease specialist if culture remains positive

4. Duration of therapy
a. *S. pneumoniae*—10 days; longer for strains not fully susceptible.
b. *L. monocytogenes*—14 to 21 days
c. *N. meningitidis* or *H. influenzae*—7 days
d. Gram-negative bacilli (other than *H. influenzae*)—21 days

B. Corticosteroids

1. Dexamethasone (0.15 mg/kg IV every 6 hours for 2 to 4 days)
a. Begin immediately before or simultaneous with first antibiotic dose
b. Reduced neurologic complications of *H. influenzae* meningitis in children
c. Reduced mortality of *S. pneumoniae* meningitis in adults

C. Supportive care

1. Maintenance fluid therapy.
2. Monitor and treat for neurologic complications—seizures, increased intracranial pressure.
3. Monitor and treat for systemic complications—hypotension, disseminated intravascular coagulation (DIC), metastatic infection.

D. Infection control

1. Respiratory isolation—until 24 hours after start of antibiotic (*N. meningitidis* or *H. influenzae*)
2. Chemoprophylaxis
a. *N. meningitidis*
i. Indications—household and day care contacts, intimately exposed hospital staff (e.g., intubation)
ii. Drugs—rifampin, ciprofloxacin, or ceftriaxone

b. *H. influenzae*
i. Indications—household contacts, if household includes an unvaccinated child younger than 4 years or an immunocompromised child of any age
ii. **Drug** —rifampin

Suggested Reading

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An excellent review of the current understanding of the pathogenesis of bacterial meningitis.

Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 2004;39:1267.
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van de Beek D, de Gans J, Tunkel AR, et al. Community-acquired bacterial meningitis in adults. *N Engl J Med* 2006;354:44.
In addition to providing recommendations on evaluation, antimicrobial therapy, and use of dexamethasone, this review addresses neurologic and systemic complications of meningitis and their management.

68 INFECTIVE ENDOCARDITIS

Karen C. Carroll and Sarah H. Cheeseman

I. GENERAL PRINCIPLES

A. Definition

1. Infective endocarditis (IE) is a microbial infection of the endothelial lining of the heart, characterized on pathologic study by vegetations.

2. The infected site is usually a valve but the term encompasses infection of any vascular endothelial surface, usually hemodynamically or structurally abnormal.

B. Classification

1. Two clinical forms of native valve endocarditis (NVE) have been traditionally delineated.

a. Acute

i. Presents as a fulminant infection, with abrupt onset, high fever, leukocytosis, and rapid valve destruction and systemic toxicity.

ii. Frequently secondary to *Staphylococcus aureus* and may occur on previously normal valves.

b. Subacute

i. Insidious onset, slow development of the characteristic lesions, and absence of marked toxicity for a long period.

ii. A high proportion of these cases occur on valves damaged by congenital, rheumatic, or degenerative cardiovascular disease.

iii. Caused by organisms of relatively low virulence (e.g., viridans streptococci).

2. Prosthetic valve endocarditis (PVE)

a. Early—<12 months following surgery

b. Late—>12 months following surgery

3. Three additional categories have been added to better reflect current epidemiological trends.

a. IE in the intravenous (IV) drug user

b. Nosocomial IE

c. Health care–associated IE

II. ETIOLOGY

A. Most frequently implicated organisms:

1. Viridans streptococci most often recovered include *Streptococcus sanguis, Streptococcus mitis, Streptococcus mutans*, and *Streptococcus bovis*. The latter is commonly associated with pre-existing colon lesions and hepatic disease.

a. Nutritionally variant streptococci, *Abiotrophia defectiva* and *Granulicatella* sp., constitute 5% to 6% of cases of IE caused by viridans streptococci.

2. Staphylococci particularly *S. aureus* have surpassed streptococci in more recent series as the most common cause of IE. Coagulase negative staphylococci (CNS) are the most common pathogens in early PVE. *Staphylococcus lugdunensis* is associated with valve destruction and usually requires valve replacement.

3. Enterococci are causes of nosocomial bacteremia and less frequently IE.
4. *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella* (HACEK) group causes 3% to 4% of cases in patients with pre-existing valvular disease.
5. Culture negative endocarditis is due to prior antibiotic administration in approximately 50% of cases and to unusual or noncultivatable organisms such as *Bartonella* sp., *Tropheryma whipplei, Brucella* sp., *Legionella* sp., *Mycoplasma hominis, Coxiella burnetii,* and fungi. The microbiology laboratory should be consulted when such diseases are suspected.

III. PATHOGENESIS

A. Trauma to the valve results in the elaboration of a fibrin-platelet thrombus.
B. Introduced bacteria from transient bacteremia, a distal site of infection, indwelling catheter, or through injection drug use become trapped in the thrombus.
C. Infection of the fibrin-platelet thrombus results in enlargement of the process into a vegetation and invasion of tissue by the infection with eventual valvular disruption.
D. Specific valve involvement predicts the physiologic consequences
   1. Tissue destruction results in valvular incompetence characterized by a new regurgitant murmur.
   2. Aortic valve disease carries the worst prognosis because of greater potential for spread of infection to the conducting system, emboli to coronary arteries, and propensity to cause heart failure.
   3. A vegetation may be so large as to function as a stenotic lesion.
E. The vegetations may break off as emboli to the brain, viscera, coronary arteries, and large arteries of the extremities (fungal endocarditis).

IV. DIAGNOSIS

A. IE is diagnosed based on signs and symptoms that reflect the pathology: fever, embolic phenomena, and evidence of valvular dysfunction.
B. Criteria
   1. Histopathologic confirmation of vegetation with infecting organisms on the valve.
   2. Stringent clinical criteria called the *Duke Criteria* have been devised and revised.
C. History
   1. Most common feature is fever; but this may be minimal or absent among certain patients.
   2. Musculoskeletal complaints such as lower back pain are also common.
   3. Loss of appetite, weight loss, malaise, and night sweats.
   4. Symptoms of complications such as embolism, stroke, congestive heart failure.
D. Physical examination
   1. Mucocutaneous embolic phenomena may be observed.
      a. Petechiae on plantar surfaces of toes and fingers, the conjunctival and buccal mucosa.
      b. Subungual splinter hemorrhages that appear at rest in the hospital.
      c. Osler's nodes and Janeway lesions are uncommon in recent series of endocarditis.
         i. Osler's nodes are painful, tender, bluish-purple nodular lesions located on the pads of the fingers or toes.
         ii. The Janeway lesion is a painless, pink, nontender macular lesion that is located commonly on the palms or soles.
   2. Any heart murmur is compatible with a diagnosis of endocarditis but a new regurgitant murmur is of greatest importance.

3. Splenomegaly is found in nearly half of patients with subacute bacterial endocarditis and in very few of those with acute disease.
4. Signs of congestive heart failure are not early findings but signal a need to consider cardiac surgical intervention.

E. Laboratory studies

1. The key to the diagnosis of endocarditis is blood cultures.
   a. Three or four separate sets of blood cultures within a 24-hour interval are recommended
   b. 20 to 30 mL from adults, drawn from a single site, are needed for a single set (two bottles) of blood cultures.
   c. In cases that are culture negative, the advice of a clinical microbiologist should be sought regarding the need for special media, such as those for the propagation of *Brucella* sp., *Bartonella* sp., *Legionella*, and cell wall defective forms.
   d. Noncultivatable or difficult-to-cultivate organisms may be detected by serologic or molecular testing. Such organisms include *Coxiella burnetii* (the agent of Q-fever endocarditis), *Chlamydia* sp., *Bartonella* sp., *Tropheryma whipplei*, and some fungi.
2. An electrocardiogram is the simplest test for evaluation of perivalvular extension of infection in endocarditis.
   a. Persistent prolongation of the PR interval in the absence of digitalis toxicity; new persistent bundle-branch block or complete heart block is quite specific for predicting extension beyond the valve leaflet and the subsequent need for surgery.
3. Echocardiography is a valuable adjunct in the patient with endocarditis. Current roles for echocardiography include:
   a. Diagnosis of IE by demonstration of valvular vegetations
   b. Characterization of underlying valvular disease
   c. Clarification of destructive nature of endocarditis
   d. Assessment of the persistently febrile patient for evidence of perivalvular extension
   e. Assessment of valvular function in PVE
   f. Types of studies
      i. Transthoracic two-dimensional (2D) echocardiography (TTE) has an overall sensitivity for vegetation detection of 60% to 65%. TTE has very limited ability to detect valve perforations and abscess extension, especially on prosthetic heart valves. Specificity is high at 98%.
      ii. Transesophageal echocardiography (TEE) has a sensitivity of 85% to 95%, with vegetations as small as 1 mm being seen. TEE is also superior to TTE for detection of perivalvular abscess, with approximately 87% sensitivity; TEE appears to be the optimal tool to assess prosthetic valve dysfunction.

V. TREATMENT

A. Types

1. Medical: 4 to 6 weeks of IV antimicrobial agent(s) bactericidal for pathogen.
2. Approaches for typical pathogens based on American Heart Association (AHA) Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease recommendations:
   a. NVE (uncomplicated)
      i. Viridans group streptococci, *S. bovis* penicillin minimum inhibitory concentration (MIC) ≤0.12 μg/mL—penicillin G (penG) 12 to 18 mU/24 hours IV continuously or in 4 or 6 equally divided doses for 4 weeks *or* ceftriaxone 2.0 g/24 hours IV in 1 dose for 4 weeks when used alone; penG or ceftriaxone at same doses *plus*

gentamicin (gent) 3 mg/kg/24 hours IV/IM in 1 close for 2 weeks is acceptable if patients meet certain criteria (see Baddour and Hoen references).

ii. Viridans streptococci group, *S. bovis* MIC >0.12 μg/mL and ≤0.5 μg/mL—penG 24 mU/24 hours IV *or* ceftriaxone 2 g/24 hours IV/IM in 1 dose for 4 weeks *plus* gent 3 mg/kg/24 hours in 1 dose IV/IM for 2 weeks.

iii. Viridans streptococci group, *S. bovis* MIC >0.5 μg/mL as well as nutritionally variant streptococci—treat as per enterococcal IE.

iv. For patients allergic to penicillin or cephalosporins in any scenario above—vancomycin (vanco) 30 mg/kg/24 hours IV in 2 equally divided doses (maximum 2 g/d) for 4 weeks.

v. Susceptible enterococci—ampicillin 12 g/24 hours IV in 6 equally divided doses for 4 to 6 weeks *or* penG 18 to 30 mU/24 hours IV either continuously or in 6 equally divided doses for 4 to 6 weeks *plus* gent 3 mg/kg/24 hours in 3 equally divided doses IV/IM for 4 to 6 weeks.

vi. Enterococci resistant to penicillin or patients allergic to penicillin—vancomycin as above for viridans group streptococci *plus* gentamicin for 6 weeks.

vii. Enterococci resistant to Pen/Amp, vancomycin and high level of resistance (HLR) to aminoglycosides.

(a) Consider infectious disease (ID) consultation

(b) Quinupristin/dalfopristin (Synercid) 22.5 mg/24 hours IV in 3 equally divided doses for at least 8 weeks (*Enterococcus faecium* only) *or* linezolid 1,200 mg/24 hours IV/PO in 2 equally divided doses for at least 8 weeks

viii. Methicillin-susceptible staphylococci, tricuspid valve—Nafcillin *or* oxacillin 12 g/24 hours IV in 4 to 6 equally divided doses IV with gent 3 mg/kg/24 hours in 2 or 3 equally divided doses IV/IM for 2 weeks; daptomycin 6 mg/kg IV once daily for 4 to 6 weeks.

ix. Methicillin-susceptible staphylococci left-sided infection—nafcillin *or* oxacillin 12 g/24 hours IV in 4 to 6 equally divided doses *or* cefazolin 6 g/24 hours IV in 3 equally divided doses for 4 to 6 weeks with optional gent 3 mg/kg/24 hours IV/IM in 2 or 3 equally divided doses for 3 to 5 days.

x. Methicillin-resistant staphylococci—vancomycin 30 mg/kg/24 hours IV in 2 equally divided doses for 6 weeks; quinupristin/dalfopristin or linezolid for failures or vanco intolerance; for right-sided endocarditis only, daptomycin 6 mg/kg IV once daily for 4 to 6 weeks.

xi. HACEK group bacteria—ceftriaxone 2.0 g/day IV/IM in 1 dose for 4 weeks *or* ampicillin–sulbactam 12 g/24 hours IV in 4 equally divided doses or ciprofloxacin 1,000 mg/24 hours PO or 800 mg/24 hours IV in 2 equally divided doses.

b. PVE

i. Viridans group streptococci, *S. bovis* penicillin MIC ≤0.12 μg/mL—penG 24 mU/24 hours IV either continuously or in 4 or 6 equally divided doses for 6 weeks *or* ceftriaxone 2.0 g/24 hours IV/IM for 6 weeks with or without gent 3 mg/kg/24 hours IV/IM in 1 dose for 2 weeks; Viridans group streptococci, *S. bovis* penicillin MIC >0.12 μg/mL—same penG and ceftriaxone doses *plus* gent same dose for 6 weeks.

ii. Methicillin-susceptible staphylococci—Nafcillin as per native valve (NV) *plus* rifampin 900 mg/24 hours IV/PO in 3 equally divided

doses for 6 weeks *plus* gent 3 mg/kg/24 hours IV/IM in 2 or 3 equally divided doses for 14 days.

iii. Methicillin-resistant staphylococci—Vanco per NV *plus* rifampin 900 mg/24 hours IV/PO in 3 equally divided doses for 6 weeks *plus* gent 3 mg/kg/24 hours IV/IM in 2 or 3 equally divided doses for 14 days.

iv. Enterococci same as for NV.

v. HACEK group same as for NV.

3. Surgical management

a. Definitive indications for valve replacement as per American College of Cardiology (ACC)/AHA guidelines

i. Congestive heart failure requiring more than simple therapy

ii. Acute IE and aortic or mitral valve regurgitation with hemodynamic evidence of elevated left ventricular end diastolic or left atrial pressures

iii. IE caused by fungal or highly resistant organisms

iv. NVE complicated by heart block, annular or aortic abscess or destructive penetrating lesions

v. PVE associated with dehiscence by echocardiography

vi. PVE complicated by obstruction, worsening regurgitation, or abscess formation

b. Surgery is reasonable and should be considered in the following patients:

i. NVE and recurrent emboli, persistent vegetations despite appropriate therapy, mobile vegetations in excess of 10 mm.

ii. PVE and evidence of persistent bacteremia or recurrent emboli despite appropriate therapy.

iii. Patients with PVE and relapsing infection.

Suggested Reading

ACC/AHA. Guidelines for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease): developed in collaboration the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation* 2006;114:450–527.
Important consensus document that provides guidance for surgery in patients with endocarditis.

Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for health care professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki disease, Council on Cardiovascular disease in the young and the Councils on clinical cardiology, stroke and cardiovascular surgery and anesthesia, American Heart Association—executive summary: endorsed by the Infectious Diseases Society of America. *Circulation* 2005;111:3167.
A well written guide to management of native valve and prosthetic valve endocarditis with consensus recommendations for treatment displayed in numerous easy to use tables.

Birmingham GD, Rahko PS, Ballantyne F. Improved detection of infective endocarditis with transesophageal echocardiography. *Am Heart J* 1992;123:774.
A careful study of the incremental value of transesophageal over transthoracic echocardiography.

Birmingham MC, Rayner CR, Meagher AK, et al. Linezolid for the treatment of multi-drug resistant, gram positive infections: experience from a compassionate-use program. *Clin Infect Dis* 2003;36:159–168.

Included in this large series of patients are clinical and microbiologic outcomes on 40 cases of endocarditis with VRE and MRSA. Important data on complications of therapy is presented.

Brouqui P, Raoult D. Endocarditis due to rare and fastidious bacteria. *Clin Microbiol Rev* 2001;14:177–307.
Comprehensive discussion of the clinical presentation and diagnostic strategies for detecting a broad range of fastidious organisms causing IE most notably Bartonella sp., and T. whipplei.

Carroll KC, Cheeseman SH. Infective endocarditis and infections of intracardiac prosthetic devices. In Irwin RS III, Rippe JM, eds. *Critical care medicine.* Baltimore: Lippincott Williams & Wilkins, 2007:1055–1071.
Comprehensive review of all aspects of endocarditis and infection of intracardiac devices.

Chambers HF, Korzeniowski OM, Sande MA, et al. *Staphylococcus aureus* endocarditis: clinical manifestations in addicts and nonaddicts. *Medicine* 1983;62:170.
Classic study defining the differences in Staphylococcal endocarditis between injection drug users and all others.

Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: Summary article. A report of the American College of Cardiology/American Heart Association Task force on practice guidelines (ACC/AHA/ASE Committee to Update the 1997 guidelines for the clinical application of echocardiography.). *J Am Soc Echocardiogr* 2003;16:1091–1110.
Changes to the 1997 guidelines include the addition of the Duke criteria and the value of TEE when TTE is negative in settings of high clinical suspicion and PVE.

Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. *Am J Med* 1994;96:200–209.
Original Duke criteria which incorporated predisposing factors, blood culture information and echocardiographic findings into probability assessments for predicting likelihood of IE.

Eishi K, Kawazoe K, Kuriyama Y, et al. Surgical management of infective endocarditis associated with cerebral complications: multicenter retrospective study in Japan. *J Thorac Cardiovasc Surg* 1995;110:1745–1755.
A retrospective study of 181 patients with cerebral complications that concludes that valve replacement surgery may be safely performed four weeks or more after the neurologic event.

Fowler VG, Miro JM, Hoen B, et al. *Staphylococcus aureus* endocarditis: a consequence of medical progress. *JAMA* 2005;293:3012–3021.
Large cohort study that demonstrates the shift in the microbiology of IE from viridans streptococci to S. aureus as a result of invasive procedures and other healthcare interventions.

Fowler VG, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med* 2006;355:653–665.
Multicenter randomized trial of 124 patients with S. aureus bacteremia with or without endocarditis assigned to receive either standard therapy or daptomycin. At 42 days following the end of therapy, daptomycin at 6 mg/kg daily was shown to be not inferior to standard therapy for S aureus bacteremia (both MSSA and MRSA) and right sided endocarditis.

Hoen B. Epidemiology and antibiotic treatment of infective endocarditis: an update. *Heart* 2006;92:1694–1700.
Recent review that summarizes important shifts in the epidemiology of IE and details both the AHA and European Society of Cardiology revised treatment recommendations.

Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;30:633–638.

Proposed modified criteria which have added positive Q-fever serology to major criteria and physical findings and laboratory tests, such as splenomegaly and C-reactive protein, respectively to the minor criteria.

Moreillon P, Que YA. Infective endocarditis. *Lancet* 2004;363:139–149.
Review article that has an excellent discussion of the pathogenesis and pathophysiology of IE.

Mylonakis E, Calderwood SB. Infective endocarditis in adults. *N Engl J Med* 2001;345:1318–1330.
One of the better written and more comprehensive reviews of endocarditis complete with color photos of the peripheral stigmata.

Reinhatz O, Hermann M, Redling F, et al. Timing of surgery in patients with acute infective endocarditis. *J Cardiovasc Surg (Torino)* 1996;37:397–400.
Frequently cited publication on demonstrated improved outcome with surgery when performed prior to deterioration in cardiac performance.

Rosen AB, Fowler VG, Corey GR, et al. Cost effectiveness of transesophageal echocardiography to determine the duration of therapy for intravascular catheter-associated *Staphylococcus aureus* bacteremia. *Ann Intern Med* 1999;130:810.
One of the landmark studies that justifies using transesophageal echocardiography to stratify patients with S. aureus bacteremia to short duration versus long duration therapy.

INTRAVENOUS LINE- AND INJECTION DRUG USE-ASSOCIATED INFECTIONS

69

Jennifer Wang

I. INTRAVENOUS LINE-ASSOCIATED INFECTIONS

A. General principles

1. Infections per year: >2,500,000 in the United States, predominantly central venous catheter (CVC) associated.
2. The longer a CVC remains in place, the higher the risk of infection.
3. Routine changes of CVCs over a guide wire are not recommended.
4. CVC insertion in the lower extremities should be avoided, if possible, due to higher rates of infection.
5. Placement of CVC and pulmonary artery catheters always requires maximal sterile barrier precautions, including cap, mask, sterile drapes, gowns, and gloves.
6. Disinfection of the site with chlorhexidine before insertion is associated with lower rates of infection than alcohol or povidone-iodine.

B. Etiology

1. Most common organisms are coagulase-negative staphylococci and *Staphylococcus aureus*. Others include *Enterococcus* spp., *Corynebacterium* spp., enteric gram-negative bacilli, *Pseudomonas* spp., and *Candida* spp.
2. Sources of microorganisms
   a. Most common source is the patient's skin.
   b. May result from secondary seeding from a bloodstream infection.
   c. Occasionally, infection may result from a contaminated infusion product.

C. Pathophysiology

1. Nontunneled catheters: The insertion and exit sites are the same.
   a. Extraluminal colonization of the catheter may serve as source of infection.
   b. Intraluminal colonization of the hub and lumen of the CVC is also a potential infection source.
2. Tunneled catheter: The original insertion site is closed after a tunnel and separate exit site have been created (e.g., Hickman, Broviac, Groshung, Portacath).
   a. Intraluminal and/or hub contamination is the most important source of infection.

D. Diagnosis

1. Sample collection
   a. Diagnosis with removal of the catheter
      i. The catheter is removed, the tip is cut off with sterile scissors, and the tip is sent to the laboratory in a sterile cup.
      ii. The catheter tip is rolled on an agar plate to determine the number of colonies. A semiquantitative culture with ≥ 15 colonies correlates with infection.
      iii. Blood culture from a peripheral vein is simultaneously obtained.
   b. Diagnosis without removal of the catheter
      i. Blood cultures of adequate and equal volumes should be drawn from the catheter and from a peripheral vein at the same time, and labeled as such. Drawing of cultures from catheter alone is strongly discouraged.
2. If exudate from the insertion/exit site is present, swab cultures should be obtained.

E. Treatment

1. For most patients with documented catheter-related infection, the catheter should be removed as soon as possible. Ideally, another central catheter should not be placed until it is shown that blood cultures are negative.
2. For patients with limited vascular access and dependence on a semipermanent catheter, treatment with antibiotics alone can be successful with coagulase-negative staphylococci infections. *S. aureus*, *Candida*, and gram-negative bacilli almost always require catheter removal. Lines should always be removed if there is a tunnel or exit site infection.
3. Empiric treatment
   - **a.** Vancomycin is preferred because of activity against *S. aureus*, including methicillin-resistant *S. aureus* (MRSA) and coagulase-negative staphylococci.
   - **b.** An extended-spectrum penicillin or third- or fourth-generation cephalosporin, should be considered for coverage of gram-negative bacilli. Empiric antibiotic selection should be guided, if possible, by knowledge of the patient's indigenous flora.
     - **i.** Coagulase-negative staphylococci
       - **(a)** First-line therapy—vancomycin.
         - **(1)** Length of therapy is usually 7 to 10 days after line removal.
     - **ii.** *S. aureus*
       - **(a)** Nafcillin or cefazolin for methicillin-susceptible organisms; vancomycin for MRSA.
         - **(1)** Length of therapy can be 2 weeks of IV antibiotics only if the catheter is removed immediately, fever resolves promptly, no metastatic foci are found, and bacteremia resolves as documented by repeatedly negative blood cultures.
         - **(2)** Patients with bacteremia or fever >3 days after catheter removal and antibiotics are at high risk of developing complications including endocarditis. Echocardiography is recommended and 4 to 6 weeks of therapy is generally required.
     - **iii.** Gram-negative bacilli
       - **(a)** Third or fourth generation cephalosporin or extended-spectrum penicillin (e.g., piperacillin–tazobactam) until identification and susceptibility data return.
       - **(b)** Length of therapy is typically 2 weeks after blood cultures become negative.
     - **iv.** *Candida* spp.
       - **(a)** Candidemia always requires treatment with an antifungal agent.
       - **(b)** Until species is identified, can use fluconazole or an echinocandin.
       - **(c)** Length of therapy is usually 2 weeks after blood cultures become negative.

F. Complications

1. Complications most commonly occur with *S. aureus* and *Candida* spp.
2. These include suppurative thrombophlebitis, endocarditis, endophthalmitis, and metastatic foci of infection.
   - **a.** Ophthalmologic exam should be performed for line-associated candidemia.

II. INJECTION DRUG USE–ASSOCIATED INFECTIONS

A. General principles

1. Illicit drug use causes >25,000 deaths per year. Infectious complications account for 60% to 80% of hospital admissions and 20% to 30% of deaths in injection drug users.
2. Infectious complications include skin and soft tissue infections including cellulitis and abscesses. Bacteremia may lead to complications including infectious endocarditis, vertebral osteomyelitis and/or epidural abscess, and

septic arthritis of joints such as the sacroiliac, sternoarticular, or symphysis pubis joints.

B. Etiology

1. Skin and soft tissue infection: Predominant flora in skin and soft tissue infections include *S. aureus, Streptococcus pyogenes, S. milleri, Fusobacterium* spp., *Veillonella* spp., *Prevotella* spp. Most specimens contain polymicrobial flora.
2. Infectious endocarditis: *S. aureus* is the leading pathogen, followed by viridans streptococci, *S. pyogenes, Enterococci, Pseudomonas aeruginosa, Serratia marcescens*, other gram-negative bacilli, and *Candida* spp.
3. Bone and joint infections: These are typically caused by staphylococci and streptococci. *Mycobacterium tuberculosis* should be considered particularly in cases of vertebral osteomyelitis.

C. Pathophysiology

1. Skin and soft tissue infection: The practice of "skin popping" is the strongest risk factor for abscess formation and results from repeated nonsterile injection.
2. Endocarditis: Infections of the right side of the heart often present with fever or pleuropulmonary symptoms and multiple patchy, pleural-based, infiltrates on chest radiography. Left-sided endocarditis is often complicated by arterial embolization to the renal and cerebral arteries and result in brain abscesses.
3. Bone and joint infections: These usually present with weeks or months of pain and may not be associated with high fever. Vertebral osteomyelitis may extend into the subdural or epidural spaces with complications of cord compression. Lumbosacral vertebral osteomyelitis may be associated with psoas abscess.

D. Diagnosis

1. Skin and soft tissue infections: Soft tissue infections may be indistinguishable from simple cellulitis in early stages. The presence of vesicles or bullae, an area of central necrosis within a larger area of erythema, subcutaneous crepitus, or gas in soft tissues on radiograph can suggest necrotizing fasciitis.
2. Endocarditis: Blood cultures are almost invariably positive. Negative blood cultures in a patient with the appropriate clinical syndrome should raise the possibility that the patient has recently taken antibiotics.
3. Bone and joint infections: Magnetic resonance imaging is the imaging study of choice when osteomyelitis is of concern. Biopsy or needle aspiration of the involved bone or joint is imperative to direct antimicrobial therapy.

E. Treatment

1. Skin and soft tissue infection: Abscesses should be incised and drained. If necrotizing fasciitis is suspected, immediate surgical management is necessary.
2. Endocarditis: Empiric therapy should be directed against *S. aureus*, streptococci, anaerobes, and aerobic gram-negative bacilli. Right-sided endocarditis generally has a favorable prognosis.
   a. Limited data suggest that patients without evidence of left-sided involvement, renal failure, extrapulmonary metastatic infection, or MRSA may be treated with a 2-week course or nafcillin or oxacillin, plus an aminoglycoside.
3. Bone and joint infections: Open drainage and debridement are often required in conjunction with a 4 to 6 weeks course of antibiotics.

F. Complications

1. Chronic infections associated with injection drug use are human immunodeficiency virus (HIV) and hepatitis C.
2. Sinopulmonary infections may result from snorting, sniffing, or smoking drugs such as cocaine and heroin.
   a. "Crack lung" is a syndrome of chest pain, hemoptysis, and diffuse pulmonary infiltrates.

b. Aspiration pneumonia may result from periods of unconsciousness.
c. Clinicians must maintain a high index of suspicion for tuberculosis in drug users, particularly if they are infected with HIV.

Suggested Reading

Intravenous Line-Associated Infections

Chaiyakunapruk N, Veenstra DL, Lipsky BA. Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: a meta-analysis. *Ann Intern Med* 2002;136(11):792.
This meta-analysis showed a reduced risk of catheter-associated bloodstream infections when chlorhexidine rather than povidone-iodine was used for insertion site disinfection.

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Review of the complications of central venous catheterization.

Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter-related infections. *Clin Infect Dis* 2001;32:1249.
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Pappas PG, Rex JH, Sobel JD, et al. Infectious Diseases Society of America. Guidelines for treatment of candidiasis. *Clin Infect Dis* 2004;38:161.
This summary includes guidelines for the treatment of Candida blood stream infection.

Raad I, Hanna H, Maki D. Intravascular catheter-related infections: advances in diagnosis, prevention, and management. *Lancet Infect Dis* 2007;7:645.
An excellent overview of catheter-related infections, with emphasis on diagnostic methods and prevention strategies.

Raad II, Hohn DC, Gilbreath BJ, et al. Prevention of central venous catheter-related infections by using maximal sterile barrier precautions during insertion. *Infect Control Hosp Epidemiol* 1994;15:231.
This study demonstrated that maximal sterile barrier precautions during the insertion of non-tunneled catheters reduce the risk of catheter infection.

Injection Drug Use Associated Infections

Chambers HF, Miller RT, Newman MD. Right-sided *Staphylococcus aureus* endocarditis in intravenous drug abusers: two-week combination therapy. *Ann Intern Med* 1988;109:619.
This is a small study that demonstrated 94% efficacy with 2 weeks of antibiotics.

Levine DP, Cran LR, Zervos MJ. Bacteremia in narcotic addicts at the Detroit Medical Center. II. Infectious endocarditis: a prospective comparative study. *Rev Infect Dis* 1986;8:374.
This is a classic two-part series on bacteremia in narcotic addicts.

Marantz PR, Linzer M, Feiner CJ, et al. Inability to predict diagnosis in febrile intravenous drug abusers. *Ann Intern Med* 1987;106:823.
This article is frequently quoted and shows a need for hospitalization of intravenous drug abusers.

O'Connor PG, Selwyn PA, Schottenfeld RS. Medical care for injection drug users with human immunodeficiency virus infection. *N Engl J Med* 1994;331:450.
This article reviews multiple aspects of caring for the injection drug user with HIV infection.

Salomon N, Perlman DC, Friedmann P, et al. Prevalence and risk factors for positive tuberculin skin tests among active drug users at a syringe exchange program. *Int J Tuberc Lung Dis* 2000;4:47.
This study demonstrates the high annual incidence of TB infection in the injection drug user population and the increased risk of TB infection with increasing duration of injection drug use.

URINARY TRACT INFECTIONS

Heidi L. Smith and Daniel H. Libraty

70

I. GENERAL PRINCIPLES

A. Urinary tract infection (UTI) is the most common nosocomial infection in the United States. The vast majority of nosocomial UTIs are associated with indwelling urinary catheters.

B. Complications of UTIs requiring intensive care unit (ICU) admission can include pyelonephritis, urosepsis with bacteremia, and suppurative infections.

C. Distinguishing between bacterial or fungal colonization and invasive infection can be difficult in the ICU setting.

II. ETIOLOGY

A. Gram-negative bacteria are most commonly isolated in UTI.

1. *Escherichia coli* is the most common single cause of UTI.
2. Other Enterobacteriaceae (*Klebsiella, Citrobacter, Enterobacter, Serratia*) are also frequently isolated.
3. *Pseudomonas, Providencia*, and *Proteus* sp. are among the most common catheter-associated organisms.

B. Gram-positive bacteria can sometimes cause UTI in ICU settings.

1. *Staphylococcus aureus* UTI can frequently be seen in the setting of bacteremia and should prompt a search for possible extrarenal sources.
2. Enterococci (including increasingly vancomycin-resistant enterococci) and nonaureus staphylococci can cause infection in the elderly and in patients with structural abnormalities, including indwelling catheters.

C. *Candida* spp. can cause UTI and may occasionally cause ascending infection and fungemia.

III. PATHOPHYSIOLOGY

A. Noncatheter-associated UTI

1. The most common source of UTI is contamination of the lower tract with enteric organisms normally residing in the colon and resultant ascending infection.
2. Pathogens which express virulence factors that aid adhesion (such as fimbrial adhesions in *E. coli*) or alter the urinary tract environment (such as urease production by *Proteus mirabilis*) are more frequent causes of UTI.
3. Patients with anatomic or functional abnormalities that interfere with the normal flow of urine and regular emptying of the bladder are at increased risk for UTI.

B. Catheter-associated UTI

1. Frequent movement in and out of the bladder with patient repositioning increases the risk of infection through the external surface of catheter.
2. Infection can also occur through the internal lumen by allowing a standing column of urine to accumulate, elevation of the collection bag, or disruption of the closed collecting system.
3. Trauma to mucosal surfaces increases susceptibility to infection.
4. Temporary obstruction of urine outflow due to kinking can aid establishment of pathogens.

IV. DIAGNOSIS

- **A.** Clinical presentation classically consists of dysuria and urinary frequency, sometimes in the setting of fever. However, elderly individuals may only have fever or mental status changes as presenting complaints.
- **B.** Urinalysis aids in the differentiation of microbial colonization versus infection.
  1. Urinary white blood cell count >5 cell per high-powered field is suggestive of infection, but not diagnostic. Chronically catheterized patients in particular may have chronic pyruia in the absence of infection.
  2. Leukocyte esterase is usually positive in the setting of infection.
- **C.** Urine culture establishes the identity of the pathogen and provides antimicrobial susceptibilities to allow narrowing of therapy.
  1. Quantitative culture with >100,000 colony forming units of a single species of bacteria is suggestive of infection, though in symptomatic individuals with pyuria, lower bacterial counts should not be disregarded.
  2. Urine should be collected from the urine port, not the drainage bag, to minimize contamination. In chronically catheterized patients, a sample from a newly placed catheter can be helpful.
  3. Sampling should include the nephrostomy tube, if present.
  4. Urine culture should be refrigerated if transport is to be delayed >1 hour.
- **D.** Blood cultures should be drawn before antibiotic administration in any patient with signs of developing sepsis or with suspicion of pyelonephritis.
- **E.** Imaging (renal ultrasound, computed tomography [CT] scan, magnetic resonance imaging [MRI]) should be performed if the patient fails to improve promptly.
  1. Obstruction of the urinary tract may prevent drainage of infected fluids.
     - **a.** Intrinsic obstruction may be due to stones or strictures.
     - **b.** Extrinsic obstruction may be due to external compression by intra-abdominal masses.
  2. Abscess formation may interfere with effective penetration of antibiotics.
     - **a.** Renal cortical abscesses can occur secondary to hematogenous seeding.
     - **b.** Renal corticomedullary abscesses can be caused by ascending processes.
     - **c.** Perinephric collections can result from rupture of infrarenal abscesses.
  3. Emphysematous pyelonephritis, which is most commonly seen in diabetic patients, may require surgical management.

V. TREATMENT

- **A.** Treatment of bacterial UTI
  1. Obtain blood and urine cultures before empiric antibiotics whenever possible to guide subsequent treatment.
  2. Renal dosing adjustments are required with most antibiotics, and renal dysfunction is present in many individuals requiring ICU level care.
  3. Empiric treatment of suspected gram-negative septic shock or urosepsis consists of a β-lactam (extended spectrum penicillins, third- or fourth-generation cephalosporins, carbapenem) in combination with an aminoglycoside or quinolone.
  4. Monotherapy consisting of a β-lactam, quinolone, or aminoglycoside can be considered for immunocompetent individuals coming from the community with less severe infections and no recent antibiotic use.
  5. If enterococci are suspected, ampicillin or vancomycin should be added. If the patient is known to be colonized with vancomycin-resistant enterococci, linezolid should be considered.
  6. Alternatives for coverage of gram-negative enterics in patients with penicillin or other β-lactam allergies include aztreonam, quinolones, and aminoglycosides.

7. Sensitivity data from a patient's past isolates as well as the antibiotic-resistance patterns for the institution should be used to guide choice of initial empiric therapy.
8. Antibiotic spectrum should be narrowed whenever possible once sensitivities are available.
9. Always remove catheter if no longer necessary. If a catheter is present at the time of infection, it should be changed. Continually reassess the need for catheterization if the device remains in place.
10. Most patients respond to promptly initiated and appropriate antibiotic therapy within 72 hours. Failure to respond to antibiotic therapy should prompt a search for continuing sources of urinary flow obstruction or suppurative complications.
11. Therapy may be switched from parenteral to oral antibiotics once the patient has defervesced. Failure to defervesce should prompt a search for complications of UTI.
12. Duration of antibiotic treatment for severe UTI requiring ICU admission is generally 2 weeks.

B. Treatment of UTI with *Candida* sp.
1. Candiduria is a common in finding in ICU patients, particularly those on antibacterial therapies.
2. Colony counts and pyuria are not as helpful in distinguishing colonization from infection.
   a. Candiduria in the setting of neutropenia or recent urinary tract manipulations generally requires treatment, even if asymptomatic.
   b. In other patients, treatment should be reserved for symptomatic infections.
3. Removal of urinary catheter if possible is the best treatment and may result in spontaneous clearance.
4. Fluconazole is the drug of choice for UTI secondary to *Candida* sp. as it achieves good urinary concentrations. Some *Candida* spp. can have varying levels of resistance, however.
   a. *Candida krusei* is uniformly resistant to fluconazole and requires the use of caspofungin, voriconazole, or amphotericin.
   b. *Candida glabrata* can exhibit intermediate resistance, which can be overcome with higher doses of fluconazole.
   c. Resistance can also be found in some *Candida albicans* isolates, particularly in the setting of prolonged fluconazole use.
5. In catheterized patients, candiduria frequently recurs even after therapy with fluconazole.
   a. In chronically catheterized patients, placement of new catheters or a period of intermittent catheterization may decrease colonization.
6. Amphotericin B bladder washes result in only transient clearing of candiduria; they are not generally recommended.

C. Prevention of catheter-associated UTI
1. Minimize the duration of catheterization.
2. Specialized catheters may decrease infection in cases where catheterization cannot be avoided, though studies are ongoing. These include siliconized and antibacterial-coated catheters.
3. Meatal care and/or topical antimicrobials have not been found to be effective.
4. Minimize trauma.
5. Avoid elevation of drainage bag and backflow through the catheter.

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TOXIN-MEDIATED ILLNESSES (TOXIC SHOCK SYNDROME, TETANUS, AND BOTULISM)

71

Iva Zivna and Richard T. Ellison

I. TOXIC SHOCK SYNDROME

A. General principles

1. Toxic shock syndrome (TSS) is a toxin-mediated multisystem disease characterized by the acute onset of high fever, hypotension, diffuse macular erythroderma, mucous membrane inflammation, severe myalgia, vomiting or diarrhea, and altered consciousness without focal neurologic signs.
   a. It arises as a result of infection or colonization with toxin-producing strains of *Staphylococcus aureus* (*S. aureus*) or *Streptococcus pyogenes* (*S. pyogenes*, group A streptococcus). In the initial epidemic, 50% of cases of staphylococcal TSS occurred in menstruating women using tampons.

B. Pathogenesis

1. Staphylococcal TSS is mediated by *S. aureus* exotoxins (e.g., TSS toxin-1) that act as superantigens capable of activating large number of T cells. Activated T cells then release massive amounts of cytokines that mediate the signs and symptoms of TSS. The pathogenesis of streptococcal TSS appears comparable although the precise toxins involved have not been as clearly defined.

C. Diagnosis

1. Five clinical features are needed for the diagnosis of TSS:
   a. Fever
   b. Mucositis (often with rash)
   c. Hypotension
   d. Desquamation over the palms and soles, typically 1 to 2 weeks after the onset of illness
   e. Evidence of multiorgan failure
2. Additionally there should be evidence of *S. aureus* or *S. pyogenes* by Gram stain or culture from a wound, mucosal surface, or normally sterile body site. Blood cultures are usually negative in *S. aureus* TSS but are positive in streptococcal TSS.

D. Treatment

1. Correct hypovolemic shock rapidly.
2. Surgically treat infected areas, draining abscesses and removing foreign bodies.
3. Empiric antibiotic therapy for presumed staphylococcal TSS must provide coverage for methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin is currently preferred. Alternatives include linezolid, daptomycin, or trimethoprim–sulfamethoxazole (although this last agent is not reliably active for *S. pyogenes*). All patients with suspected TSS should receive clindamycin to suppress bacterial toxin production.
4. Intravenous immunoglobulin (IVIG) can be considered for severe cases.

II. BOTULISM

A. General principles

1. Botulism is a rare but potentially life-threatening neuroparalytic syndrome resulting from the action of a neurotoxin produced by *Clostridium botulinum*, an anaerobic, spore-forming, gram-positive bacillus.

2. The syndrome of botulism is characterized by acute onset of bilateral cranial neuropathies associated with symmetric descending weakness.
3. It occurs in five forms based on the route of toxin exposure:
   a. Foodborne botulism
   b. Wound botulism
   c. Infant botulism
   d. Adult enteric infectious botulism
   e. Inhalational botulism (that would occur if aerosolized toxin was released in an act of bioterrorism)

B. Pathogenesis

1. Regardless of the route of entry into the body, *C. botulinum* toxin (types A, B, E, and rarely F and G) disperses widely through the vascular system and acts at the neuromuscular junctions, where it inhibits release of acetylcholine at cholinergic synapses.

C. Diagnosis

1. Key features of the botulism include:
   a. Absence of fever
   b. Symmetric neurologic (cranial nerve and motor) deficits
   c. Unchanging level of consciousness
   d. Normal or slow heart rate and normal blood pressure
   e. No sensory deficits with exception of blurred vision
2. The diagnosis can be confirmed by detection of botulinum toxin in the patient's serum, feces, or food; culture; or by repetitive nerve stimulation.
   a. Routine laboratory studies are nonspecific.

D. Treatment

1. Proceed with elective intubation when:
   a. Oropharyngeal paresis is present because of risk of aspiration
   b. Falling vital capacity over 4 to 6 hours
   c. Clinical signs of respiratory fatigue at a vital capacity of 15 mL/kg
   d. Vital capacity falls below 1 L
2. Administer trivalent antitoxin (A, B, E) to neutralize any circulating toxin in the serum.
   a. Contact the Centers for Disease Control and Prevention (CDC) at 404-639-2206 or 770-488-7100 to obtain antitoxin.
3. In foodborne botulism, remove the unabsorbed toxin from the gastrointestinal tract using a nasogastric tube for lavage and a cathartic or a tap water enema.
4. In wound botulism, treat with debridement and intravenous penicillin G as well as trivalent antitoxin. Penicillin allergic patients should receive metronidazole.

III. TETANUS

A. General principles

1. Tetanus is a disease of the nervous system characterized by persistent tonic spasms with severe brief exacerbations. The disease results from the action of tetanospasmin, a potent neurotoxin produced by *Clostridium tetani*, a large, spore-forming, anaerobic gram-positive bacillus.
2. The spores of *C. tetani* are found worldwide in soil.

B. Pathogenesis

1. After a puncture wound or laceration, spores inoculated deep into tissue convert to vegetative forms that proliferate under anaerobic conditions. The growing bacteria release tetanospasmin that interferes with neurotransmitter release at the motor end plates of skeletal muscles, the spinal cord, brain, and within the sympathetic nervous system.

C. Diagnosis

1. The diagnosis is primarily based on clinical manifestations. There are three principal forms:
   a. Localized tetanus—with muscle spasms limited to the site of injury
   b. Cephalic tetanus—with paralysis of the cranial nerves (trismus or risus sardonicus)
   c. Generalized form of the disease
2. Serologic testing is of no value as disease is produced by toxin levels that are too low to induce an antibody response.
3. Routine laboratory studies are nonspecific.

D. Treatment

1. Assess airway and ventilation.
2. Control the spasms and decrease muscular rigidity with benzodiazepines; add paralytic agents if necessary.
3. Administer human tetanus immunoglobulin.
4. At a different site, administer tetanus toxoid to induce protective antibodies.
5. Begin antibiotic active against anaerobic bacteria (e.g., metronidazole or clindamycin).
6. Surgically debride any wounds.
7. Use short-acting drugs to manage autonomic dysfunction.

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72 INFECTIONS IN IMMUNOCOMPROMISED HOSTS

Ajanta Sen and William L. Marshall

I. THE FEBRILE, NEUTROPENIC PATIENT

A. General principles

1. Cancer chemotherapy and hematopoietic stem cell transplantation (HSCT) result in neutropenias that can predispose to serious infections.

B. Etiology

1. Cancer chemotherapy can be very cytotoxic to the gastrointestinal (GI) tract and bone marrow, causing mucositis and neutropenia <500 white blood cell (WBC) per mm^3 leading to infections that can be life-threatening if not treated promptly with broad spectrum anti-infective agents.

C. Pathophysiology

1. Malignancies and deficiencies of neutrophils, T-lymphocytes, and B-lymphocytes increase the risk of infections from fungal, intracellular, and encapsulated organisms, respectively.
2. Mucositis following chemotherapy results in the translocation of bacteria and fungi from the GI tract, sometimes resulting in detectable infection but more often causing fever (T>38.0° C) without positive cultures in neutropenic patients.
3. Bacteremia and positive blood cultures are often the result of catheter-associated skin flora, enteric bacteria, or *Pseudomonas aeruginosa*.
4. Prolonged neutropenia, acute leukemia, broad spectrum antibiotics, corticosteroids, and total parenteral nutrition predispose patients to invasive fungal infections.

D. Diagnosis

1. Physical findings may be obscured by diminished signs of inflammation, including fever. A thorough history must be taken and a physical examination must be performed initially and repeated daily, with special attention to the oropharynx, sinuses, optic fundi, anorectal region, lungs, skin, recent surgical wounds, and vascular catheter sites.
2. Initial diagnostic tests should include the following:
   a. Cultures of blood and urine
   b. Chest radiograph or computed tomography (CT) scan
   c. Sputum culture in patients with evidence of pulmonary disease
   d. Stool culture and *Clostridium difficile* toxin assay in patients with diarrhea
   e. Semiquantitative culture of central venous catheters removed due to fever
   f. Swab, aspiration, or biopsy of suspicious skin or mucous membrane lesions for smears, cultures (bacterial, fungal, and viral), and pathologic examination
   g. Studies of liver, biliary tract, pancreas, and renal function if indicated
3. Diagnosis may require histologic examination and special culture techniques of specimens obtained by tissue biopsy, bronchoalveolar lavage, GI endoscopy, surgery, or other invasive procedures.

4. Patients with fever persisting >3 days need to be thoroughly reevaluated.
   a. Particularly consider chest and abdomen/pelvic CT
   b. Consider serum galactomannan and 1,3-β–D-glucan assays for suspicion of invasive fungal disease

E. Treatment

1. Because of the high risk of life-threatening infections, all febrile patients with an absolute neutrophil count (ANC) of $<500/mm^3$ or a falling ANC of 500 to $1,000/mm^3$ should be treated with high doses of intravenous broad spectrum antibiotics promptly after appropriate culture specimens are obtained.
2. Recommended empiric antibiotic regimens include:
   a. Ceftazidime 2 g IV every 8 hours plus vancomycin 1 g IV every 12 hours (discontinue vancomycin in the absence of a documented pathogen requiring this agent, *or*
   b. Piperacillin/tazobactam 3.375 g IV every 4 hours (suspected oral, dental, or other polymicrobial or anaerobic infection) plus vancomycin 1 g IV every 12 hours (discontinue vancomycin in the absence of a documented pathogen requiring this agent *or*
   c. Aztreonam 2 g every 6 hours plus vancomycin 1 g IV every 12 hours (severe penicillin allergy) *or*
   d. Imipenem 500 mg IV every 6 hours (suspected extended spectrum β-lactamase–producing organism) plus vancomycin 1 g IV every 12 hours (discontinue vancomycin in the absence of a documented pathogen requiring this agent).
3. Other adjunctive therapies
   a. Removal of indwelling central venous catheters should be considered in cases of:
      i. Bacteremia due to *Staphylococcus aureus*, vancomycin-resistant enterococci, *Pseudomonas* species, *Candida* species, *Corynebacterium jeikeium*, *Bacillus* species, and *Fusarium* species
      ii. Evidence of tunnel or exit site infection
      iii. The presence of septic thrombophlebitis
      iv. Persistent or recurrent bacteremia
4. Empiric therapy for *Aspergillus* species and other filamentous fungi should be considered after 4 to 7 days of fever using either:
   a. Voriconazole 4 mg/kg PO or IV q12 h, *or*
   b. Amphotericin B; dose depends upon the type of liposomal amphotericin used
5. Empiric antibiotics may be discontinued when fever and neutropenia have resolved.

F. Complications

1. Fever and pulmonary disease
   a. The differential diagnosis includes not only infection (bacteria, fungi, protozoa, viruses, and helminths) but also acute respiratory distress syndrome, bronchiolitis obliterans with organizing pneumonia, malignancy, pulmonary hemorrhage, radiation injury, drug toxicity, and many others.
      i. Focal or multifocal infiltrates suggest bacterial or invasive fungal pneumonia.
      ii. Diffuse interstitial disease is more characteristic of viruses, *Pseudomonas jiroveci*, or a noninfectious process.
      iii. Cavitary and nodular disease can be associated with bacteria (e.g., *P. aeruginosa*, *S. aureus*, anaerobes), *Nocardia* species, mycobacteria, *Legionella*, endemic or invasive fungi, and noninfectious processes.

II. THE ASPLENIC PATIENT

A. General principles

1. Sepsis is a serious risk in asplenic patients. Postsplenectomy sepsis (PSS) can present as a fulminant disease with a mortality rate of 50% to 70%.
2. Prompt consideration of PSS may be critical to survival.

B. Etiology

1. Risk of sepsis increases following splenectomy or in patients who are functionally asplenic due to congenital asplenia, sickle cell disease and other hemoglobinopathies, celiac disease, non–Hodgkin's lymphoma, bone marrow transplantation, and so on.

C. Pathophysiology

1. The spleen has many immunologic functions including the efficient clearance of encapsulated bacteria coated by opsonizing antibodies.

D. Diagnosis

1. Assessment of splenic function
   a. A focused history and physical examination should provide clues to the patient's splenic function, for example, the presence of a surgical scar or a history of recurrent infections with encapsulated bacteria.
   b. Additionally, laboratory clues such as Howell-Jolly bodies (nuclear remnants) and "pocked" red blood cells (RBCs) are indicators of splenic dysfunction.
   c. A high level of bacteremia with an organism typical for PSS also suggests the diagnosis.
2. Typical presentation
   a. PSS has a short prodrome with fever, chills, pharyngitis, myalgias, nausea, vomiting, or diarrhea.
   b. PSS rapidly progresses to hypotension, disseminated intravascular coagulation (DIC), altered sensorium, seizures, coma, and cardiovascular compromise.
   c. Tissue damage can be complicated by the development of purpura fulminans, in which extremity gangrene occurs, possibly necessitating amputations.
3. Other laboratory findings
   a. WBC count can be either markedly elevated or depressed with a predominant left shift.
   b. Occasionally, intracellular or extracellular organisms can be visualized directly on blood smear or on Gram or Wright stain of the white cell buffy coat.
   c. Elevated creatinine and aminotransferases, thrombocytopenia, DIC, and other laboratory evidence of multiorgan dysfunction may be present.
4. Microbiology laboratory findings
   a. *Streptococcus pneumoniae* is the most important organism implicated in PSS and the most common causative organism of PSS across all age-groups, but increases with age. It comprises roughly 60% of all PSS cases.
   b. Type b *Haemophilus influenzae* (Hib) is the second most common organism related to PSS. Most cases classically occurred in children before the advent of the conjugated Hib vaccine that decreased the incidence of invasive Hib disease dramatically so that cases now occur in older, nonvaccinated patients.
   c. *Neisseria meningitidis*, or meningococcus, is often cited as the third most common cause of PSS, but this may not be the case, as meningococcemia is neither more frequent nor more severe in asplenic patients.
   d. *Capnocytophaga canimorphus*, transmitted from dog bites, is another cause of PSS.

e. *Salmonella* species, especially in sickle cell patients, other β and α hemolytic streptococci, staphylococci, *Bacteroides, Escherichia coli* and other Enterobacteriaceae have also been anecdotally linked to PSS. Of note, *Streptococcus suis* has caused PSS in patients after swine exposure.
f. *Bordetella holmesii* has recently been described as a cause of PSS as well. There is also some suggestion that human *Bartonella* infection may be more prominent in asplenic patients.
g. Splenectomized patients with babesiosis have higher grade parasitemias, severe hemolysis, and overall more cases of morbidity and mortalitity when compared to nonsplenectomized patients.
h. Human granulocytic ehrlichiosis has been reported to be recurrent, prolonged and/or more severe in asplenic patients.

E. Treatment

1. Cultures should be obtained as indicated and the patient should receive aggressive fluid resuscitation and hemodynamic support.
2. Antibiotics should not be delayed for culturing more than several minutes in PSS as their timely administration can be life saving.
3. If a patient suspected to have PSS is first evaluated in a physician's office or in the field, an antimicrobial such as ceftriaxone should be administered parenterally before hospital transfer (whether or not blood cultures can be obtained).
4. Vancomycin + third- or fourth-generation cephalosporin are reasonable options. For patients with documented allergy to cephalosporins or penicillins, a quinolone, such as levofloxacin 750 mg PO q24 h can be substituted.
5. For treatment of babesiosis, severe infections warrant both clindamycin 900 mg IV q8 h + quinine 650 mg PO q8 h 7 days and consider exchange transfusion.

F. Complications (prevention of)

1. Asplenic patients should be educated that they carry a risk for life-threatening infection and that measures to prevent PSS are crucial.
   a. Appropriate administration of pneumococcal, meningococcal, Hib, and yearly influenza vaccines is necessary.
   b. Additionally, patients should be instructed to self-medicate with oral antibiotics in the presence of evolving febrile illness.
      i. Potential oral antibiotic empiric therapies of PSS include high-dose amoxicillin-clavulanate, cefuroxime axetil, or extended spectrum quinolones.

III. INFECTIONS IN PATIENTS RECEIVING ANTI-TUMOR NECROSIS FACTOR (TNF) THERAPY

A. General principles

1. The use of TNF-α inhibitors is growing in multiple inflammatory disorders.
   a. Examples include rheumatoid arthritis, Crohn's disease, psoriasis, and seronegative spondyloarthropathies.

B. Etiology

1. There are currently three anti-TNF agents available for use in clinical practice:
   a. Two monoclonal antibodies (infliximab and adalimumab)
   b. One soluble receptor (etanercept)

C. Pathophysiology

1. TNF-α plays an important role in host immunity against many intracellular organisms and is involved in granuloma formation.
   a. Inhibition of TNF-α can therefore potentially increase the risk of serious bacterial and opportunistic infections, as has been observed in clinical trials and postmarketing reports.

D. Diagnosis

1. The risk for four general classes of infections increases with anti-TNF therapy.
   - **a.** Tuberculosis (TB)
     - **i.** More than sevenfold increased incidence of TB in patients treated with infliximab.
     - **ii.** Atypical presentation of TB with extrapulmonary/disseminated TB is more common.
     - **iii.** TB with etanercept has been reported less frequently.
     - **iv.** All patients in the intensive care unit (ICU) on anti-TNF therapy with pulmonary infiltrates and/or clinical signs of extrapulmonary TB should undergo thorough investigation including bronchoscopy, endoscopy, biopsies, and so on with acid-fast bacillus (AFB) staining and culture
   - **b.** Histoplasmosis and other endemic mycoses
     - **i.** Patients commonly present with fever, malaise, cough, dyspnea, and interstitial infiltrates on chest x-ray (CXR).
     - **ii.** Appropriate diagnostic studies include bronchoalveolar lavage, lung biopsy, and urine histoplasma antigen.
   - **c.** Bacterial infections
     - **i.** Pneumonia, cellulitis, necrotizing fasciitis, abscesses, urosepsis, septic arthritis, and meningitis have been reported.
     - **ii.** Organisms include *S. pneumoniae, S. aureus, E.coli, Listeria monocytogenes, Salmonella enterica* and *Proteus mirabilis.*
     - **iii.** *L. monocytogenes*—infections were noted in several patients on anti-TNF therapy, including patients with meningitis who expired. Empiric therapy with ampicillin 2 gm IV q4 h should be added to patients with meningitis/encephalitis on anti-TNF therapy.
   - **d.** Opportunistic infections
2. Reported associations include:
   - **a.** Herpes zoster and cytomegalovirus (CMV) infections
   - **b.** Nocardiosis
   - **c.** Toxoplasmosis
   - **d.** Local and systemic candidiasis
   - **e.** Cryptococcal infections
   - **f.** Aspergillosis and disseminated sporotrichosis

E. Treatment

1. Active TB
   - **a.** See Chapter 74. Stop anti-TNF therapy if possible.
   - **b.** All patients on anti-TNF therapy should have undergone tuberculin skin testing (TST) and CXR before initiation of therapy.
   - **c.** Liver function tests should be followed closely while the patient is on anti-TB therapy.
2. Histoplasmosis
   - **a.** Severe disease—liposomal amphotericin B 3 mg/kg initially, then itraconazole 200 mg bid
   - **b.** Mild disease—use itraconazole 200 mg every day or bid
3. **Bacterial infection/sepsis**
   - **a.** Empiric therapy for sepsis or bacterial infection—see Chapter 123.
   - **b.** If meningitis is suspected, rocephin (Ceftriaxone) 2 gm IV q12 h + vancomycin +ampicillin 2 gm IV q4 h should be administered.
   - **c.** As a general rule, withhold anti-TNF therapy if infection develops while on therapy, until the infection is controlled and treated.

IV. INFECTIONS IN PATIENTS UNDERGOING T-CELL IMMUNOSUPPRESSION

A. General principles

1. T-cell immunosuppression has permitted many lives to be saved by facilitating antigen-mismatched sold organs and allogeneic bone marrow transplants, but at the cost of a variety of opportunistic infections.

B. Etiology

1. Agents affecting T-lymphocyte activity, such as fludarabine and anti–T-lymphocyte antibodies, are among the most severe suppressants of cell-mediated immunity.
2. Calcineurin inhibitors, steroids, and mycophenolic acid all significantly inhibit T-cell function in organ recipients.
3. Prevention and treatment of graft-versus-host disease (GVHD) significantly raises the level of T-cell–associated immunodeficiency.

C. Pathophysiology

1. Organisms identified in potential organ/marrow donors that may be transmitted to and cause infection in recipients include herpes viruses, hepatitis viruses, *Toxoplasma gondii*, and *Histoplasma capsulatum*.
2. Similarly, pathogens previously well controlled by the recipient's immune system may reactivate, such as herpesviruses CMV, Epstein-Barr virus (EBV), and human herpes virus-6 (HHV-6) and *T. gondii*.
3. Abdominal surgery, therapy with broad spectrum antibiotics or steroids, and total parenteral nutrition predispose patients to fungal infections.

D. Diagnosis

1. Infections with specific pathogens are most common during predictable time periods following hematopoietic or solid organ transplantation.
   - **a.** Typical infections within the first month are similar to those of other hospitalized medical and surgical patients.
     - **i.** Gram-positive and gram-negative bacteria
     - **ii.** Candida infections
     - **iii.** Reactivation of herpes simplex virus can also occur during this period
   - **b.** Opportunistic infections typically associated with immunosuppression occur most frequently during the second through the sixth months.
     - **i.** These pathogens include herpesviruses, *P. jiroveci, T. gondii, Mycobacterium tuberculosis*, fungi such as *Cryptococcus neoformans, Aspergillus*, endemic mycoses (*Coccidioides immitis* and *H. capsulatum*), and environmental pathogens such as *Nocardia, Listeria*, and *Legionella*.
   - **c.** Bronchoscopy with bronchoalveolar lavage or lung biopsy is indicated in patients with a nondiagnostic evaluation for pulmonary disease or lack of clinical improvement on initial empiric therapy.
   - **d.** CT scan of the chest, abdomen, and pelvis may be considered in addition to routine cultures described in earlier sections.
   - **e.** Beyond 6 months
     - **i.** Infections common in the general population can also affect immunocompromised patients, including respiratory viruses, community-acquired pneumonia, and urinary tract infections.
     - **ii.** Adenoviruses, polyoma viruses (BK and JC viruses), and reactivation of varicella-zoster virus (VZV) can occur during this late period.
     - **iii.** Patients with chronic infections such as CMV and hepatitis viruses, allograft rejection requiring increased immunosuppression, and those who have completed antimicrobial prophylactic drug regimens may develop infections that are more common during earlier periods.

E. Treatment

1. Prophylaxis
   a. Pneumocystis and toxoplasmosis
      i. Trimethoprim (TMP)-sulfa one single strength (80 mg TMP component) every day. If allergic—dapsone plus TMP or atovaquone 1,500 mg PO every day.
   b. Herpes viruses,
      i. Preemptive therapy protocol: definite plasma viremia, >1,000 CMV copies/mL should trigger initiation of valganciclovir 900 mg PO bid or IV therapy 5 mg/kg q12 h adjusted for renal function for at least 2 weeks beyond the resolution of plasma viremia, or
      ii. HSV/VZV (CMV)-acyclovir 800 mg tid × 1 year (discontinue when on valganciclovir)
2. Patients with fever and pulmonary infiltrates should be started promptly on antibiotics targeting the most likely pathogen(s):
   a. Include TMP-sulfamethoxazole 5 mg/kg q8 h if *P. jiroveci* is suspected
   b. Include liposomal amphotericin B 3 mg/kg or voriconazole 4 mg/kg IV/PO for suspected fungal disease.

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HUMAN IMMUNODEFICIENCY VIRUS IN THE INTENSIVE CARE UNIT

73

Aruna Sree and Raul Davaro

I. GENERAL PRINCIPLES

A. In the era of combined antiretroviral therapy (ART) the spectrum of patients with human immunodeficiency virus (HIV) infection admitted to the intensive care unit (ICU) falls into three general categories.

1. Acute immunodeficiency syndrome (AIDS)-related opportunistic infections

2. Complications related to ART

3. Medical problems unrelated to HIV infection

B. Throughout the AIDS epidemic, respiratory failure has been the most common cause of ICU admission.

1. Bacterial pneumonias and acute respiratory distress syndrome (ARDS) are the most common cause of respiratory failure.

2. *Pneumocystis jirovecii* pneumonia (PCP) incidence has been declining since the introduction of ART.

3. Tuberculosis (TB), fungal infection and noninfectious HIV-associated pulmonary disorders are other common complications in patients with HIV infection admitted to the ICU.

II. PNEUMOCYSTIS PNEUMONIA (PCP)

A. Etiology

1. Caused by soil-based fungus, *P. jirovecii*

2. Distribution: worldwide

B. Pathogenesis

1. PCP almost always occurs in patients with absolute CD4 counts <200.

C. Diagnosis

1. Patients with PCP complain of progressive dyspnea, nonproductive cough and low grade fever.

2. The physical examination often reveals tachypnea, crackles, and trending hypoxemia. Although unusual, PCP can sometimes rapidly lead to acute respiratory failure.

3. The classic radiologic pattern in patients with PCP is diffuse alveolar or interstitial pulmonary infiltrates; however, almost every conceivable radiographic pattern has been reported.

4. Definitive diagnosis is by identification of organisms in pulmonary secretions or lung tissue. Sputum induction has a sensitivity of 55% to 94%. If sputum is negative, then bronchoscopy with bronchoalveolar lavage (BAL) should be performed. BAL has a sensitivity of 89% to 98%.

D. Treatment (Table 73-1)

1. Trimethoprim–sulfamethoxazole (TMP–SMX) is the treatment of choice for moderate to severe PCP. TMP–SMX is dosed at 15 to 20 mg/kg/day of TMP in three or four divided doses for 21 days.

a. In patients with life-threatening reactions to TMP–SMX (Table 73-1), pentamidine isethionate is the preferred alternative therapy. Pentamidine is administered as a single daily dose of 4 mg/kg intravenously.

b. In patients with arterial oxygen pressure <70 mm Hg, or A-a gradient >35 mm, adjunctive therapy with steroids reduces mortality—give

TABLE 73-1 Treatment of Moderate to Severe Pneumocystis Pneumonia

Drug	Dose	Comments
Trimethoprim (TMP)–sulfamethoxazole (SMX)	15–20 mg/kg TMP in three or four divided doses for 21 d	Drug of choice; toxicity includes rash, fever, cytopenias, hepatitis, pancreatitis, nephritis, hyperkalemia, metabolic acidosis, central nervous system reaction, toxic epidermal necrolysis, Stevens–Johnson syndrome, and anaphylaxis; adverse reactions occur in up to 80% of human immunodeficiency virus (HIV)-infected patients necessitating alternative therapy in up to 50%
Pentamidine isethionate	3–4 mg/kg IV daily	Alternative therapy in patients with life-threatening reactions to TMP–SMX; adverse reactions to pentamidine include hypotension, cardiac arrhythmias, pancreatitis, hypoglycemia, hyperglycemia, hyperkalemia, hypomagnesemia, hypocalcemia, neutropenia, hepatitis, and bronchospasm
Prednisone	40 mg PO bid on days 1–5, 40 mg PO daily on days 6–10 and 20 mg PO daily on days 11–20	Adjunctive therapy in patients with arterial oxygen pressure ≤70 mm Hg or A-a gradient >35 mm, with steroids reduces the mortality

prednisone 40 mg PO bid on days 1 to 5, 40 mg PO daily on days 6 to 10 and 20 mg PO daily on days 11 to 20.

III. TB

A. General principles

1. HIV increases the risk of developing active TB.
2. Drug-resistant TB is more common in patients with HIV.

B. Etiology

1. Caused by infection with *Mycobacterium tuberculosis*

C. Pathogenesis

1. In patients with HIV infection, TB can occur as a reactivation of latent disease or from newly acquired infection.
2. HIV-positive patients with latent TB infection have a 7% to 10% annual risk for developing active disease.

D. Diagnosis

1. Clinical features
   a. Patients with high CD4 cell counts (>400/mm^3) tend to have similar presentations to those without HIV (upper lobe disease, low risk of extra pulmonary dissemination).
   b. Patients with AIDS tend to have disseminated disease with prominent constitutional symptoms.

- **c.** Sometimes patients may present with ARDS or sepsis syndrome with multisystem organ failure.
- **d.** Immune reconstitution syndrome (IRIS) or paradoxical reactions may occur within 2 to 3 weeks of starting anti-TB treatment in HIV patients.

2. Diagnostic procedures
- **a.** Sputum and/or BAL fluid for acid fast bacilii (AFB) smears and cultures
- **b.** Isolator blood cultures and tissue biopsy of the involved site especially in disseminated disease

E. Treatment

1. Isoniazid/rifampin/pyrazinamide/ethambutol. Duration of therapy 6 to 12 months.

2. Drug-resistant TB requires treatment for a period of 18 to 24 months.

3. See Chapter 74 for additional details regarding treatment of active TB.

IV. CRYPTOCOCCOSIS

A. General principles

1. Most common central nervous system (CNS) fungal infection in patients with AIDS

B. Etiology

1. *Cryptococcus neoformans* causes most cases worldwide.

C. Pathogenesis

1. Cryptococcosis is the result of newly acquired primary infection rather than reactivation of previously acquired disease.

D. Diagnosis

1. Presents as subacute meningitis or meningoencephalitis with fever, malaise and headaches. Most patients are symptomatic for 2 to 4 weeks before seeking medical care.
- **a.** Less common manifestations include lethargy, altered mental status, personality changes, memory loss, or seizures.

2. Classic symptoms and signs of meningitis such as neck stiffness and photophobia are usually absent.

3. Elevated intracranial pressure (opening pressure >200 mm H_2O) is present in >50% of the patients.

4. Poor prognostic factors are change in mental status on presentation, high cerebrospinal fluid (CSF) cryptococcal antigen titers, low CSF leukocyte count, positive blood culture, or hyponatremia.

5. CSF shows lymphocytic meningitis with a white blood cell (WBC) count of 100 to 200 cells/mm^3, protein is mildly elevated, and glucose is low.

6. Diagnosis is by identification of C. *neoformans* in the CSF by:
- **a.** Staining and culture
- **b.** Cryptococcal antigen in CSF and/or serum

E. Treatment

1. Induction therapy with amphotericin B (0.7 to 1 mg/kg/day) once daily with or without flucytosine (100 mg/kg/day) in four divided doses for 2 weeks
- **a.** Consolidation therapy with fluconazole (400 mg/day) for another 8 weeks or until CSF cultures are sterile

2. Management of intracranial pressure
- **a.** In HIV-infected patients with cryptococcal meningitis, elevated intracranial pressure occurs in >50% of cases and can be reduced through percutaneous lumbar drainage, or removing enough CSF to reduce the opening pressure by 50%.

V. TOXOPLASMIC ENCEPHALITIS (TE)

A. General principles

1. TE is the most common cause of focal neurologic disease in patients with HIV infection.

a. Multifocal lesions are more common than single lesions.

b. Typically occurs when CD4 count is <100.

B. Etiology/pathogenesis

1. *Toxoplasma gondii* is an obligate intracellular parasite whose definitive host is the cat.

C. Diagnosis

1. Clinical features include headaches, confusion, fever, lethargy, focal neurologic signs, and seizures.

2. Patients with TE showed multiple contrast enhancing intracranial mass lesions on computed tomography (CT) scan of the brain or magnetic resonance imaging (MRI). MRI with intravenous gadolinium has superior sensitivity than CT scan.

3. Definitive diagnosis is by demonstration of tachyzoites in biopsy specimen of the brain; biopsy is done only when there is no clinical and radiologic improvement after 2 weeks of presumptive treatment.

4. The absence of antibodies against toxoplasma has a negative predictive value close to 100%.

D. Treatment

1. Pyrimethamine (200 mg oral loading dose followed by 50 to 100 mg orally per day) plus sulfadiazine (1 to 1.5 g orally every 6 hours) for 2 to 3 weeks.

a. In patients intolerant to sulfadiazine, clindamycin (450 to 600 mg orally or 600 to 1,200 mg IV four times a day) can be used with pyrimethamine.

b. Patients must be properly hydrated while using sulfadiazine to avoid crystalluria.

c. Folinic acid at a dose of 10 mg PO daily must be used along with pyrimethamine to avoid bone marrow toxicity.

d. In patients intolerant to the above regimens, atovaquone can be used as salvage therapy (1,500 mg oral twice daily or 750 mg orally four times a day) either with pyrimethamine or sulfadiazine.

e. In patients where oral regimens cannot be given TMP–SMX at the dose of 6.6 mg/kg/IV/daily of TMP can be used.

2. Adjunctive therapy:

a. Corticosteroids to reduce the cerebral edema, sodium valproate for seizures.

3. All patients receiving empiric therapy should have follow-up imaging studies after 2 weeks of treatment. Patients with AIDS and TE who ultimately respond to therapy should exhibit a favorable clinical response within 14 to 21 days and a radiologic response in all lesions within 3 weeks.

VI. IRIS

A. General principles

1. IRIS is a paradoxical worsening of underlying opportunistic infections in HIV patients initiated on ART.

B. Pathogenesis

1. Restoration of CD4 and CD8 T lymphocytes and cytokine release caused by initiation of ART.

2. IRIS is more common when treatment-naïve HIV patients are started on ART near the time of diagnosis with an opportunistic infection, and experience a rapid fall in HIV viral load.

C. Diagnosis

1. Soon after ART is begun, the patient experiences clinical or radiologic deterioration caused by an exacerbation of preexisting opportunistic infection or with appearance of new lesions in a patient responding to treatment of opportunistic infections.
   a. Most common organisms include *Mycobacterium avium complex*, *M. tuberculosis*, and *C. neoformans*.
   b. Patients with active TB treated with antituberculous therapy and ART experienced a higher incidence of paradoxical reactions (fever, worsening or emergence of lymphadenopathy, pulmonary infiltrates and pleural effusions) than HIV-infected patients with TB not treated with ART.

D. Treatment

1. In most patients with IRIS, opportunistic infections improve with continuation of ART.
2. In cases where IRIS is life threatening, ART should be temporarily discontinued until the underlying infection is treated.
   a. In antiretroviral-naïve patients with active TB, it is recommended that ART be delayed until 2 months after initiation of antituberculous treatment if possible.
3. In severe cases, adjunctive therapy with steroids may be used.

VII. LACTIC ACIDOSIS

A. General principles

1. Lactic acidosis is a life-threatening complication caused by mitochondrial dysfunction that occurs in HIV-infected patients receiving nucleoside reverse transcriptase inhibitors (NRTIs)-based therapy.

B. Pathogenesis

1. Lactic acidosis is caused by mitochondrial dysfunction through inhibition of DNA polymerase gamma.
2. The combination of NRTIs with the highest risk of lactic acidosis is stavudine plus didanosine.
3. There are some reports of lactic acidosis associated with (Non-nucleoside reverse transcriptase inhibitor) NNRTIs and protease inhibitors (PIs).

C. Diagnosis

1. Patients with NRTI-induced lactic acidosis present with fatigue, weakness, weight loss, nausea, emesis, abdominal pain, exercise-induced dyspnea, and unexplained tachycardia and tachypnea.
   a. There may be associated polyneuropathy, pancreatitis, myositis, lipoatrophy, and cardiomyopathy.
   b. Laboratory abnormalities include elevated lactate levels, pancreatic enzymes, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), and prolonged prothrombin time.

D. Treatment

1. Immediate discontinuation of NRTIs/offending agent(s)
2. Bicarbonate therapy and hemodialysis in severe acidosis

VIII. HISTOPLASMOSIS

A. General principles

1. Primary disease is limited to endemic areas. Reactivation may occur many years after travel or residence in endemic areas.

B. Etiology

1. *Histoplasma capsulatum*—a dimorphic fungus

C. Pathogenesis
1. The $CD4^+$ T-cell count generally dictates the form of histoplasmosis seen in patients with HIV infection.
a. Localized forms of disease are generally seen in those with a $CD4^+$ T-cell count >200 cells/mm^3.
b. Extrapulmonary disseminated forms of disease are generally seen in those with a $CD4^+$ T-cell count <100 cells/mm^3.

D. Diagnosis
1. Clinical syndromes:
a. Pulmonary histoplasmosis—forms include localized infiltrates, diffuse infiltrates, and chronic cavitary disease.
b. Acute progressive disseminated histoplasmosis: fever, malaise, cough, dyspnea, diarrhea, mucosal ulcers, cutaneous lesions, lymphadenopathy, hepatosplenomegaly, and hematologic abnormalities.
c. Subacute progressive disseminated histoplasmosis—in addition to the above features gastrointestinal (GI) manifestations in the form of ulcerations of the intestines, endocarditis and infection of other vascular structures, CNS, and adrenal gland involvement can occur.
2. Radiographic features include diffuse interstitial or reticulonodular infiltrates and hilar or mediastinal adenopathy.
3. Microbiologic diagnosis by:
a. Blood cultures (isolator tube), BAL, or tissue cultures
b. Detection of histoplasma antigen in urine or blood

E. Treatment
1. Severe disseminated disease: amphotericin B 0.7 mg/kg IV every 24 hours or liposomal amphotericin B 4 mg/kg IV every 24 hours for 3 to 10 days or until clinical improvement followed by sporanox (Itraconazole) 200 mg PO bid for 3 to 6 months.
2. Less severe disease: Itraconazole 200 mg PO tid for 3 days followed by 200 mg PO bid for 3 to 6 months.

IX. ART IN THE ICU

A. General principles
1. Physicians must be aware of available methods of administration, drug interactions, and adverse effects of antiretroviral drugs in patients receiving ART when admitted to the ICU.
a. Most antiretrovirals are available only in oral form with only zidovudine (intravenous) and enfuvirtide (subcutaneous) available in parenteral form. Although there are antiretrovirals available in liquid form, erratic oral absorption in critically ill patients may lead to subtherapeutic levels hastening development of antiretroviral resistance.
b. Drug–drug interactions can occur between protease inhibitors and other agents used in critically ill patients most commonly through inhibition or induction of the hepatic cytochrome P-450 system. Medications that are used frequently in critically ill patients which can interact with protease inhibitors include azoles, benzodiazepines, neuroleptics, and calcium channel blockers.
2. HIV patients who are ART naïve—there is no conclusive evidence supporting the initiation of ART in critically ill treatment naïve patients.
3. HIV patients already on ART:
a. There is little consensus on what to do in terms of continuing the treatment, unless the admission is directly related to highly active antiretroviral therapy (HAART).

X. HIV TESTING IN THE ICU

A. General principles

1. Specific informed consent for HIV testing is required in all 53 US states and territories. In 34 states, no exceptions to this rule have been enacted to allow nonconsented HIV testing among patients who are incompetent. When caring for a critically ill patient who is unable to consent to HIV testing, physicians might order tests considered surrogate markers of HIV infection such as a CD4 cell count. The information obtained from a CD4 cell count in absence of HIV serology represents an unethical attempt to circumvent current restrictions.

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74 TUBERCULOSIS IN THE INTENSIVE CARE UNIT

Michael D. Mancenido and Jennifer S. Daly

I. GENERAL PRINCIPLES

- **A.** Recent global estimates of 1.6 to 2 million deaths from tuberculosis (TB) each year.
- **B.** The changing epidemiologic features and resistance patterns of TB make this disease more difficult to recognize and treat for all health care providers, including those in the intensive care setting.
- **C.** Prompt recognition of TB and early institution of effective therapy will allow successful treatment of the patient and the prevention of transmission.
- **D.** Most patients with localized disease who adhere to a full course of anti-TB therapy are cured.

II. ETIOLOGY

- **A.** TB is usually a subacute or chronic illness caused by *Mycobacterium tuberculosis* (MTB), also known as an acid-fast staining bacillus (AFB).
  - **1.** MTB commonly affects the lung but may also cause disease in other organs of the body.

III. PATHOPHYSIOLOGY

- **A.** Primary infection
  - **1.** Usually asymptomatic—tubercle bacilli gain entry into the lungs, then are phagocytized by alveolar macrophages. In most patients, a localized inflammatory process occurs with the development of granulomas.
  - **2.** In some individuals, the bacilli multiply in the lungs and cause extensive regional lymphadenitis which produces symptoms.
  - **3.** Primary infection may disseminate in the bloodstream, and seed the central nervous system (CNS), liver, spleen, kidney and other organ systems (rare in adults).
  - **4.** Tuberculin skin test (TST) usually becomes positive in 2 to 10 weeks after primary infection.
- **B.** Latent TB
  - **1.** Classically characterized by a positive TST and lack of symptoms or signs of active disease.
  - **2.** Immunocompetent persons develop a granulomatous inflammatory process and usually control but do not eradicate MTB infection.
  - **3.** Chest x-ray (CXR) is normal.
  - **4.** New interferon-γ release assays (IGRA) using whole blood detect latent infection and may be used as an alternative to the TST.
    - **a.** Use of the tests to replace TST is controversial.
    - **b.** The tests use antigens not present in Bacillus Calmette-Guárin (BCG), so crossreactivity is not observed.
- **C.** Active TB
  - **1.** Occurs in approximately 10% of immunocompetent individuals infected with MTB over their lifetime.
    - **a.** Half of these cases develop within the first 1 to 2 years after infection.
    - **b.** The other half may occur at any point during an individual's lifetime (reactivation disease).

2. Associated with classic symptoms of cough, hemoptysis, fevers, night sweats, and weight loss.
3. In patients with defects in cell-mediated immunity, the risk of progressive primary, reactivation, or disseminated disease is increased.
   a. The *annual* risk of developing active TB is 5% to 7% among human immunodeficiency virus (HIV)-infected persons with latent TB infection.
   b. These patients often have poorly formed granulomas, higher AFB burden in tissues, and may have atypical presentations.

IV. DIAGNOSIS

A. Patients critically ill from TB often have predisposing risks and/or comorbidities.
   1. High-risk patients:
      a. History of positive TST or prior active TB
      b. Contact with known or suspected active TB case
      c. Immigration from countries with a high risk for TB
      d. Presence of fibrotic lung lesions or upper lobe scarring
      e. Advanced age
      f. Alcohol or other drug use
      g. Institutional exposure (i.e., congregate living)
      h. Immunocompromised host (HIV infection, chemotherapy, or use of steroids or anti–tumor necrosis factor agents)
   2. There can also be critical involvement of multiple organ systems.
      a. Lungs—respiratory failure from fulminant tuberculous pneumonia, life-threatening (severe) hemoptysis, or acute respiratory distress syndrome (ARDS)
      b. Cardiac—pericardial tamponade from pericardial TB
      c. CNS—TB meningitis
      d. Gastrointestinal (GI)—TB enteritis and perforation, pancreatitis
      e. Systemic—disseminated TB with hepatosplenomegaly and pancytopenia

B. Chest radiograph or chest computed tomography (CT) is the primary diagnostic and screening test for active TB.
   1. Immunocompetent patients with pulmonary TB usually have abnormal CXR or chest CT findings.
      a. Primary or childhood TB: lower lobe infiltrate (Ghon focus) with ipsilateral hilar adenopathy (Ghon's complex, especially in children)
      b. Reactivation or adult pulmonary TB: fibrotic and/or cavitary infiltrates in the apical segment of the upper lobes, superior segment of the lower lobes
      c. Primary TB infections in adults may present with either classic "primary" or "reactivation" radiologic findings
      d. Disseminated (miliary) disease: diffuse nodules 1 to 3 mm in size
      e. Old disease: upper lobe parenchymal scars or calcified granulomas representing fibrotic foci of healed inactive TB
   2. Immunocompromised patients may have a normal-appearing CXR.

C. Detection of MTB—microscopy (smear) and culture:
   1. Sputum microscopy (AFB smear)
      a. The most important diagnostic tool.
      b. Sputum samples positive by auramine-stained smear or Ziehl–Nielsen stain may be examined with direct nucleic acid amplification tests to distinguish MTB from nontuberculous mycobacteria.
      c. AFB stains and cultures of gastric aspirates, other body fluids, and blood may be diagnostic *in the appropriate clinical setting.*
   2. Culture
      a. Obtain sputum specimens, as well as infected fluids, blood, bone marrow, lymph nodes, and tissue biopsies (e.g., pleural and pericardial) for AFB culture.

   b. Timing—MTB grows slowly but some laboratories use a radiometric assay to detect MTB within 2 to 6 days and then identification may be done promptly with genetic probes (1- to 3-week turnaround time compared to traditional 4 to 8 weeks).
   c. Susceptibility testing—may be available (within 1 to 3 weeks for AFB smear-positive sputum specimens) with direct susceptibility testing. Additional weeks needed if the laboratory sends isolates to a reference laboratory after initial isolation.
3. Characteristic histology and AFB staining on tissue biopsy

D. A diagnosis of TB may be delayed if antibiotic treatment, especially with fluoroquinolones, is empirically given to patients with "community-acquired pneumonia" that later are found to have TB.

V. TREATMENT

A. Empiric initiation of four-drug combination therapy:
1. Isoniazid (INH), rifampin, pyrazinamide, and either ethambutol or streptomycin.
2. When the strain is known to be susceptible to all agents, the total duration of treatment is usually 6 months, with INH and rifampin being used throughout the course; pyrazinamide and ethambutol (or streptomycin) can be discontinued after 8 weeks.

B. If the medications cannot be orally administered:
1. INH may be given intramuscularly. Rifampin and streptomycin are available for IV use. Second-line drugs including moxifloxacin and levofloxacin may also be given IV.
2. Other agents should be given through nasogastric (NG) or jejunal tube if the oral route cannot be used.

C. In patients with renal failure:
1. INH and rifampin may be given at standard doses.
2. Ethambutol, pyrazinamide, streptomycin, and the fluoroquinolones require dose adjustments based on creatinine clearance.
3. Pyrazinamide should be dose reduced or avoided in a patient requiring hemodialysis.

D. When the strain is known to be resistant to both isoniazid and rifampin, usually therapy is required for at least 18 to 24 months and consultation with specialists in the treatment of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) is advised.

E. Failure to convert to a negative smear and/or culture after 3 months indicates treatment failure from either nonadherence or drug-resistant TB.
1. In general, never add a single new anti-TB drug to a failing regimen. All new anti-TB drug regimens should ideally contain at least two drugs to which the organism is susceptible based on *in vitro* testing.
   a. Improper drug regimens may promote the emergence of drug-resistant TB strains.
   b. Consultation with specialists is recommended for management of patients with apparent treatment failure.
2. In cavitary pulmonary TB, when cultures remain positive after 2 months into therapy, yet the organism remains susceptible to all drugs, therapy should be extended to 9 months.

F. After discharge from the hospital, consider referring the patient to an outpatient program with directly observed therapy (DOT) and notify the local public health authorities.
1. Cure rates of >95% can be achieved with a 6-month regimen among patients with drug-susceptible organisms.

G. Corticosteroids are indicated for all patients with tuberculous meningitis and tuberculous pericarditis.

VI. COMPLICATIONS

A. Immune reconstitution inflammatory syndrome (IRIS). This syndrome is a transient, paradoxical worsening of the patient's condition with fevers, increasing lymphadenopathy, new infiltrates, pleural effusions, or ARDS.

1. It can occur after initiation of treatment for TB and/or the underlying immunodeficiency, such as occurs with the initiation of antiretroviral therapy in HIV/acquired immunodeficiency syndrome (AIDS) patients.

2. In patients with suspected IRIS, drug-resistant MTB, febrile response to therapy, coinfection with nontuberculous pathogens, or other alternative diagnoses must be ruled out.

B. Infection control and respiratory isolation:

1. Major concern is to prevent nosocomial transmission. Guidelines from the Centers for Disease Control and Prevention and the Occupational Health and Safety Administration form the basis of infection control policy.

2. A high index of suspicion and early recognition are key to allow the appropriate use of respiratory isolation and prompt initiation of treatment.

a. The infectiousness of TB begins to decrease within days of the initiation of effective therapy.

3. Respiratory precautions:

a. Negative pressure isolation rooms with at least six air changes per hour.

b. The use of closed suctioning systems to avoid generation of infectious aerosols and the use of submicron filters for air exhausted from ventilated patients.

c. Personal protective devices (N95 masks or personal powered respirators) are required for the health care workers who will be in contact with the patient.

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SEVERE COMMUNITY ACQUIRED RESPIRATORY VIRAL INFECTIONS

75

Iva Zivna and Richard T. Ellison

I. HUMAN INFLUENZA AND AVIAN INFLUENZA (H5N1)

A. General principles

1. Seasonal influenza is an acute febrile illness caused by influenza A subtypes H3N2 and H1N1, and influenza B viruses that occur in outbreaks of varying severity every winter season.
2. Highly pathogenic avian influenza virus A (H5N1) is a new influenza strain now endemic among bird and poultry population in Eurasia that is rarely causing human disease.
3. Suspect avian influenza (H5N1) infection in a patient who has traveled in an H5N1-affected country within 10 days of symptom onset and develops an acute respiratory distress syndrome (ARDS) or other severe respiratory illness for which an alternate etiology cannot be established.
4. Secondary bacterial pneumonia, due to *Staphyloccocus aureus, Streptococcus pneumoniae*, or *Haemophilus influenzae*, is an important complication of influenza infection and needs to be considered when exacerbation of fever and respiratory symptoms occurs after initial improvement.

B. Pathogenesis

1. Human cases of H5N1 influenza have almost exclusively occurred after direct exposure to infected birds, with viral replication occurring in the retropharyngeal area and lower respiratory tract.

C. Diagnosis

1. Flu-like illness and epidemiologic features.
2. Routine laboratory studies are nonspecific.
3. Molecular techniques (e.g., polymerase chain reaction [PCR] assay).
4. Diagnosis can be confirmed by detection of virus or viral antigen or fourfold or greater rise in specific antibody titers.
5. Growth of the H5N1 virus should only be attempted in a Biosafety Level 3 plus laboratory. This must be coordinated in conjunction with state and local health departments and, if highly suspected, the Centers for Disease Control and Prevention (CDC).

D. Treatment

1. Institute droplet precaution: In suspected avian influenza (H5N1) infection, place the patients in airborne precautions in a negative pressure room.
2. Oseltamivir or zanamivir can reduce duration of symptoms, although oseltamivir resistance has been reported in H5N1 strains.
3. Start empiric antibiotic therapy if secondary bacterial pneumonia is suspected.

II. HANTAVIRUS CARDIOPULMONARY SYNDROME (HCPS)

A. General principles

1. HCPS is an acute febrile illness, characterized by bilateral diffuse interstitial edema that may radiographically resemble the ARDS, with respiratory compromise requiring supplemental oxygen, and often developing within 72 hours of hospitalization in previously healthy person.

B. Pathogenesis

1. The illness is caused by rodent-borne viruses within the genus *Hantaviridae*.
2. Aerosols of virus-contaminated rodent urine or perhaps feces represent the main vehicle for transmission. Infection results in a severe increase in pulmonary vascular permeability leading to shock and acute lung injury.

C. Diagnosis

1. Clinical manifestation and epidemiologic features.
2. Common laboratory abnormalities include simultaneous appearance of thrombocytopenia, leukocytosis with left shift, and presence of immunoblasts in peripheral smear.
3. Serologic studies.
4. Detection of the virus from peripheral blood or serum.
5. Molecular techniques (e.g., PCR assay).

D. Treatment

1. Adequate cardiopulmonary support.
2. Early use of vasopressors and cautious use of intravenous fluids due to associated capillary leak syndrome.
3. Ribavirin use in early stage of the illness may be beneficial, but is of uncertain benefit.

III. SEVERE ACUTE RESPIRATORY SYNDROME(SARS)

A. General principles

1. Rapidly progressive respiratory illness caused by a novel coronavirus present in southern China. No human disease has been noted since 2003.
2. This disease should be suspected in a patient with fever, cough, or difficulty in breathing, who had close contact with a person diagnosed with SARS or has a history of travel to an area with recent local transmission of SARS, within 10 days of symptoms onset.

B. Pathogenesis

1. Knowledge of the pathogenesis is limited. Viral replication occurs in the lower respiratory tract.

C. Diagnosis

1. Clinical manifestation and epidemiologic features
2. Serologic studies
3. Molecular techniques (e.g., PCR assay)
4. Routine laboratory studies are nondiagnostic

D. Treatment

1. Place patient in airborne precautions in a negative pressure room.
2. Provide general supportive therapy.
3. No specific treatment has been found to be effective.

Suggested Reading

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76 TICK-BORNE ILLNESS

Iva Zivna and Richard T. Ellison

I. ROCKY MOUNTAIN SPOTTED FEVER (RMSF)

A. General principles

1. RMSF is a potentially lethal tick-borne disease caused by the intracellular parasite *Rickettsia rickettsii*.
2. RMSF is widespread in the United States. At present, prevalence of the disease is higher in the South Atlantic states and in the Southeast and Central regions than in the Rocky Mountain states. The highly endemic areas include primarily North Carolina and regions of Oklahoma and Arkansas.

B. Pathogenesis

1. After inoculation and intracellular proliferation, the organism attaches to vascular endothelium causing vasculitis, hemorrhage, edema, and eventually shock.

C. Diagnosis

1. Clinical manifestation of high fever, severe headache, and maculopapular rash that may involve palms and soles, typically develops 3 to 5 days after fever onset, plus presence of risk factors and epidemiologic features. Rash never occurs in up to 10% of patients.
2. Routine laboratory studies reveal thrombocytopenia, hyponatremia, elevated serum transaminases, but mostly are nonspecific.
3. Evidence of *R. rickettsii* on a skin biopsy; molecular techniques (e.g., polymerase chain reaction [PCR] assay) or a fourfold rise in specific antibody titers confirms the diagnosis.

D. Treatment

1. Doxycycline 100 mg orally or intravenously twice a day or chloramphenicol (50 to 75 mg/kg/day) usually administered for 7 days

II. BABESIOSIS

A. General principles

1. Babesiosis is a tick-borne disease seen predominantly on the Northeast coast of the United States.
2. In the United States, babesiosis is caused by the protozoan, *Babesia microti*, which infects red blood cells and produces mild to severe hemolytic anemia.
3. It can occur concurrently in patients coinfected with Lyme disease, ehrlichiosis, or anaplasmosis (prevalence of coinfection approximately 25%).

B. Pathogenesis

1. After inoculation, the organism multiplies inside erythrocytes causing hemolysis. Greater disease severity and higher incidence are seen in asplenic individuals.

C. Diagnosis

1. Clinical manifestations can range from asymptomatic infection to severe hemolytic anemia with multisystem organ failure.
2. Routine laboratory findings are nondiagnostic, but frequently include anemia, thrombocytopenia, and conjugated hyperbilirubinemia.
3. Definitive diagnosis is made by evidence of intraerythrocytic parasites on thick and thin peripheral blood smear, serologic studies, or molecular techniques (e.g., PCR assay).

D. Treatment

1. Combination antibiotic therapy
   a. Azithromycin 500 mg once followed by 250 mg daily thereafter and atovaquone 750 mg orally twice a day or
   b. Quinine orally 650 mg every 6 to 8 hours and clindamycin 300 to 600 mg intravenously or intramuscularly every 6 hours for 7 to 10 days.
2. In severe cases transfusion exchange therapy can be effective.

III. EHRLICHIOSIS AND ANAPLASMOSIS

A. General principles

1. Tick-borne diseases are caused by intracellular pathogens *Ehrlichia chaffeensis* (human monocytic ehrlichiosis) and *Anaplasma phagocytophilium* (human granulocytic anaplasmosis).
2. Although human monocytic ehrlichiosis and human granulocytic anaplasmosis are recognized as separate disease entities, their clinical and laboratory manifestations are similar.
3. Ehrlichiosis is endemic in the southern part of the United States, especially Arkansas, whereas anaplasmosis is found mainly along the Northeast coast of the United States.
   a. *A. phagocytophilium* may be transmitted by *Ixodes scapularis*, the tick that is also the vector of Lyme disease and babesiosis. It can occur in up to 25% of patients coinfected with *Borrelia burgdorferi* (agent of Lyme disease) or *B. microti*.

B. Pathogenesis

1. *E. chaffeensis* primarily infects mononuclear leukocytes and forms inclusion bodies "morulae" in the cytoplasm, whereas *A. phagocytophilium* infects granulocytes.

C. Diagnosis

1. Clinical manifestations of high fever, severe headache, malaise, and myalgia in association with risk factors and epidemiologic features.
2. Routine laboratory studies are nonspecific and reveal leukopenia, thrombocytopenia, elevated serum transaminase levels.
3. Presence of intraleukocytic morulae, serologic studies, or molecular techniques (e.g., PCR assay) confirms the diagnosis.

D. Treatment

1. Doxycycline orally or intravenously at dose 100 mg twice daily or chloramphenicol usually administered for 10 days.

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VI Gastrointestinal and Hepatobiliary Problems in the Intensive Care Unit

77 GASTROINTESTINAL BLEEDING: PRINCIPLES OF DIAGNOSIS AND MANAGEMENT

Yume Nguyen and C. Prakash Gyawali

I. GENERAL PRINCIPLES

Acute gastrointestinal (GI) bleeding is a common clinical emergency. Early recognition of clinical and endoscopic prognostic signs helps in the triage to the intensive care unit of patients at risk of rebleeding. Bleeding from the upper GI tract is more common than lower GI bleeding.

A. Prognosis

1. The mortality rate from upper GI bleeding remains approximately 6% to 12%, while that from lower GI bleeding typically is <5%.
2. Newer nonsurgical therapies may improve survival.

II. ETIOLOGY

A. Upper GI bleeding

1. Common causes
   - a. Duodenal and gastric ulcers and erosions
   - b. Esophageal and gastric varices
   - c. Esophagitis
   - d. Mallory–Weiss tears
2. Uncommon causes
   - a. Angiodysplasia
   - b. Cancer

c. Dieulafoy's lesions
d. Portal gastropathy
e. Other causes, including hemobilia, Cameron's erosions, aortoenteric fistula

B. Lower GI bleeding

1. Common causes
   a. Diverticulosis
   b. Angiodysplasia
   c. Cancer and polyps, including postpolypectomy bleeding
   d. Colitis, including inflammatory bowel disease, infectious colitis, ischemic colitis
   e. Hemorrhoids
2. Uncommon causes
   a. Anal fissure, rectal ulcers including stercoral ulcers, solitary rectal ulcer syndrome
   b. Radiation proctopathy and colopathy
   c. Vasculitis
   d. Meckel's diverticulum
   e. Colonic varices
   f. Other causes, including endometriosis, intussusception, aortoenteric fistula

III. DIAGNOSIS

A. Clinical presentation

1. Hematemesis indicates an upper GI bleed.
2. Passage of red or dark red blood in the stool usually indicates lower intestinal bleeding.
3. Repeated passage of liquid bloody stool indicates ongoing or recurrent bleeding, because fresh blood has laxative properties.
4. Passage of black, sticky, tarry stool (melena) usually indicates upper GI bleeding.
5. Melena can persist for several days, and the stool may remain positive for occult blood for up to 2 weeks after GI bleeding has ceased.
6. Bright or dark red blood in the stool is infrequently seen with an upper GI bleeding source, but, when it occurs, indicates rapid bleeding; it is usually associated with hemodynamic compromise.

B. Diagnostic tests

1. Nasogastric aspiration
   a. Passage of a nasogastric tube may help to detect upper GI bleeding in patients with an obscure bleeding site.
   b. However, the nasogastric aspirate may be nonbloody if a tightly closed pylorus prevents reflux of blood from a duodenal bleeding site.
   c. Further use of the nasogastric tube for lavage to control bleeding is unsubstantiated, although lavage may help remove clots from the stomach in preparation for endoscopy and provide an indication of the acuity and rapidity of bleeding.
2. Endoscopy
   a. Endoscopy is performed when the patient is hemodynamically stable, but resuscitation usually is ongoing at the time of the procedure.
   b. When a bleeding site proximal to the jejunum is suspected, esophagogastroduodenoscopy (EGD) is the diagnostic procedure of choice.
   c. When a lower GI bleeding source is suspected, sigmoidoscopy or colonoscopy, after bowel preparation, may be helpful. These procedures may help to detect and treat colonoscopic bleeding sources or to localize fresh blood to a segment of colon and to direct other therapeutic measures.

d. Push enteroscopy evaluates the proximal small bowel when a bleeding site is not found in the upper GI tract or colon on conventional endoscopy.
e. While EGD is frequently performed with therapeutic intent early in the course of bleeding, other endoscopic procedures typically are performed after the bleeding has ceased or in patients with subacute bleeding.

3. Imaging studies
   a. A ^{99m}Technetium (^{99m}Tc)-labeled red blood cell scan can detect bleeding rates as low as 0.1 mL/minute and is a reasonable initial imaging test in the patient with signs of active bleeding distal to the upper GI tract.
   b. In some centers, arterial phase multidetector row computed tomography (CT) is being used to localize the bleeding source. Sensitivity of this imaging examination is comparable to radiolabeled red blood cell scans. Choice of investigative modality depends on availability of technique and local expertise.
   c. If active bleeding is found, angiography often is indicated for confirmation of the site and administration of intra-arterial vasopressin or embolization of the bleeding artery for bleeding control.
   d. Patients who continue to bleed in spite of intra-arterial vasopressin or embolization may require surgical management.
   e. Avoid barium studies in the setting of acute bleeding.
4. Newer techniques
   a. Wireless capsule endoscopy may help localize bleeding to the small bowel if no bleeding source is identified on conventional endoscopy.
   b. Absence of real-time viewing of images and therapy limits the usefulness of this procedure. Double balloon enteroscopy, available in selected centers, is a therapeutic option.

IV. TREATMENT

A. Initial approach

1. Rapid evaluation
   a. Mental confusion, agitation, diaphoresis, mottled skin (livedo reticularis), and cold extremities accompany hypotension with hemorrhagic shock.
   b. A quantitative estimate of the amount of bleeding is helpful because the initial blood count may not reflect the degree of blood loss.
   c. Initial blood testing should be performed urgently to obtain baseline hemoglobin/hematocrit values, measure platelet count and coagulation parameters, and type and crossmatch blood for transfusion.
   d. Abdominal pain is not common with GI bleeding and may indicate the presence of hemobilia, intestinal infarction, or perforation.
   e. Chest pain may imply a superimposed myocardial infarction or dissecting aneurysm.
   f. Previous vascular graft surgery is a risk factor for bleeding from an aortoenteric fistula.
2. Resuscitation
   a. Resuscitation of the unstable patient takes precedence over other treatments.
   b. Recognizing and aggressively treating intravascular volume depletion is of the highest priority and should proceed concurrently with the initial diagnostic evaluation.
   c. Intravenous access with large-bore peripheral catheters or a central venous catheter is needed for aggressive administration of fluids or blood products.
   d. Massive hematemesis may require endotracheal intubation for airway protection before endoscopy.

e. Exsanguinating hemorrhage may require immediate surgical management, at times with assistance of limited endoscopy to help direct the surgical approach.

3. Acid suppression
   a. Rationale for using acid suppression in acute upper GI bleeding is based on the coagulopathy resulting from an acid milieu.
   b. A randomized trial showed that the proton-pump inhibitor omeprazole (40 mg orally every 12 hours for 5 days) significantly decreased the incidence of recurrent bleeding and surgery in hospitalized patients with peptic ulcers; the study was restricted to patients who had duodenal ulcers with high likelihood of recurrent bleeding, yet none underwent any commonly performed endoscopic therapies.
   c. Nevertheless, early treatment with oral or intravenous proton-pump inhibitors is standard in acute upper GI bleeding.
4. Octreotide
   a. Octreotide (usually administered as 25 to 100 μg IV bolus followed by a continuous infusion at 25 to 50 μg/hour for 48 to 120 hours) should be initiated early if a variceal bleed is suspected.

B. Endoscopy

1. Endoscopic therapy, using thermal devices (heater probe, electrocoagulation, laser), hemoclips, injection therapy (sclerosing solutions, hypertonic saline, epinephrine), or banding devices, offers a convenient and expedient method of treating upper GI bleeding from many causes.
2. These treatments can decrease further bleeding, shorten hospital stay, decrease transfusions, decrease emergency surgery, and lower costs in acute upper GI bleeding.
3. Recurrent bleeding occurs in up to 30% of patients with bleeding ulcers despite successful endoscopic therapy, and continued observation for up to 72 hours is recommended.
4. Endoscopic therapy is of use for some colonic bleeding sites, such as angiodysplasia.

C. Angiographic therapy

1. Intra-arterial vasopressin has been used for angiographic management of upper and lower GI bleeding.
2. Vasopressin use is attended by risk of cardiovascular complications.
3. Gelfoam or metal coil embolization of the bleeding artery is an alternate approach which causes localized thrombosis and vessel occlusion; tissue ischemia and perforation are potential complications.
4. In the upper GI tract, angiographic therapy is usually reserved for patients with bleeding peptic ulcer disease in whom endotherapy has failed or who are ineligible for this endotherapy and have a prohibitive surgical risk.

D. Surgery

1. Surgical consultation should be obtained early in patients with clinical and endoscopic risk factors for high morbidity and mortality.
2. Patients with massive ongoing hemorrhage that overwhelms the resuscitative effort need urgent surgical assessment.
3. Patients failing to respond to endoscopic or angiographic management also need surgical assessment.
4. Arterial embolization and transjugular intrahepatic portosystemic shunts for variceal bleeding are alternatives in high-risk surgical candidates.

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78 STRESS ULCER SYNDROME

Sonal Kumar and C. Prakash Gyawali

I. GENERAL PRINCIPLES

A. Definition

1. The term *stress ulcer* refers to mucosal damage in the upper gastrointestinal (GI) tract that occurs with extreme physiologic stress.
2. When associated with clinical bleeding or perforation, the condition is called *stress ulcer syndrome* (SUS).

B. Description

1. Superficial erosions or deeper ulcerations are typically located in the proximal stomach, in contrast to distal stomach lesions in peptic ulcer disease.
2. Duodenal ulcers are uncommon in SUS, but when seen, are usually in conjunction with proximal gastric lesions.
3. As many as 52% to 100% of patients admitted to intensive care units (ICUs) have endoscopic evidence of gastric mucosal damage within the first day of ICU admission, but most are asymptomatic.
4. Bleeding from SUS typically occurs within 2 weeks of ICU admission and usually presents as hematemesis, gross blood from a nasogastric tube, or melena.
5. Abdominal pain is unusual except in the infrequent setting of perforation.

C. Prognosis

1. Mortality rates can be as high as 50% to 80% in patients who bleed, although death usually is attributed to the underlying disease.
2. Stress ulcer bleeding may serve as a marker for severely ill patients.

II. ETIOLOGY

A. Patients in ICU with coagulopathy or requiring mechanical ventilation for >48 hours are statistically more likely to develop SUS.

B. Shock, hypotension, sepsis, and major burns (>35% body surface area) are more common in patients with SUS.

C. Patients with acute intracranial head trauma and coma (Curling's and Cushing's ulcers, respectively) are also at increased risk of having stress ulcers.

D. The incidence of GI bleeding increases with each risk factor up to two; additional risk factors do not further increase the incidence.

E. Patients with minor burns, chronic brain disease, malignancy, chronic obstructive pulmonary disease, transient respiratory illness, dialyzed chronic renal failure, myocardial infarction, arrhythmias, and congestive heart failure are presumed not to be at high risk for SUS.

III. PATHOGENESIS

A. Mucosal damage

1. Although gastric acid is essential for stress ulceration, a breakdown of some or all of the following mucosal defense mechanisms also is required:
   - **a.** Mucus and mucus-bound bicarbonate, providing an anatomic barrier while buffering intraluminal hydrogen ions
   - **b.** Intact intramucosal blood flow, bringing systemic bicarbonate to buffer intramural pH shifts

c. Mucosal cell restitution to rapidly restore the mucous-cell layer when the epithelium is damaged

2. Stress results in splanchnic vasoconstriction leading to gastric mucosal ischemia and decreased delivery of oxygen and nutrients resulting in a deficit in aerobic metabolism and high energy phosphate compounds. This leads to a drop in intramucosal pH from a deficit of systemic bicarbonate that normally buffers back diffusion of hydrogen ions.
3. Subsequent reperfusion contributes to injury from hyperemia and an enhanced inflammatory response by the formation of toxic oxygen-derived free radicals and superoxides while decreasing the synthesis of cytoprotective prostaglandins.
4. The role of *Helicobacter pylori* in the pathogenesis remains unknown.

IV. DIAGNOSIS

A. Clinical presentation

1. Stress ulcers come to clinical attention when they bleed.
2. Significant stress ulcer bleeding occurs in 2% to 6% of critically ill patients and presents within 14 days of the onset of physiologic stress or ICU admission as hematemesis, gross blood from the nasogastric tube, or melena.
3. Patients with thermal injury from burns or with acute intracranial disease including head trauma and coma appear to be at increased risk (Curling's ulcers and Cushing's ulcers).

B. Endoscopy

1. The earliest mucosal changes are found in the most proximal part of the stomach and include pallor, mottling, and submucosal petechiae.
2. Superficial linear erosions and ulcers are formed when these lesions coalesce.
3. Eventually diffuse mucosal damage may result, with bleeding and rarely, perforation.

V. TREATMENT

A. Principles

1. The risk of bleeding and overall prognosis are related to the severity of underlying illness, aggressive management of which should always take precedence. Maintaining adequate hemodynamic support is key in prevention of SUS.
2. Prophylactic agents enhance mucosal integrity in patients at risk for stress ulceration.
3. Upper GI endoscopy helps establish the diagnosis and determines the need for endoscopic therapy.
4. Acid suppression, preferably with a proton pump inhibitor, is indicated when GI bleeding occurs.

B. Prophylaxis

The logic of prophylaxis lies in the assumption that the formation of stress ulcers can be prevented or that, once these ulcers are formed, the progression from ulcer to bleeding or perforation can be halted.

1. Antisecretory drugs
   a. Histamine-2-receptor antagonists
      i. Administered by intermittent IV bolus or continuous infusion.
      ii. Continuous infusion more effectively maintains the desired gastric intraluminal pH.
      iii. Patients with a creatinine clearance of <30 mL/minute should receive half the recommended dose, and caution should be exercised in patients with thrombocytopenia.
      iv. The optimal gastric pH level is unknown, and the need for 24-hour pH control is not essential for a prophylactic effect.

v. Reduces the incidence of clinically important bleeding without increasing the risk for ventilator-associated pneumonia.
vi. Effectiveness of raising pH may be limited by a tolerance that develops to the drug.

b. Proton pump inhibitors
i. Block the final pathway for acid secretion by irreversibly inhibiting H+/K+-ATPase in gastric parietal cells
ii. Can be administered enterally or intravenously at once a day dosing
iii. May be as effective as IV cimetidine at preventing stress ulcer bleeding and more effective in maintaining gastric pH >4
iv. The need for aggressive acid suppression with a proton pump inhibitor is not established for stress ulcer prophylaxis

2. Antacids
a. Antacids (10 to 80 mL) can be administered through a nasogastric tube every 1 to 2 hours and ideally titrated to keep the gastric pH >4.0, measured 1 hour after administration.
b. Some antacids may cause diarrhea, may be contraindicated in renal failure, and may affect the bioavailability of oral medications.
c. Antacid use involves expensive and time-consuming processes of frequent administration and monitoring of gastric pH.

3. Sucralfate
a. Sucralfate consists of a core of sucrose molecules surrounded by aluminum hydroxide sulfate cells.
b. Sucralfate coats the early shallow mucosal lesions and protects them from further acid and pepsin damage without altering gastric pH.
c. It is delivered in the form of a slurry through a nasogastric tube at a dose of 4 to 6 g per day.
d. Although it is safe for long-term use in critically ill patients, sucralfate should be used with caution in patients with chronic renal insufficiency.
e. Sucralfate may have a lower incidence of nosocomial pneumonia. It has a low side effect profile and is inexpensive.

4. Other agents
a. Prostaglandins, free radical scavengers such as dimethylsulfoxide and allopurinol, and the bioflavin meciadanol have also been used for stress ulcer prophylaxis with varying results.
b. Retrospective studies on burn patients and patients receiving assisted ventilation suggest that upper GI bleeding may be reduced by enteral feeding.

C. GI bleeding

1. Injection of epinephrine, hemoclipping and/or thermal therapy can be attempted during endoscopy.
2. If endoscopic measures fail, angiography can be attempted, using intra-arterial vasopressin or embolization if the bleeding site can be demonstrated.
3. Surgical therapy is reserved for severe, life-threatening hemorrhage unresponsive to all other measures.
4. The mortality of total gastrectomy approaches 100% in these critically ill patients, whereas subtotal gastrectomy can be associated with rates of recurrent bleeding approaching 50% from the remnant gastric mucosa.
5. Vagotomy and oversewing of any remaining ulcers during subtotal gastrectomy may decrease the high rate of recurrent bleeding.

VI. COMPLICATIONS

A. Complications of stress ulcers

Stress ulcers can develop bleeding, and rarely, perforation.

B. Complications of prophylaxis

1. Nosocomial pneumonia as a complication of stress ulcer prophylaxis is a growing concern.
   a. Gastric alkalinization and colonization with gram-negative bacilli are thought to play a causal role, and, consequently, some studies suggest a higher incidence of nosocomial pneumonia in patients who receive antisecretory drugs. It is for this reason that aggressive antisecretory medications (proton pump inhibitors) are used less frequently for prophylaxis of stress ulcers.
   b. Further studies are needed before one prophylactic agent confidently can be recommended over another because of either higher efficacy or lower complications from treatment.

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VARICEAL BLEEDING

Joseph Merrill and C. Prakash Gyawali

79

I. GENERAL PRINCIPLES

A. Variceal bleeding is the most common lethal complication of cirrhosis.

B. The mortality of an acute bleeding episode is 20% at 6 weeks.

C. Varices are present in 50% of patients with cirrhosis and 85% of Child C patients.

D. Spontaneous bleeding occurs at a rate of 5% to 15% per year.

E. While exsanguination remains the most immediate threat to life, mortality is often related to liver decompensation, aspiration, hepatic encephalopathy, hepatorenal syndrome, septicemia, and alcohol withdrawal.

F. Survival is dependent on early accurate diagnosis, stabilization of hemodynamics, immediate hemostasis, and anticipating and preventing superimposed complications and recurrent bleeding.

II. PATHOPHYSIOLOGY

A. Portal hypertension

1. The initial cause of portal hypertension is mechanical obstruction to portal venous flow.

2. This is most commonly caused by the fibrous tissue and architectural liver distortion of cirrhosis.

3. Other causes include portal vein and hepatic vein thrombosis, and unusual disorders, such as congenital hepatic fibrosis and schistosomiasis.

4. Secondary hemodynamic changes associated with cirrhosis, including intrahepatic vasoconstriction, peripheral vasodilatation, decreased systemic vascular resistance, increased cardiac output, and splanchnic hyperemia, contribute to increased portal pressure. These are all potential therapeutic targets.

B. Development of varices

1. As with most obstructions to vascular flow in the body, a collateral circulation develops to decompress the portal venous system, the most clinically significant locations being the junctions of squamous and columnar mucosae (gastroesophageal, anal, and peristomal). These collateral vessels progressively enlarge to form varices.

2. Risk factors for variceal rupture include a portosystemic pressure gradient >10 to 12 mm Hg, large variceal size (>5 mm), and progressive hepatic dysfunction.

III. DIAGNOSIS

A. Clinical presentation

1. Variceal bleeding typically is brisk, presenting as hematemesis, melena or bright red blood per rectum, and varying degrees of hemodynamic instability.

2. Acute bleeding is self-limited in 50% to 60% of cases; however, in these cases there is a high rate of rebleeding without appropriate therapy.

3. Approximately a third of the patients with stigmata of chronic liver disease who present with acute upper gastrointestinal bleeding have nonvariceal sources of hemorrhage, and endoscopic verification is required.

B. Endoscopy

1. Variceal bleeding is diagnosed by upper endoscopy.
2. Detecting blood pouring from a variceal rent is unlikely.
3. Findings suggestive of a variceal bleed include a fresh fibrin clot protruding from a varix, a nipple-like protrusion from a varix, red signs, or varices with no other potential bleeding source.
4. Nonbleeding varices are the most common findings; in such cases, in the absence of an alternate bleeding source, variceal band ligation is warranted because of the high rate of early recurrent bleeding.

IV. TREATMENT

The three main goals in the management of variceal bleeding are resuscitation, diagnosis, and therapy. Diagnosis and therapy are not possible until resuscitation and stabilization are initiated.

A. Initial resuscitation

1. Appropriate resuscitative efforts should be initiated without delay, and before endoscopic evaluation (see Chapters 75 and 146). Resuscitation must be performed based on the patient's hemodynamics and laboratory values. Hemodynamic stability and hemoglobin of approximately 8 g/dL are the goals.
2. Packed red blood cell transfusion, fresh frozen plasma, and platelet infusion may be necessary before endoscopy, depending on initial laboratory test results. When massive transfusions are necessary, the patient should be monitored for resultant hypocalcemia and thrombocytopenia.
3. Nasogastric aspiration may be necessary when the diagnosis of an upper gastrointestinal hemorrhage is in doubt; fears of trauma to a varix from the tube largely are unfounded, but good lubrication and careful technique should be exercised. Nasogastric aspiration not only aids in diagnosis, but can guide resuscitation efforts based on degree of hemorrhage and clear the stomach and esophagus of blood before upper endoscopy. Up to 10% of apparent brisk lower gastrointestinal hemorrhages are eventually localized to the upper gastrointestinal tract.
4. Airway protection with endotracheal intubation is mandatory in the massively bleeding or obtunded patient.
5. Patients with alcoholism should receive thiamin and be monitored closely for alcohol withdrawal.

B. Pharmacotherapeutic agents

1. Octreotide is the pharmacotherapeutic agent of choice in acute variceal bleeding.
   a. This synthetic octapeptide shares structural and functional properties with somatostatin in reducing splanchnic blood flow and portal pressure.
   b. Aside from transient nausea and abdominal pain, significant adverse effects are rare.
   c. A bolus of 50 μg is followed by a continuous infusion of 50 μg/hour for 48 to 72 hours.
   d. Octreotide is effective in stopping active bleeding from varices and has an important role in the prevention of early recurrent bleeding after initial hemostasis.
   e. Octreotide should be initiated immediately with suspicion of variceal bleeding.
2. Vasopressin, when infused intravenously, is a potent vasoconstrictor that reduces splanchnic blood flow and portal pressure.
   a. Adverse cardiac effects (myocardial ischemia, hypertension) interfere with treatment in approximately 30% of patients and contribute to the limited success rate of this approach.

   b. The starting dose is typically a 0.4 U bolus and 0.4 U/minute, titrated to a maximum of 1 U/minute if required for bleeding control.
   c. Concurrent intravenous nitroglycerin infusion, starting at 10 μg/minute and titrated to maintain a systolic blood pressure (SBP) of 100 mm Hg, has been shown to reduce the systemic side effects of vasopressin.
   d. Vasopressin currently is used only when octreotide is not available.
3. Nonselective β-blockers should not be used in acute variceal bleeding as they can contribute to hypotension and block the physiologic increase in heart rate. These medications are indicated for primary and secondary prevention of variceal bleeding, but are initiated electively and not in the acute bleed setting.

C. Endoscopic therapy

1. Band ligation is the technique of choice for endoscopic control of bleeding varices.
   a. Small elastic "O" rings are placed endoscopically over the varices.
   b. Subsequent strangulation of the vessel with sloughing and fibrosis of the adjacent esophageal tissues results in the obliteration of the varix, decompressing the downstream vessels.
   c. Active bleeding is controlled in 80% to 90% of patients after one or two treatments.
   d. Band ligation has a lower incidence of esophageal ulceration, stricture formation, perforation, bacteremia, and respiratory failure compared to sclerotherapy.
   e. Serial scheduled endoscopic treatment sessions at weekly to monthly intervals ensure obliteration of the varices.
2. Sclerotherapy
   a. A sclerosant solution is injected into the variceal lumen or into the adjacent submucosa.
   b. This technique is reserved for massive bleeding, wherein visualization of the variceal columns to perform band ligation is impossible, and for gastric variceal bleeding.
3. Antibiotic prophylaxis is recommended to prevent infection and rebleeding in all cirrhotic patients with variceal bleeding. Norfloxacin 400 mg bid for 7 days would be an appropriate choice. If fluoroquinolone resistance is likely from long-term SBP prophylaxis or based on regional antibiotic resistance, then ceftriaxone 1 g/day is also effective.

D. Transjugular intrahepatic portosystemic stent (TIPS) shunt

1. TIPS is an iatrogenic fistula between radicals of the hepatic and portal veins, created by interventional radiologists using ultrasonographic and fluoroscopic guidance. An expandable metal stent is left in place, and the portosystemic pressure gradient is reduced to <12 mm Hg. Cross-sectional imaging of the liver is necessary before TIPS placement to evaluate the patency of the portal vessels as well as to rule out liver masses.
2. TIPS is recommended if bleeding continues despite combined pharmacologic and endoscopic therapy. TIPS is also indicated if bleeding recurs after two endoscopic attempts at prevention, or if bleeding has occurred from gastric varices or portal hypertensive gastropathy.
3. The technical success rate in constructing a TIPS is >90%, with near-universal success in bleeding control. Overall mortality is similar to endoscopic therapy.
4. Some degree of shunt insufficiency is seen in 15% to 60% of patients within 6 months.
5. Doppler ultrasound examination for determining shunt patency is recommended for postprocedure bleeding recurrence. The shunt usually can be revised with little morbidity.

6. Twenty percent to 30% of patients develop transient deterioration of liver function after elective shunt placement, and up to one fourth of patients may experience new or worsened hepatic encephalopathy.

E. Balloon tamponade

1. Gastric and esophageal balloon devices for direct tamponade of the bleeding varices (Sengstaken–Blakemore, Minnesota, and Linton–Nachlas balloons) may be required for patients with severe or persistent bleeding.
2. Initial success approaches 90%, but rates of recurrent bleeding are high, and definitive plans for portal decompression should be made before deflating the balloon.
3. Complications occur in 15% to 30% of patients; balloon-related deaths occur in up to 6%.
4. Endotracheal intubation should precede balloon placement for airway protection.

F. Other measures

1. Surgical shunts:
   a. Surgical shunts are considered in patients with good long-term prognosis who need portal decompression, such as patients with Child A cirrhosis and patients with noncirrhotic portal hypertension.
   b. The utility of surgical shunting in the acutely bleeding patient with cirrhosis is limited by high operative mortality. Postprocedure encephalopathy and control of bleeding is similar to TIPS.
2. Nonshunting operations, such as the Sugiura procedure (mucosal transection and devascularization of the esophagus), are infrequently used because varices reform and bleeding recurs in >20% of patients.
3. Embolization of the short gastric veins in gastric variceal bleeding and splenectomy in splenic vein thrombosis are other potential management options.

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80 GASTROINTESTINAL MOTILITY PROBLEMS IN THE CRITICAL CARE SETTING

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I. GENERAL PRINCIPLES

- **A.** Abnormalities of gastrointestinal (GI) motility are common in the intensive care unit (ICU) setting, occurring as a consequence of multiorgan dysfunction, medications, and metabolic derangements.
- **B.** Up to two thirds of ICU patients are affected, predominantly with disordered gastric and colonic motor function.
- **C.** Motility disorders manifest as gastric stasis (that can produce gastroesophageal reflux disease [GERD]), colonic dysfunction (abdominal distension, constipation), and diarrhea.
- **D.** Recognition may be difficult, because typical signs and symptoms are masked in the unresponsive or sedated patient.
- **E.** GI motility complications prolong ICU stays and nearly double mortality.

II. ETIOLOGY

A. Critical illness alone

1. Causes of gastric stasis (delayed gastric emptying, gastroparesis) include:
   - **a.** Head injury
   - **b.** Pancreatitis
   - **c.** Spinal cord injury
   - **d.** Acute pain
   - **e.** Sepsis
2. Medications
   - **a.** Anticholinergic medications
   - **b.** Sympathomimetics/pressor agents
   - **c.** Narcotics
   - **d.** Phenothiazines/antipsychotics
3. Comorbid illnesses
   - **a.** Cirrhosis
   - **b.** Diabetes mellitus
   - **c.** Hypothyroidism (untreated)
   - **d.** Prior gastric surgery and vagotomy
   - **e.** Parkinson's disease
   - **f.** Miscellaneous (neuropathy, amyloidosis, scleroderma)
4. Metabolic derangements
   - **a.** Hypercalcemia
   - **b.** Hypokalemia
   - **c.** Hypomagnesemia
   - **d.** Hyperglycemia
   - **e.** Acidosis/alkalosis
5. Sympathetic neural stimulation often accompanies many severe medical and surgical illnesses, which results in selective suppression of excitatory motor reflexes and sustained intrinsic inhibitory neural overactivity.
   - **a.** Adverse outcomes from gastric stasis are:
     - **i.** Poor absorption of oral- or nasogastric-administered medications
     - **ii.** Intolerance to feeding

- **b.** Predisposition to GERD and its complications (e.g., GI bleeding, dysphagia); GERD is further exacerbated by supine positioning, use of nasogastric tubes, and mechanical ventilation.
  - **i.** Tracheobronchial aspiration and pulmonary compromise
- **c.** Causes of colonic dysfunction (distension, constipation) include:
  - **i.** Medications and metabolic disturbances that can delay colonic transit (see II.A.1)
  - **ii.** Medical comorbidities
  - **iii.** Burns or trauma
  - **iv.** Metabolic or electrolyte imbalances
  - **v.** Hypothyroidism
  - **vi.** Organ failure (respiratory failure, acute renal failure, congestive heart failure)
  - **vii.** Infection, either systemic (pneumonia, sepsis) or GI (*Clostridium difficile*, cytomegalovirus)
  - **viii.** Ischemia (intestinal, cerebrovascular)
  - **ix.** Surgical intervention
- **d.** Autonomic imbalance; this can accompany a host of medical and surgical illnesses and has been incriminated in acute colonic dilatation.
  - **i.** Supine position, because it is not conducive to voluntary elimination.
  - **ii.** The withholding or strict limitation of luminal nutrition, a major stimulant of colonic motor function, can act as a contributor.
  - **iii.** Combinations of factors are often incriminated in massive colonic dilatation or pseudoobstruction.
- **e.** Causes of diarrhea, a complication seen in at least one third of ICU patients and which interferes with medical management and outcome, include (also see Chapter 84)

6. Enteral feedings
- **a.** Of ICU patients receiving enteral nutrition, 40% to 60% develop diarrhea.
- **b.** Hyperosmolar formulas, higher infusion rates, and colonic fermentation of malabsorbed carbohydrates have been invoked as etiologies.

7. Infections, including *C. difficile*, and, in immunocompromised patients, cytomegalovirus, herpes simplex virus, Cyclospora, Strongyloides, and Microsporidium.

8. Medications (antacids, antibiotics, lactulose, sorbitol-containing medication suspensions).

9. Fecal impaction, with stool overflow around the impaction.

III. DIAGNOSIS

A. Gastric stasis (delayed gastric emptying, gastroparesis)

1. Gastric stasis is suspected with impaired tolerance to gastric feeding, including clinical evidence of oral regurgitation or tracheobronchial aspiration (e.g., airway suctioning of enteral nutrition products).

2. Gastric residual volumes of 200 mL or greater indicate retention.

3. More reliable measurements of gastric emptying are accomplished using scintigraphic techniques or the octanoate breath test, but they are rarely performed.

4. Mechanical obstruction is evaluated by upper endoscopy or radiographic imaging techniques.

5. GERD, as an outcome of gastric stasis, typically presents with heartburn and regurgitation, though critically ill patients may not relay these symptoms.
- **a.** Chest pain is an atypical symptom of GERD that requires exclusion of cardiopulmonary explanations.

b. GERD should be suspected in the setting of unexplained tracheobronchial aspiration, upper GI bleeding, vomiting, or regurgitation.
c. Endoscopy typically is reserved for evaluation of GERD complications (e.g., GI bleeding) (see Chapters 12 and 77).
d. Methylene blue dye can be added to enteral nutrition to facilitate recognition of regurgitation events when suspected.

B. Acute colonic pseudoobstruction (Ogilvie's syndrome)

1. Patients typically present with marked abdominal distension, pain, and altered bowel movements.
2. Progression leads to colonic ischemia and perforation, complications that carry a mortality rate of up to 30%.
3. Colonic distension can be found incidentally on radiographs obtained for other reasons.
4. Plain abdominal films or computed tomography (CT) images demonstrate
   a. Diffuse dilatation of the colon with normal mucosal markings and haustra
   b. Absence of small bowel dilatation
5. A water-soluble contrast enema or CT may be necessary to exclude mechanical obstruction. CT imaging is now the preferred imaging modality in this setting.
6. CT imaging is the most sensitive test for detecting intestinal perforation.

C. Diarrhea

Diarrhea (see Chapter 84) is defined by change in stool frequency or consistency, but more objectively by a stool weight of >250 g/day.

1. Diarrhea can result in significant nutrient, water, and electrolyte loss, as well as perineal and sacral skin breakdown.
2. Review medications for those that may precipitate diarrhea.
3. Maintain high suspicion for antibiotic-associated diarrhea, especially in the setting of unexplained leukocytosis, and diagnose by finding *C. difficile* toxin in the stool.
4. Perform rectal examination to exclude a distal impaction; abdominal radiographs are required to exclude more proximal impaction.
5. Sigmoidoscopy or colonoscopy with biopsy is helpful when diarrhea remains unexplained.

IV. TREATMENT

A. Gastric stasis (delayed gastric emptying, gastroparesis)

1. Initial approach
   a. Eliminate iatrogenic factors and exclude mechanical obstruction.
   b. Minimize or eliminate narcotics and other medications known to slow gastric emptying.
   c. Improve feeding tolerance by positioning the feeding tube ports beyond the pylorus (e.g., jejunal or gastrojejunal feeding tube); this maneuver does not eliminate the risk of tracheobronchial aspiration.
   d. Parenteral nutrition can be considered if enteral feeds are not tolerated, but comes with higher rates of infection and hyperglycemia.
2. Pharmacologic treatment
   a. Few prokinetic agents are available.
   b. Metoclopramide is the only clinically approved prokinetic in the United States and is the agent of choice in the ICU.
      i. The drug accelerates gastric emptying, but does not prevent aspiration pneumonia.
      ii. Significant side effects include confusion, agitation, somnolence, and dystonic reactions.

c. Intravenous (IV) erythromycin, a motilin agonist, accelerates gastric emptying and facilitates postpyloric tube placement.
   i. To improve gastric emptying, erythromycin is given at a dose of 1 to 3 mg/kg three to four times daily.
   ii. Side effects include nausea, vomiting, abdominal cramps, and diarrhea.
   iii. Tolerance to the prokinetic effect of erythromycin occurs rapidly with repeated use from downregulation of motilin receptors.
   iv. Erythromycin in combination with metoclopramide may be more effective than either agent alone.

B. Managing GERD as an outcome of gastric stasis
1. Use conservative measures that may reduce reflux
   a. Maintain the head of the bed at a 45-degree elevation.
   b. Avoid large-bolus tube feedings.
   c. Consider postpyloric feeding tube placement.
2. Pharmacologic treatment also is required:
   a. Patients with a preceding history of reflux disease should remain on medications at least as effective as their usual acid-suppression regimens.
   b. Proton pump inhibitors (PPIs) are the most effective acid-suppressant agents.
   c. PPIs may be given by mouth or by nasogastric tube, using appropriate formulations.
   d. The IV route may be used when the enteral route is not feasible, or absorption is in question; pantoprazole and lansoprazole, and esomeprazole are available in IV preparations.

C. Acute colonic pseudoobstruction (Ogilvie's syndrome)
1. Initial approach
   a. Recognition of potentially reversible precipitants, such as electrolyte imbalances, infection, or medications that slow transit, is essential.
   b. Correct electrolyte and metabolic abnormalities
   c. Reduce narcotic medication use.
   d. Give patient nothing by mouth and use low, intermittent nasogastric suction.
   e. Exclude fecal impaction and place a rectal tube.
   f. Follow serial abdominal radiographs every 12 to 24 hours depending on clinical examination.
2. Pharmacologic treatment
   a. IV neostigmine can be used when the patient fails to improve with conservative measures and reversal of underlying factors.
   b. The acetylcholinesterase inhibitor neostigmine 2 mg is given intravenously over 5 minutes in a closely monitored setting.
   c. The medication is contraindicated in face of bradycardia, active bronchospasm, or mechanical bowel obstruction.
   d. This approach is effective in approximately 90% of cases, and has a low rate of recurrence.

D. Colonic decompression
1. Colonoscopy for decompression is considered when distension worsens or persists and clinical condition of the patient appears compromised.
2. Overall success of colonoscopic decompression is 88%, though mortality with the procedure in the setting of colonic pseudoobstruction is as high as 2%.
3. The general value of colonoscopic decompression in colonic pseudoobstruction remains controversial; the procedure should be used selectively.

4. Surgical decompression occasionally is required when physical examination reveals progressive findings of peritoneal irritation or if imaging indicates perforation.

E. Diarrhea

1. Initial approach
   - **a.** Decrease feeding rate in tube-fed patients to improve diarrhea until the gut adapts to the osmotic and volume load.
   - **b.** Identify and correct electrolyte and other relevant metabolic abnormalities.
   - **c.** If possible, discontinue medications potentially responsible for diarrhea, including offending antibiotics in presence of *C. difficile* infection.
   - **d.** Use of devices to address fecal leakage or incontinence (e.g., rectal tube) will minimize skin complications.
2. Pharmacologic treatment
   - **a.** Antidiarrheal agents should be used cautiously in ICU patients; maintain a focus on addressing infectious or other reversible etiologies.
   - **b.** Metronidazole remains the drug of choice for *C. difficile* infection.
     - **i.** Initiate therapy in the more severely ill ICU patient (i.e., in the setting of fever, leukocytosis, colonic distension) while the toxin assay results are pending, and continue treatment for 14 days in toxin-positive patients.
     - **ii.** Response of diarrheal symptoms may take as long as 7 to 10 days.
     - **iii.** The IV administration route is required in patients intolerant of oral metronidazole.
     - **iv.** If broad spectrum systemic antibiotics cannot be discontinued, maintain metronidazole until their treatment courses are completed.
     - **v.** Relapse of *C. difficile* infection is common and typically requires retreatment.
   - **c.** Oral vancomycin is reserved for patients intolerant of, or who fail to improve with metronidazole.
   - **d.** Approaches including use of cholestyramine as a toxin-binder and probiotics may be used as adjuncts to antibiotic therapy.

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81 FULMINANT COLITIS AND TOXIC MEGACOLON

Christina Y. Ha and C. Prakash Gyawali

I. GENERAL PRINCIPLES

A. Definitions

1. Fulminant colitis
   - **a.** Fulminant colitis implies a serious progression of colonic mucosal inflammation, extending into the deeper layers of the colon.
   - **b.** Patients typically manifest severe bloody diarrhea, abdominal tenderness, and systemic toxicity.
2. Toxic megacolon
   - **a.** In the face of fulminant colitis, colonic circular muscle paralysis can precipitate *acute colonic dilatation* or *toxic megacolon,* the term used to describe this entire sequence of events.
   - **b.** Toxic megacolon is most commonly seen as a complication of ulcerative colitis but can occur with both idiopathic and infectious colitis, Crohn's disease, amebic colitis, pseudomembranous colitis, and other infections.
   - **c.** Factors associated with increased mortality include age older than 40 years, the presence of colonic perforation, and delay of surgery.
   - **d.** Early recognition and treatment of toxic megacolon can substantially lower mortality from as high as 50% (with colonic perforation) to <15%.

II. DIAGNOSIS

A. Clinical presentation

1. History
   - **a.** Toxic megacolon usually occurs in the background of extensive colitis associated with chronic inflammatory bowel disease.
   - **b.** Toxic megacolon typically occurs during of relapse of established ulcerative colitis; however, 25% to 40% of cases present during an initial attack.
   - **c.** Progressive bloody diarrhea and crampy abdominal pain are typical symptoms. A paradoxical decrease in stool frequency with passage of bloody "membranes" is an ominous sign.
   - **d.** Manipulation of the inflamed bowel with diagnostic examinations such as barium enema or colonoscopy, medications (including vigorous laxatives, antidiarrheals, anticholinergics), electrolyte imbalances, and pH disturbances can contribute to the development of the condition.
   - **e.** Corticosteroids can suppress signs of perforation and peritonitis, but whether these drugs can precipitate toxic megacolon is controversial.
2. Physical examination
   - **a.** Systemic toxicity is heralded by fever and tachycardia, and can progress to confusion, agitation, or apathy.
   - **b.** Abdominal pain and distension, with diminished bowel sounds on auscultation, are common.
   - **c.** Peritoneal signs indicate transmural inflammation or perforation, but they may be minimal or absent in elderly patients or in patients receiving corticosteroids.

B. Diagnostic tests

1. Laboratory studies
   - **a.** Laboratory tests should assess the degree of systemic toxicity, fluid and electrolyte deficits, pH disturbances, and the need for blood transfusion.
   - **b.** Leukocytosis with a significant left shift is common.
   - **c.** Anemia, hypokalemia, and hypoalbuminemia also commonly occur.
   - **d.** Stool should be sent for *Clostridium difficile* toxin and other pathogens.
2. Radiologic studies
   - **a.** Abdominal imaging (plain x-ray, computed tomography) may reveal intraperitoneal air, loss of colonic haustration, segmental or total colonic dilatation with mucosal thumbprinting, or pneumatosis cystoides coli in severe transmural disease.
   - **b.** Small bowel ileus may accompany toxic megacolon and is a poor prognostic sign for conservative medical management.
   - **c.** Discrepancies may exist between physical and radiographic findings.
3. Endoscopy
   - **a.** A limited proctoscopic examination may show extensive ulceration with friable, bleeding mucosa, or pseudomembranes. Biopsies may be obtained for histology if the etiology of the colitis is uncertain.
   - **b.** More extensive endoscopic examination is contraindicated due to the risk of perforation.

III. TREATMENT

A. General measures

1. Vigorous fluid, electrolyte, and blood replacement must be instituted early in the resuscitative effort, because hemodynamic instability is typical.
   - **a.** Hypoalbuminemia, persistently elevated acute-phase reactants, small bowel ileus, and deep colonic ulcers are poor prognostic factors for successful medical therapy.
   - **b.** Total body potassium depletion is common and needs urgent repletion; phosphate, magnesium, and calcium deficiency also should be corrected parenterally.
2. Oral intake is discontinued and nasogastric suction is employed for small bowel ileus.
3. Anticholinergic and narcotic agents should be stopped immediately.

B. Treatment of inflammatory bowel disease

1. When inflammatory bowel disease is diagnosed or suspected, use of parenteral corticosteroids or adrenocorticotropic hormone is essential.
   - **a.** Augmented doses (hydrocortisone, 100 mg every 6 hours, or methylprednisolone, 6 to 15 mg every 6 hours) should be administered. A continuous infusion may help maintain steady plasma levels.
   - **b.** Aminosalicylates (e.g., mesalamine, sulfasalazine) have no role in the treatment of fulminant colitis or toxic megacolon and should be withheld until the patient has recovered and has resumed eating.
2. Intravenous cyclosporine (2 to 4 mg/kg/24 hours in a continuous infusion) can be used when there is no improvement of severe ulcerative colitis after 7 to 10 days of intensive intravenous steroid therapy. The role of cyclosporine in toxic megacolon is controversial.
3. The role of infliximab in severe to fulminant ulcerative colitis remains to be determined.

C. Antibiotics

1. Broad spectrum antibiotics are administered intravenously once toxic megacolon or transmural inflammation is suspected and are continued until the patient stabilizes over several days to a week.
2. Broad spectrum antibiotics should be followed by pathogen-specific therapy in infectious colitis.

3. Metronidazole or vancomycin should be used if *C. difficile* infection is considered likely from the clinical presentation or proctoscopic findings.

D. Surgical indications

1. Surgery is indicated if clinical deterioration or no significant improvement occurs despite 12 to 24 hours of intensive medical management. Delay of operative therapy may promote higher mortality.
2. Failure to respond to parenteral steroids or intravenous cyclosporine after 7 days of therapy is an indication for surgery.
3. Evidence of colonic perforation, uncontrollable bleeding, and progressive dilation are unequivocal indications for emergency surgery.
4. Other indications for emergency surgery include signs of septic shock and imminent transverse colon rupture (the most dilated region in most cases of toxic megacolon), especially if the diameter is > 12 cm.
   a. The absence of acute colonic dilatation may permit delay of surgical intervention for 5 to 7 days.
   b. The potential for prolonged intensive medical management and complications must be balanced against early surgical intervention to reduce mortality and morbidity.
5. Surgical options
   a. The type of surgery performed for the treatment of fulminant colitis or toxic megacolon depends on the clinical status of the patient and the experience of the surgeon.
   b. Most surgeons prefer a limited abdominal colectomy with ileostomy, leaving the rectosigmoid as a mucous fistula, or oversewing the rectum, using a Hartmann procedure. This allows less operating room time in acutely ill patients, yet leaves the option for a subsequent sphincter-saving ileoanal anastomosis.
   c. In less acutely ill patients, a one-stage resection with ileostomy may be appropriate.

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82 HEPATIC DYSFUNCTION

Kevin M. Korenblat

I. GENERAL PRINCIPLES

A. Hepatic dysfunction in the intensive care unit (ICU) setting can present as either:
  1. Abnormalities of liver chemistries
  2. Signs and symptoms of liver disease (e.g., jaundice, synthetic dysfunction, complications of portal hypertension).

B. Hepatic metabolic processes are commonly disturbed in the setting of critical illness. These processes and their normal physiology include:
  1. Bilirubin metabolism
    a. Bilirubin is the end product of the catabolism of heme, the prosthetic moiety of hemoglobin, myoglobin, and other hemoproteins.
    b. Heme from senescent erythrocytes is the source of 80% of bilirubin.
    c. Unconjugated bilirubin is transported bound to albumin to the liver.
    d. Bilirubin is made soluble by conjugation with glucuronic acid within the hepatocytes.
    e. Conjugated bilirubin is transported into the bile canaliculus and from the bile duct into the intestine.
  2. Drug metabolism
    a. The liver is frequently a site of first-pass metabolism of medications and other xenobiotics.
    b. Metabolic processes can be categorized as phase I or phase II reactions.
      i. Oxioreductases and hydrolases catalyze phase I reactions that increase water solubility of substances and potentially generate toxic metabolites.
      ii. Transferases catalyze phase II reactions that produce biologically less active metabolites.
  3. Hemostasis
    a. The liver is the site of production of many of the vitamin K dependent coagulation factors and the anticoagulants, protein C and protein S.

II. ETIOLOGY

A. Clinical disorders commonly encountered in the critical care setting that result in hepatic dysfunction include:
  1. Ischemic hepatitis (Table 82-1)
    a. Develops in the setting of reduced liver blood flow, persistent hypotension, or severe hypoxemia.
    b. A clearly defined period of hypotension may not be identifiable.
    c. A variable degree of central vein (zone 3) necrosis and collapse are present on liver histology.
  2. Congestive hepatopathy
    a. Any process that increased hepatic vein pressures (e.g., right heart failure, pericardial disease, or pulmonary hypertension) can cause hepatic congestion.
    b. Other diagnosis that may resemble congestive hepatopathy include:
      i. Budd–Chiari syndrome (hepatic vein thrombosis)

TABLE 82-1 Causes of Ischemic Hepatitis

Hypovolemic shock
Burns
Hemorrhage
Cardiogenic shock
Hypoxemia
Obstructive sleep apnea
Sepsis
Sickle cell crisis
Hepatic artery occlusion post liver transplantation
Heat stroke

   ii. Sinusoidal obstruction syndrome (veno-occlusive disease)
   iii. Inferior vena cava thrombosis at its hepatic portion (obliterative hepatocavopathy).
- **c.** Mild elevations in serum aminotransferases, alkaline phosphatase, and bilirubin may be present.
- **d.** Long-standing hepatic venous congestion may result in cirrhosis (cardiac cirrhosis).

3. Total parenteral nutrition (TPN)-related liver injury
- **a.** Hepatic steatosis and steatohepatitis are the most common hepatic complications in adults.
- **b.** Asymptomatic elevations in serum chemistries are a common presentation of hepatic steatosis and steatohepatitis.
   i. Deficiencies of essential fatty acids (linoleic acid) or choline may contribute to the development of steatosis.
- **c.** Cholestasis is the predominant clinical finding in infants.
   i. Conditions associated with the development of cholestasis include large doses of lipid emulsion (>1 g/kg/day), short-gut syndrome, and bacterial overgrowth.
   ii. Elevations in serum bilirubin may be mild to severe.
   iii. Cholestasis, particularly in infants, may result in progression to cirrhosis and liver failure.
- **d.** Biliary sludging
   i. Biliary sludging may develop in >50% after 6 weeks of TPN
   ii. Clinical manifestations of sludging may vary from asymptomatic to cholecystitis.

4. Sepsis
- **a.** Hepatic dysfunction is common in sepsis and is a consequence of alterations in hepatic blood flow, activation of reticuloenthelial cells, and release of inflammatory cytokines.
- **b.** Elevations in serum aminotransferases two to three times the upper limits of the reference range may occur 2 to 3 days after the onset of bacteremia.
- **c.** Jaundice with elevations in serum levels of alkaline phosphatase may also occur and is known as the sepsis-induced cholestasis. These elevations may become very high, particularly in human immunodeficiency virus (HIV)-1 infected patients.

5. Drug hepatotoxicity
- **a.** There are a myriad of patterns associated with drug-induced liver injury. The pattern observed may depend on the dose and duration of drug exposure and host susceptibility factors.

b. Idiosyncratic reactions (e.g., isoniazid, phenytoin): The damage is dose independent and unpredictable.
c. Intrinsic hepatotoxicity is dose dependent, as is seen with acetaminophen and methotrexate.

III. DIAGNOSIS

A. History
1. Pertinent historical features include episodes of symptomatic hypotension, a history of right or biventricular heart failure and new medications associated with liver injury.
2. Concurrent symptoms of abdominal or right upper quadrant abdominal pain may suggest mechanical biliary obstruction.
3. The history should be scrutinized for the use of nonprescription medications, including complementary and alternative medicines.

B. Physical examination
1. Physical findings associated with congestive hepatopathy include jaundice, tender hepatomegaly, jugular venous distension, edema, and, in severe cases, ascites.

C. Laboratory studies
1. In ischemic hepatitis, serum aminotransferases tend to rise rapidly to levels 10 to 40 times the upper limits of the reference range. Increases in alkaline phosphatase and bilirubin may rise as transaminase elevations decrease.
2. Hyperbilirubinemia should be further investigated by measuring both direct-reacting (conjugated) bilirubin and indirect-reacting (unconjugated) bilirubin. The latter is calculated by subtracting the direct fraction from the total bilirubin.
a. Indirect hyperbilirubinemia may result from hemolysis, decreased hepatic clearance due to impairment of bilirubin conjugation or circumstances in which both processes occur simultaneously.
i. Gilbert's syndrome and Crigler–Najjar syndrome types I and II are inherited disorders resulting in decreased bilirubin conjugation.
ii. Gilbert's syndrome affects a 8% in the general population and is characterized by a mild, unconjugated hyperbilirubinemia to levels that rarely exceed 4 mg/dL and normal liver function.
b. Mixed direct and indirect hyperbilirubinemia or pure direct hyperbilirubinemia can be the result of heritable disorders of bilirubin canalicular excretion, liver disease, or biliary obstruction.

D. Radiographic studies
1. Sonography (with Doppler studies) of the right upper quadrant can provide information about liver architecture; diameter of intrahepatic and extrahepatic bile ducts; and flow in hepatic veins, portal vein, and hepatic artery.
2. Combined right heart and transjugular portal pressure measurements can differentiate ascites development from chronic passive congestion from hepatic cirrhosis.

IV. TREATMENT

A. Treatment of ischemic hepatitis and congestive hepatopathy is supportive in nature; emphasis should be placed on maintaining organ perfusion and improving venous return.

B. The cholestasis of sepsis is best managed by treatment of the underlying infectious process, correction of fluid and electrolyte imbalances, and introduction of enteral feeding as soon as the clinical condition permits.

C. TPN steatosis may be amenable to decreasing the carbohydrate load, decreasing total calories (25 to 40 kcal/kg/day), and cycling infusion schedule.

D. Ursodeoxycholic acid (10 to 45 mg/kg/day) orally has been of variable success in the management of TPN-related cholestasis.

E. Immediate cessation of the medication responsible for liver injury is the treatment of drug-induced liver injury.

1. The development of jaundice in drug-induced liver injury is associated with a 10% to 50% case fatality rate and should prompt consideration for liver transplantation in appropriate candidate for organ transplantation.

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83 EVALUATION AND MANAGEMENT OF LIVER FAILURE

Kevin M. Korenblat

I. GENERAL PRINCIPLES

A. Acute liver failure (ALF), also known as fulminant hepatic failure, is an uncommon condition.

B. ALF is defined as the development of encephalopathy within 24 weeks of the onset of jaundice in individuals without preexisting liver disease.

C. ALF can be subdivided into three categories based on the time from jaundice to encephalopathy:

1. Hyperacute liver failure (7 days)

2. ALF (8 to 28 days)

3. Subacute liver failure (>29 days)

D. Chronic liver failure results from continuous hepatic injury over a prolonged time period and typically is characterized by:

1. Cirrhosis of the liver

2. Portal hypertension

II. ALF

A. Etiology

1. The causes of ALF are many (Table 83-1). Identification of the cause of ALF is important for several reasons:

a. Specific treatments are available for drug and toxin overdoses.

b. Infectious causes may have implications for public health and be amenable to postexposure prophylaxis.

c. Prognosis varies with cause.

2. A specific cause for ALF may be unidentifiable in as many as 20% of adult cases.

3. Acetaminophen overdose is the most common cause of ALF in the United States.

a. Acetaminophen hepatotoxicity is frequently the consequence of the intentional overdosage at doses >140 mg/kg body weight.

b. Hepatic damage results from the formation of a toxic intermediate, *N*-acetyl-*p*-benzoquinone-imine, formed in the process of metabolism of acetaminophen through the cytochrome P-450 system when cellular glutathione levels are depleted.

c. One third of overdoses may be unintentional and occur in individuals exposed to <140 mg/kg body weight. These "therapeutic misadventures" are prone to occur in individuals at risk for either depletion of intracellular glutathione (e.g., chronic alcohol use) or in those with increased cytochrome P-450 2E1 activity (e.g., chronic anticonvulsive exposure).

B. Complications

1. Encephalopathy and cerebral edema

a. By definition, all patients with ALF have encephalopathy, with symptoms ranging from subclinical confusion (grade 1) to coma (grade 4).

b. Cerebral edema occurs in up to 80% of patients with ALF and grade 4 encephalopathy and can result in death from brain herniation.

TABLE 83-1 Causes of Acute Liver Failure

Acute viral hepatitis
Hepatitis A
Hepatitis B
Hepatitis C
Delta agent
Hepatitis E
Cytomegalovirus
Varicella zoster virus
Adenovirus
Paramyxovirus
Ebstein barr virus
Cytomegalovirus
Herpes virus
Metabolic disorders
Acute fatty liver of pregnancy
HELLP syndrome
Wilson's disease
Reye's syndrome
Cardiovascular disorders
Budd Chiari syndrome
Sinusoidal obstruction syndrome
Cardiovascular shock
Hyperthermia
Drug and toxins
Acetaminophen
Sodium valproate
Isoniazid
Halothane
Tetracycline
Fialuridine
Amanita phalloides
Cereulide
Hypoglycin

HELLP, hemolytic anemia elevated liver enzymes, and low platelet count.

2. Coagulopathy
   a. Prolongation of international normalized ratio (INR) and activated partial thromboplastin time occurs as a consequence of reduced hepatic synthesis of vitamin K-dependent coagulation factors.
   b. Overt bleeding is uncommon; the combination of severe coagulopathy and platelet dysfunction can result in bleeding from even minor mucosal lesions.
3. Cardiorespiratory complications
   a. Typical hemodynamic changes in ALF mimic distributive shock: increased cardiac output, decreased peripheral oxygen extraction, and low systemic vascular resistance.
   b. The development of arterial hypertension may herald the development of cerebral edema.
   c. Hypoxemia can result from cardiogenic shock, noncardiogenic pulmonary edema, pneumonia, or alveolar hemorrhage.

4. Renal failure
   a. Renal failure in ALF can result from acute tubular necrosis, prerenal azotemia, or the hepatorenal syndrome (HRS).
   b. In acetaminophen overdosage, acute tubular necrosis from the effect of the toxic metabolite on the kidney can be observed in as many as 75% of cases.
5. Metabolic disorders
   a. Lactic acidosis develops as the combined consequence of tissue hypoxia with increased lactate production and impaired hepatic metabolism of lactate. Renal dysfunction also may contribute.
   b. Hypoglycemia occurs as a consequence of the loss of hepatic gluconeogenesis and glycogenlysis and signifies severe hepatocellular injury.
6. Infection
   a. Patients with ALF are at risk for bacterial and fungal sepsis; impaired neutrophil and Kupffer cell function, decreased bacterial opsonization, and bacterial gut translocation and altered cytokine signaling contribute to immunologic impairment.
   b. The most common organisms isolated include *Staphylococcus, Streptococcus*, gram-negative enteric organisms, and *Candida* spp.
   c. Fungal infections occur late in the course of illness and are associated with high mortality.
   d. Signs of infection can be protean; one third of septic subjects may be afebrile and lack leukocytosis.

C. Treatment

1. General measures
   a. Early identification of the cause of ALF is critical.
   b. Laboratory assessment of hepatic synthetic function, renal function, and acid–base status provides useful prognostic information.
   c. Invasive hemodynamic monitoring is useful in the management of hemodynamic changes associated with ALF.
2. Sepsis
   a. Surveillance cultures of blood, sputum, and urine should be collected with a low threshold for the use of empiric antibacterial and/or antifungal therapy; the use of prophylactic antibiotics remains controversial.
3. Coagulopathy: The correction of the coagulopathy with fresh frozen plasma (FFP) or platelet transfusion should be reserved for active bleeding or prevention of bleeding during invasive procedures, as excessive blood product transfusion may worsen cerebral and pulmonary edema.
   a. Administration of vitamin K is safe but often ineffective.
   b. Parenteral administration of recombinant factor VIIa may reverse the coagulopathy and is helpful when there is a need to avoid the large volumes associated with FFP.
4. Encephalopathy and cerebral edema
   a. Frequent neurologic examination, including assessment of level of alertness, papillary response to light, and motor reflexes are important in the assessment of encephalopathy and intracranial pressure (ICP).
   b. Avoidance of excessive oral suctioning, and visual and auditory stimuli may prevent sudden increases in ICP; nursing with head of bed at >30 degree elevation may improve cerebral venous drainage.
   c. Placement of an ICP monitor is indicated for the identification and treatment of cerebral edema in subjects who are candidates for liver transplantation (LT) and progress beyond grade 2 encephalopathy.
      i. The cerebral perfusion pressure (CPP) is the difference between mean arterial pressure (MAP) and ICP; the goal of ICP monitoring is to maintain the CPP >50 mm Hg and ICP <15 mm Hg.
      ii. Risks of ICP monitoring include epidural and intracranial bleeding and infection.

iii. Treatment options for increased ICP include permissive hypernatremia, hyperventilation to maintain an arterial carbon dioxide partial pressure 25 to 30 mm Hg, intravenous (IV) mannitol (0.5 to 1 g/kg), and hypothermia to a core body temperature of 32°C.

5. Metabolic disorders
   a. Volume resuscitation with colloid is preferable for the treatment of prerenal azotemia.
   b. Hemodialysis may be required.
   c. Prevention of hypoglycemia is essential for preservation of neurologic function; frequent glucose monitoring and infusions of 10% to 50% dextrose solutions may be required.
6. Acetaminophen toxicity. The administration of *N*-acetylcysteine (NAC) is an effective, life-saving antidote to acetaminophen toxicity.
   a. The decision to use NAC is based on reference to a standardized treatment nomogram and requires knowledge of serum acetaminophen level and time of ingestion.
   b. NAC is most effective when given within the first 24 hours after ingestion; NAC may still be useful even when treatment is delayed >24 hours or when signs and symptoms of ALF have developed.
   c. The oral dose of NAC is 140 mg/kg loading dose followed by 17 doses of 70 mg/kg every 4 hours.
   d. NAC can be given as a continuous IV infusion and various dosing regiments are available. One dosing schedule is 150 mg/kg IV given over 15 minutes followed by 50 mg/kg IV given over 4 hours then 100 mg/kg IV given over 20 hours.
   e. Electrolyte imbalances, particularly hypophosphatemia, are common with acetaminophen-induced liver failure and correction of electrolyte disorders is essential.
7. LT: Patients with ALF without contraindications to LT should be managed at LT center.
   a. LT with a full-size orthotopic graft, partial graft, or auxiliary graft have all been used in the treatment of ALF.
   b. The King's College criteria (Table 83-2) can be useful to identify poor prognostic factors that identify individuals who require LT for survival. These criteria are subdivided into acetaminophen and nonacetaminophen causes of ALF.
   c. The admission Acute Physiology and Chronic Health Evaluation (APACHE) II system is comparable to the King's College criteria in acetaminophen-induced ALF.

III. CHRONIC LIVER FAILURE

A. Etiology

1. Chronic liver failure is the consequence of long-standing hepatic injury from multiple different causes (Table 83-3).

B. Pathophysiology

1. Chronic liver injury results in activation of stellate cells within the space of Disse; stellate cell activation leads to the deposition of collagen and, in time, histologic changes of cirrhosis.
2. The time course from injury to cirrhosis is variable and dependent on the nature of the injury, the age at which the injury occurs, environmental factors, and unknown host factors.
3. Cirrhosis also results in endothelial dysfunction and increased resistance to flow within the hepatic sinusoids. Sinusoidal hypertension and endothelial dysfunction produce portal hypertension and its three cardinal features:
   a. Increased resistance to mesenteric vascular flow.
   b. Activation of the renal-angiotensin-aldosterone system resulting in sodium and water retention and increased intravascular volume.

TABLE 83-2 King's College Criteria for Liver Transplantation for Acute Liver Failure (ALF)

Nonacetaminophen causes of ALF
INR >7.7 (irrespective of grade of encephalopathy) or
Any three of the following
Age <10 or >40
Unfavorable cause
Non-A, non-B hepatitis
Drug reaction
Wilson's disease
Period of jaundice to encephalopathy >7 days
INR >3.85
Serum biliburin > 17 mg/dL
Acetaminophen-related ALF
PH <7.3 (irrespective of grade of encephalopathy) or
All three of the following
Grade III–IV encephalopathy
INR >7.7
Serum creatinine >3.4 mg/dL

INR, international normalized ratio.

c. Increased mesenteric blood flow as a consequence of a hyperdynamic circulation.

4. Portal hypertension is responsible for the five complications of chronic liver disease:

a. Gastrointestinal bleeding
b. Ascites
c. Portosystemic encephalopathy
d. HRS
e. Pulmonary disease
i. Hepatopulmonary syndrome
ii. Portopulmonary hypertension

C. Diagnosis

1. History

a. Common symptoms include fatigue, increased abdominal girth, emotional liability, day–night sleep reversal, and poor mental concentration.

TABLE 83-3 Causes of Chronic Liver Failure

Hepatitis B
Hepatitis C
Autoimmune hepatitis
Hereditary hemochromatosis
α_1-Antitrypsin deficiency
Wilson's disease
Nonalcoholic fatty liver disease
Primary biliary cirrhosis
Primary sclerosing cholangitis
Alcohol related liver disease

2. Physical examination
   a. Common physical findings include jaundice, temporal wasting, abdominal ascites, splenomegaly, asterixis, spider angiomata, and male gynecomastia.
3. Blood tests
   a. Varying degrees of thrombocytopenia and leucopenia may be present as a consequence of hypersplenism.
   b. Anemia associated with liver disease is typically macrocytic. In advanced liver disease, a spurr cell (acanthocytes) hemolytic anemia may develop.
   c. Elevations in serum transaminases and alkaline phosphatase are variable; hypoalbuminemia and prolongation of INR are common with cirrhosis and indicate synthetic dysfunction.
   d. A mixed direct- and indirect-reacting hyperbilirubinemia is common, particularly in cholestatic liver diseases.
   e. Serum ammonia is a casual marker of encephalopathy and should not supercede physical examination findings in the diagnosis of encephalopathy.
4. Ascites studies
   a. Ascites from portal hypertension is characterized by a difference of >1.1 g/dL between serum albumin and ascites albumin; this difference is known as the serum–ascites albumin gradient (SAAG).
   b. Spontaneous bacterial peritonitis (SBP) is diagnosed when the neutrophil count in ascites fluid is >250/mL or when bacteria can be cultured from ascites.
   c. The ascites fluid should be inoculated directly into blood culture bottles to increase the potential for identification of bacteria.
   d. Peritonitis from either abdominal perforation or nonperforation abdominal abscess should be considered when multiple organisms are cultured from the ascites or the neutrophil count is high.
      i. The ascites in these conditions should fulfill two of the following criteria:
         (a) Total protein >1 g/dL.
         (b) Glucose <50 mg/dL.
         (c) LDH > upper limit of the reference range.
5. Urine studies
   a. A random urine sodium <20 mmol/L is typical but not required for the diagnosis of HRS.
   b. The severity of chronic liver disease can be graded on the basis of the Child–Turcot–Pugh classification (Table 83-4).

TABLE 83-4 Child-Pugh-Turcot Scoring System

Clinical and biochemical measurements	Points scored for increasing abnormality		
	1	2	3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Bilirubin (mg/dL)	<4	4–10	>10
International normalized ratio	<1.7	1.7–2.3	>2.3
Ascites	Absent	Slight	Moderate
Encephalopathy (grade)	None	1 and 2	3 and 4

D. Treatments

1. Ascites
   a. Dietary sodium restriction to <2 g daily is the first-line treatment of ascites.
   b. The combination of a loop diuretic (20 to 160 mg daily) and spironolactone (50 to 400 mg daily) is effective in the control of ascites in most cases; IV diuretics may precipitate renal failure.
   c. Intermittent large-volume paracentesis or transjugular intrahepatic portosystemic shunt (TIPS) are alternative measures for the control of ascites refractory to diuretics or in those intolerant of diuretics (e.g., hyponatremia, renal insufficiency).
2. SBP
   a. The antibiotics of choice in the absence of bacteriologic identification are IV third-generation cephalosporins effective against *Escherichia coli, Klebsiella* spp., *Streptococcus* spp., and *Staphylococcus* spp.
   b. IV albumin (1.5 g/kg on day 1 and 1 g/kg on day 3) can reduce rates of infection-related renal dysfunction from 30% to 10%.
   c. Repeat paracentesis 48 hours after the initiation of therapy should demonstrate a 50% drop in neutrophil count and sterile cultures.
   d. The primary prophylaxis of SBP with norfloxacin 400 mg daily has been shown to reduce the incidence of SBP, delay the development of HRS, and improve survival in subjects with advanced cirrhosis.
3. Encephalopathy
   a. Patients should be investigated for precipitants of encephalopathy including gastrointestinal hemorrhage, infection, and renal failure.
   b. Lactulose orally (15 to 60 mL every 4 to 12 hours) titrated to 3 to 4 soft bowel movements per day is effective in most cases of encephalopathy.
   c. Neomycin (500 to 1,000 mg every 8 hours) or rifaximin (400 mg every 8 hours) is also effective in control of encephalopathy.
4. Variceal hemorrhage (see Chapter 65).
5. HRS
   a. Diuretics should be discontinued.
   b. Volume replacement with IV saline 1.5 L should be given.
   c. IV albumin 25 to 75 g daily may be more effective in expanding intravascular volume.
   d. A small series suggests a role for octreotide subcutaneously (100 μg) every 8 hours, midodrine (7.5 to 12 mg) every 8 hours, and IV albumin for treatment of HRS.
6. Pulmonary disease
   a. Hepatopulmonary syndrome
      i. A disorder characterized by portal hypertension (with or without cirrhosis), arterial hypoxemia (A-a gradient >15 mm Hg on room air), and evidence of pulmonary vascular dilation.
      ii. Contrast-enhanced echocardiography typically demonstrates the delayed (>3 cardiac cycles) passage into the left heart of injected agitated saline bubbles.
      iii. Supplemental oxygen administration, exclusion of other causes of shunt, and LT are treatments.
   b. Portopulmonary hypertension
      i. A disorder characterized by liver disease causing portal hypertension, mean pulmonary arterial pressure (PAP) >25 mm Hg (at rest), mean pulmonary capillary wedge pressure <15 mm Hg, and pulmonary vascular resistance >3 Woods units.
      ii. Right heart catheterization with measurement of pulmonary artery pressure is the "gold-standard" for diagnosis.

iii. LT is contraindicated in subjects with severe pulmonary hypertension (mean PAP >50 mm Hg) but can be considered in those who respond to treatment with oral or IV vasodilator therapy.

7. LT
   a. LT in appropriately selected subjects can effectively treat all the complications of end-stage liver disease.
   b. In the United States, prioritization for LT is determined by calculation of the model for end-stage liver disease (MELD) score. A MELD calculator is available at URL: http://www.unos.org/resources/meldPeldCalculator.asp

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84 DIARRHEA

Anisa Shaker and C. Prakash Gyawali

I. GENERAL PRINCIPLES

A. Diarrhea is the most common nonhemorrhagic gastrointestinal (GI) complication in the critically ill patient, occurring in 40% to 50% of patients.

B. If untreated, it can produce serious fluid and electrolyte imbalance, skin breakdown, local infection, and difficulty with nutritional management.

C. The differential diagnosis of diarrhea in patients in the intensive care unit (ICU) differs considerably from that in the general population; investigation is focused and limited to tests safely performed in the critically ill patient.

II. ETIOLOGY

A. Iatrogenic causes

1. Medications

a. Antibiotics, especially erythromycin, ampicillin, clindamycin, cephalosporins, and azithromycin, cause iatrogenic diarrhea in 3% to 29% of patients.

i. Alterations in intestinal flora, breakdown of dietary carbohydrate products, and prokinetic effects (e.g., from erythromycin) are all postulated mechanisms for antibiotic-related diarrhea.

ii. *Clostridium difficile* toxin-induced colitis is implicated in 15% to 20% of cases. Clindamycin, penicillin, and broad-spectrum cephalosporins are commonly associated with the diagnosis.

b. Other medications implicated in the development of diarrhea include antacids (magnesium containing), magnesium and phosphorus supplements, lactulose, colchicine, digitalis, quinidine, theophylline, levothyroxine, aspirin, nonsteroidal anti-inflammatory agents, cimetidine, misoprostol, diuretics, β-blocking agents, chemotherapeutic agents, proton-pump inhibitors, and antiretroviral medications such as nelfinavir. These medications rarely cause severe diarrhea.

2. Enteral feeding

a. Diarrhea frequently occurs in enterally fed patients and is usually associated with concurrent antibiotic use.

b. Osmolarity of the enteral solution can play a role in some instances, as can bolus feeding distal to the pylorus.

c. Enteral formulas high in lactose or fat content may precipitate diarrhea in susceptible patients.

B. Diarrhea secondary to underlying diseases

1. Infections, such as cytomegalovirus (CMV), neoplastic disease in immunosuppressed patients, and neutropenic enteropathy

2. GI bleeding and ischemic bowel

3. Postsurgical diarrhea, after cholecystectomy, gastric surgery, or pancreatectomy and short bowel syndrome

4. Other causes include fecal impaction and opiate withdrawal

C. Diarrhea as a primary manifestation of the disease

1. Infectious diarrhea caused by enteric pathogens and nonenteric infectious causes such as toxic shock syndrome and Legionnaire's disease.

2. Mucosal inflammation, as in inflammatory bowel disease (IBD), graft-versus-host disease (GVHD), celiac sprue.
3. Other causes include sepsis, vasculitis, diabetic diarrhea, renal failure, and adrenal insufficiency.

III. DIAGNOSIS

A. Clinical presentation

1. History
   a. Attention to historical data (e.g., onset, duration, character, relation to antibiotic usage, or enteral feeding) may lead to prompt diagnosis and management.
   b. *C. difficile*-related diarrhea may occur up to 8 weeks after the offending antibiotic is discontinued.
   c. Abdominal pain suggests ischemia, infection, or inflammatory conditions, such as vasculitis or GVHD, depending on the clinical setting.
   d. Bloody diarrhea may indicate overt GI bleeding, ischemic colitis, or occasionally pseudomembranous colitis.
   e. Passage of frequent small-volume stools with urgency or tenesmus suggests distal colonic involvement, whereas passage of less-frequent, large-volume stools suggests a more proximal process.
2. Physical examination usually is nonspecific and is most helpful in assessing severity of volume loss.
   a. Skin rashes or mucosal ulcerations may suggest GVHD, IBD, or vasculitis; other extraintestinal manifestations of diseases associated with diarrhea should be noted.
   b. Postural hypotension suggests severe volume loss, adrenal insufficiency, autonomic neuropathy.
   c. Fever suggests possible infection, vasculitis, adrenal insufficiency, or hyperthyroidism.
   d. Abdominal tenderness may suggest infection, ischemia, or vasculitis.
   e. An abnormal rectal examination may be the only sign of a partially obstructing fecal impaction.

B. Laboratory studies

1. Hyperchloremic metabolic acidosis, hypokalemia, prerenal azotemia, and other serious electrolyte imbalances may occur with severe diarrhea. Hyperkalemia may be present with adrenal insufficiency or uremia.
2. Leukocytosis may suggest infection or ischemia, neutropenia an immunosuppressed state or sepsis.
3. A falling hematocrit may suggest GI bleeding.

C. Stool studies

1. Fresh stool specimens should be sent for *C. difficile* toxin assay and culture for enteric pathogens.
2. Immunosuppressed patients may need more extensive stool tests including ova and parasite evaluation and concentration for isolation of *Cryptosporidium, Microsporidium,* or *Isospora belli.*
3. The stool osmolar gap, which is the difference between the expected stool osmolarity (290 mOsm/kg) and the calculated stool osmolarity {([stool Na^+] + [stool K^+]) × 2} may help distinguish between osmotic and secretory causes when diarrhea is severe or protracted and no diagnosis is apparent; an elevated stool osmolar gap (>70 mOsm/L) suggests osmotic causes.
4. High-volume stool output that persists with fasting supports a secretory origin.
5. A Sudan stain for fecal fat or stool pH occasionally is helpful (pH is decreased in carbohydrate malabsorption).

D. Imaging studies

1. Plain abdominal radiographs can detect partial obstruction, perforation, or changes associated with enteritis or colitis and are recommended in the presence of pain or an abnormal abdominal examination.
2. Contrast studies including computed tomography and intestinal radiographs may be required in difficult or protracted cases, when possible.

E. Endoscopy

1. Flexible sigmoidoscopy is useful in diagnosing pseudomembranous colitis, ischemic colitis, CMV colitis, herpetic proctocolitis, or GVHD and is usually considered in the presence of bright red rectal bleeding or other indicators of distal colitis.
2. Mucosal biopsies are helpful on occasion when endoscopic findings are nonspecific or absent.

IV. TREATMENT

A. General measures

1. Correction of fluid and electrolyte imbalance needs immediate attention.
2. Central venous access and monitoring may be necessary in patients with severe fluid loss.
3. Proper patient hygiene and skin care should be maintained, and patient isolation with enteric precautions should be instituted when indicated.
4. Iatrogenic causes of diarrhea are corrected by withdrawal of the offending medications.
5. Enteral feedings suspected of causing diarrhea should be reduced in volume, or temporarily discontinued. Some suggest an advantage of continuous infusion over bolus infusions. There is also evidence to suggest that the addition of fiber to continuous infusions decreases the incidence of diarrhea in tube-fed patients.
6. A change in formula to an elemental diet may be indicated in patients with short bowel syndrome, pancreatic insufficiency, radiation enteritis, fistula, or IBD.
7. In severe cases, total parenteral nutrition may be necessary as a temporary measure.

B. Specific treatment

1. Specific- or pathogen-related treatment should be administered whenever possible in both immunocompromised and immunocompetent hosts.
2. *C. difficile* colitis.
   a. If *C. difficile*-related diarrhea is suspected, the offending antibiotic should be discontinued when possible; spontaneous improvement often results from this measure alone; 15% to 23% of patients have symptom resolution within 48 to 72 hours of stopping the offending agent. Unfortunately, this option is often not possible in the intensive care setting as it is not possible to predict which patients will respond with spontaneous resolution with simple cessation of the antibiotic and delaying therapy increases the period of contagion.
   b. Earlier studies indicated that oral metronidazole (250 to 500 mg three times daily) was as effective as oral vancomycin (125 to 500 mg four times daily), yet was less expensive and did not contribute to selection for vancomycin-resistant bacteria. In moderate to severe cases of *C. difficile* colitis, however, more recent studies have suggested that oral metronidazole may be inferior to vancomycin.
   c. Vancomycin is typically reserved for treatment failures and severe cases. However, in toxic megacolon, intravenous metronidazole should be administered.
   d. Response is expected within 24 to 48 hours with improvement in diarrhea, pain, fever, and leukocytosis. Treatment should be continued for 7 to 14 days.

e. As many as 24% patients have a relapse and in these situations longer and multiple courses of treatment are often required.
f. Anion exchange resins such as cholestyramine or colestipol are reportedly useful as adjunctive measures in mild cases or in relapses. These agents can bind vancomycin making their use less desirable.
g. Antimotility agents should not be used, because they may lengthen the course of the illness.

C. Symptomatic measures

1. When a cause of diarrhea is not found, palliative treatment lessens fluid losses, patient discomfort, and morbidity.
2. Antimotility agents may decrease the frequency and severity of diarrhea, but monitoring for complications is required (e.g., central nervous system side effects, gut hypomotility).
   a. These drugs include loperamide (4 mg initially, and up to 16 mg/day), diphenoxylate with atropine (20 mg of diphenoxylate four times daily initially, then decrease and titrate to symptoms), and deodorized tincture of opium (6 to 12 gtt two to four times daily).
   b. Octreotide can be used for palliation of diarrhea in patients with acquired immunodeficiency syndrome, GVHD, hormone-producing tumors, and other causes of secretory diarrhea.

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SEVERE AND COMPLICATED BILIARY TRACT DISEASE

85

Somal S. Shah and Riad Azar

I. GENERAL PRINCIPLES

A. A wide spectrum of biliary tract diseases are seen in the intensive care unit (ICU).

B. Methods used to access the biliary tree for diagnosis and therapy are:

1. Endoscopic cannulation of the ampulla in the duodenum during endoscopic retrograde cholangiopancreatography (ERCP).
2. Percutaneous transhepatic cholangiography (PTC) or percutaneous drainage of the gallbladder (cholecystostomy tube).
3. Operative management through the peritoneal cavity.

II. ETIOLOGY

A. Cholangitis

1. Typically occurs in patients with bile duct stones or strictures and with recent manipulation of the biliary tree.
2. Cholangitis occurs when biliary obstruction promotes bacterial translocation to the biliary tract.
3. The clinical manifestations include fever, abdominal pain, and jaundice (Charcot's triad), but can also include mental status changes and hypotension.
4. Laboratory abnormalities include elevated bilirubin, alkaline phosphatase, and white cell count.
5. Blood cultures are often positive for gram-negative bacteria and anaerobes.

B. Biliary obstruction

1. Common causes include gallstone disease and tumors; other causes are listed in Table 85-1.
2. When the obstruction is painless, the most likely diagnosis is a neoplasm.

C. Bile leak

1. Leakage of bile into the peritoneal cavity space can result from cholecystectomy, hepatic resection, liver transplantation, trauma, or percutaneous biliary manipulations.
2. The resultant bile peritonitis produces dramatic pain, leukocytosis, and fever.

D. Acalculous cholecystitis

1. Typically seen in critically ill patients and can result in significant morbidity and mortality.
2. Symptoms may be masked by the underlying clinical situation.

E. Gallstone pancreatitis

1. Evidence suggests that stone impaction at the ampulla leads to pancreatitis.
2. Alternatively, gallstones may allow the reflux of bile into the pancreatic duct after passage across the sphincter of Oddi.

III. DIAGNOSIS

A. Clinical assessment

1. Physical examination may reveal icterus, ascites, or focal liver tenderness.
2. Findings range from acute abdomen to fever.

TABLE 85-1 Causes of Biliary Obstruction

Intrinsic lesions
Gallstones
Cholangiocarcinoma
Benign stricture
Sclerosing cholangitis
Periarteritis nodosa
Ampullary stenosis
Parasites
Extrinsic lesions
Pancreatic carcinoma
Metastatic carcinoma
Pancreatitis
Pancreatic pseudocyst
Visceral artery aneurysm
Lymphadenopathy
Choledochal cyst
Hepatic cyst or cysts
Duodenal diverticulum
Iatrogenic lesions
Postoperative stricture
Hepatic artery infusion chemotherapy

B. Laboratory tests
1. In acutely ill patients, bilirubin elevation can result from sepsis or hemolysis.
2. Alkaline phosphatase can be elevated from other tissues including bone; concomitant elevation of γ-glutamyl transferase helps confirm hepatobiliary origin.
3. Although serum transaminase elevations are the hallmark of hepatocellular injury, elevated levels also can be seen with biliary disease.
4. Patients with severe biliary disease can have normal laboratory values.

C. Plain radiographs
1. Plain abdominal radiographs are usually nonspecific.
2. Air in the biliary tree can result from a prior sphincterotomy, biliary–enteric surgical anastomosis, and infection with gas-producing organisms.
3. Gas within the gallbladder wall is one sign of acute cholecystitis.

D. Ultrasonography
1. Ultrasonography can be performed at the bedside.
2. It is sensitive for detecting gallstones and cholecystitis.
3. It is very useful to evaluate for bile duct dilatation, which could suggest a distal obstruction.

E. Radionuclide scanning
1. ^{99m}Technetium (^{99m}Tc) hepatic iminodiacetic acid (HIDA) scans yield both physiologic and structural information regarding the biliary tract.
2. Filling of the gallbladder confirms patency of the cystic duct to exclude acute cholecystitis.
3. Its role is limited in patients with poor hepatocellular function, complete biliary obstruction, or cholangitis, each of which prevents adequate uptake and excretion of the radiopharmaceutical into the biliary tree.
4. Evidence of radio tracer in the abdominal cavity is diagnostic of bile leaks.

F. Computed tomography (CT) and magnetic resonance imaging (MRI)
1. CT is highly accurate for the detection of the level and cause of biliary obstruction.
2. CT can accurately diagnose large collections of bile (bilomas) around the biliary tree.
3. In patients with normal renal function, an arterial and venous study with thin cuts through the pancreas is better for defining pancreatic lesions.
4. MRI techniques that incorporate cholangiopancreatography (MRCP) provide highly useful images of the hepatobiliary system.
5. These studies are impractical in many critically ill patients who are too sick for transport.

G. ERCP and PTC
1. Both can be performed emergently when necessary, for both diagnostic and therapeutic uses.

IV. TREATMENT

A. Cholangitis and biliary obstruction
1. If cholangitis is suspected, antibiotics should be started promptly; extended-spectrum penicillins or fourth-generation cephalosporins are usually recommended.
2. Aggressive supportive measures include intravenous (IV) fluids and pressors.
3. Patients should undergo emergent ERCP with sphincterotomy and biliary stenting to achieve biliary decompression.

B. Bile leaks
1. ERCP for biliary decompression and stent placement should be performed immediately once a bile leak is suspected or identified.
   a. Placing biliary stents enables the bile to preferentially flow into the duodenum, allowing the leak site to heal.
2. Broad spectrum antibiotics protect against sepsis.

C. Acute cholecystitis
1. IV fluids, antibiotics, and nasogastric suction are the initial therapies.
2. Percutaneous cholecystostomy is an alternative in patients who are too unstable for operative cholecystectomy.

D. Acute gallstone pancreatitis
1. Most patients will improve with conservative therapy; early ERCP may be indicated for removal of retained common bile duct stones.
2. Definitive therapy with elective cholecystectomy is indicated to prevent recurrences.

V. COMPLICATIONS

A. Cholangitis and biliary obstruction
1. If ERCP is unsuccessful, PTC should be performed.

B. Bile leaks
1. Bilomas usually require percutaneous drainage in addition to an ERCP.

C. Cholecystitis
1. Complications of acute cholecystitis include gallbladder perforation and emphysematous cholecystitis.
2. The cholecystostomy drainage catheter is left in place until acute symptoms resolve.
3. In patients with severe comorbid medical conditions, the tube may simply be removed with or without percutaneous stone extraction.

D. Acute gallstone pancreatitis
1. Tube feedings or total parenteral nutrition is required if symptoms do not resolve within 7 days.

2. Pseudocysts develop in 15% of patients with pancreatitis and, if they persist, some will need drainage.
3. Bacterial colonization of a pseudocyst can lead to abscess formation.
4. A symptomatic pseudocyst can be drained endoscopically, surgically or through percutaneous drainage.

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86 THE BASIC PRINCIPLES OF NUTRITIONAL SUPPORT IN THE INTENSIVE CARE UNIT

Dominic J. Nompleggi

I. GENERAL PRINCIPLES

A. Severe protein-calorie malnutrition, unfortunately, is common in critically ill patients.

B. In all patients with serious illness, appropriate measures to avoid substrate deficiency and replete nutrient deficiency are best recognized promptly, and appropriate therapy instituted without delay.

II. PATHOGENESIS

A. Malnutrition can be present on admission or develop as a result of the metabolic response to injury.

B. Changes in metabolic response are difficult to assess.

C. Assessment includes evaluation of clinical, anthropometric, chemical, and immunologic parameters reflecting altered body composition.

III. DIAGNOSIS

A. General assessment

1. The purpose of nutritional assessment is to identify the type and degree of malnutrition to devise a rational approach to treatment.
2. Percentage weight loss in the last 6 months, serum albumin level, and total lymphocyte count are commonly used measures to assess nutritional status.
3. Weight loss of 20% to 30% suggests moderate caloric malnutrition while 30% or greater indicates severe protein-calorie malnutrition; loss of 10% or more over a short period of time also is considered clinically important.
4. The general appearance of the patient, with emphasis on evidence of temporal, upper body, and upper extremity wasting of skeletal muscle mass, provides a quick, inexpensive, and clinically useful measure of nutritional status.

B. Laboratory assessment

1. Serum albumin measures visceral protein stores; it is a useful and readily available indicator of kwashiorkor (protein malnutrition).
2. Serum albumin is not a sensitive indicator of malnutrition in patients in the intensive care unit (ICU) because its synthesis is influenced by numerous factors other than nutritional status (e.g., protein losing states, hepatic function, and acute infection or inflammation). Serum prealbumin is a more sensitive marker of adequate protein delivery.
3. Malnutrition is closely correlated with alterations in immune response as measured by skin test reactivity and total lymphocyte count.
4. A total lymphocyte count $<1{,}000/mm^3$ is indicative of altered immune function and is associated with decreased skin test reactivity.
5. Loss of skin test reactivity is a measure of impaired cellular immunity, which consistently has been found to be associated with malnutrition.

C. Subjective global assessment (SGA)

1. SGA evaluates nutritional status using clinical parameters such as history, physical findings, and symptoms.
2. The SGA determines whether:
   a. Nutritional assimilation has been restricted because of decreased food intake, maldigestion, or malabsorption

b. Any effects of malnutrition on organ function and body composition have occurred
c. The patient's disease process influences nutrient requirements

3. In hospitalized patients, SGA has been shown to provide reliable and reproducible results with > 80% agreement when blinded observers assessed the same patient.

IV. TREATMENT

A. Critical depletion of lean tissue can occur after 14 days of starvation in severely catabolic patients.
B. Nutrition support should be instituted within 24 hours in malnourished patients or those not expected to resume oral feeding within 7 days.

V. ENTERAL FEEDING

A. Enteral feeding reduces infection and preserves gut integrity, barrier, and immune function.
B. It is the preferred route of nutrient administration.
C. Current recommendations support initiation of enteral nutrition as soon as possible after resuscitation.
D. The only contraindication is a nonfunctioning gut.
E. Enteral feeding technique:
1. Initiation of enteral feeding distal to the pylorus does not require active bowel sounds or the passage of flatus or stool.
2. Small bowel feedings can be given in the presence of mild or resolving pancreatitis and low output enterocutaneous fistulas (<500 mL/day).
3. Worsening abdominal distension or diarrhea in excess of 1,000 mL/day requires a medical evaluation; if distension is present, enteral feedings should be discontinued.
4. If no infectious cause is found for the diarrhea, antidiarrheals can be administered and feedings continued.
5. Standard isotonic polymeric formulations can meet most patients' nutritional needs.
6. Elemental formulas should be reserved for patients with severe small bowel absorptive dysfunction; specialty formulations have a limited clinical role.
7. Macronutrient goals resemble those for parenteral nutrition (see subsequent text): protein requirements should be provided first and dictate the total daily volume needed; remaining macronutrients are in fixed proportions, depending on the formulation selected.

VI. PARENTERAL FEEDING

A. Parenteral nutrient administration is recommended when the gastrointestinal tract is nonfunctional or inaccessible or enteral feeding is insufficient.
B. Parenteral nutrient admixtures are not as nutritionally complete as enteral formulations, but nutritional goals are achieved more often with the former than the latter.
C. Macronutrients:
1. Energy adequate to promote anabolic functions is essential.
2. Caloric requirements should be based on the usual body weight; a requirement of 25 kcal/kg is adequate for most patients.
3. The protein requirement (1.2–1.5 g/kg/day) should be calculated first to assure protein-sparing and maintain lean tissue mass.
4. Next, approximately 15% to 30% of total calories should be given as fat.
5. The remaining calories should be given as a carbohydrate.
D. Micronutrients (vitamins, trace minerals) and fluid:
1. Potassium, magnesium, phosphate, and zinc should be provided in amounts necessary to maintain normal serum levels.

2. Absolute requirements for vitamins, mineral, and trace elements have not yet been determined.
3. Normal serum and blood levels of vitamins have been established, but can vary with the laboratory in which the measurement is obtained.
4. In general, patients should receive fluid at 25 mL/kg body weight to avoid dehydration.
5. Tight glycemic control may reduce mortality

VII. SUMMARY

A. Need for nutritional support is determined by the balance between endogenous energy reserves of the body and the severity of stress.
B. Best clinical markers of stress are fever, leukocytosis, hypoalbuminemia, and a negative nitrogen balance.
C. Enteral route should be used to provide nutrients if the gut is functioning.
D. Provision of energy and protein should be tailored to the individual patient.
E. During illness, hypoalbuminemia should be viewed as a marker of injury and not as an indicator of impaired nutrition; normal concentrations are unattainable in many critically ill patients because of large fluid shifts and acute-phase protein synthesis.
F. Goal of short-term nutritional support is to optimize the body's metabolic response to injury by improving immune function, reducing inflammation, maintaining gut barrier function, and minimizing nitrogen deficit.

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Endocrine Problems in the Intensive Care Unit

VII

MANAGEMENT OF HYPERGLYCEMIA IN CRITICALLY ILL PATIENTS

87

Michael J. Thompson, Samir Malkani, Aldo A. Rossini, and John P. Mordes

I. GENERAL PRINCIPLES. Hyperglycemia is a common problem in the intensive care unit (ICU). Patients in the ICU with diabetes are particularly vulnerable to the adverse metabolic consequences of stress. Hyperglycemia predisposes to cardiovascular, renal, and infectious complications. Often, preexisting diabetes itself is the primary problem, as in ketoacidosis and hyperosmolar coma. Adequate control of hyperglycemia minimizes the risk of iatrogenic metabolic complications, cardiovascular complications, poor wound healing, and infection.

II. PATHOPHYSIOLOGY

A. Normal glycemic control. Blood glucose concentration is tightly regulated, generally ranging only between 60 and 120 mg/dL. Regulation depends in large measure on the presence of appropriate quantities of circulating insulin. Even in the fasting state, insulin continues to regulate the rates of glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis. The key to the ICU management of hyperglycemia is achieving a consistent and appropriate degree of patient "insulinization" at all times.

B. Diabetes classification system. Diabetes mellitus is not one disease but a group of syndromes sharing the common feature of hyperglycemia. The most common forms are type 1 and type 2.

1. Type 1 diabetes. Formerly designated insulin-dependent, ketosis-prone, and juvenile diabetes, it results from autoimmune destruction of insulin-producing pancreatic β cells. These patients are almost totally deficient in insulin and require exogenous insulin for survival. Discontinuation of insulin therapy, even for relatively brief intervals, can lead to serious metabolic complications.
2. Type 2 diabetes. Formerly designated noninsulin dependent or adult onset diabetes, it results from relative, rather than absolute, deficiency of insulin. It involves defects in both insulin action and insulin secretion. Some patients with type 2 diabetes can be treated with diet or oral agents, but others need insulin to control hyperglycemia. Infection, metabolic stress, and many medications commonly used in the ICU exacerbate type 2 diabetes and can lead to ketoacidosis, hyperosmolar coma, or lactic acidosis.
3. Gestational diabetes.
4. Other specific types. Occasional cases of diabetes result from pancreatectomy, genetic defects of β cells, defective insulin action, and many other factors.
5. Drug- or chemical-induced. (e.g., pressors, glucocorticoids).

III. DIAGNOSIS

A. Diagnostic criteria. All acutely ill patients should have blood glucose concentration measured on admission to the ICU and regularly throughout their stay. Seriously ill patients with hyperglycemia may have a diagnosis of preexisting diabetes, but the majority will not. Diabetes first recognized in the ICU may or may not persist after the patient recovers. Hyperglycemic ICU patients should be evaluated for persistence of impaired glucose tolerance after recovery.

B. Assessment of severity. This chapter describes the routine management of hyperglycemia in the ICU when neither ketoacidosis nor hyperosmolar coma is present. Diabetic ketoacidosis and hyperosmolar coma require urgent treatment (see Chapter 88).

1. Is the patient ketoacidotic? This is determined on the basis of history, physical findings, the presence of an anion gap acidosis, and ketonuria or ketonemia. For management, see Chapter 88.
2. Is the patient hyperosmolar? In the presence of extreme hyperglycemia, osmolarity should be measured or calculated. Hyperosmolarity is usually associated with severe dehydration and obtundation. For management, see Chapter 88.
3. Is the patient absolutely insulin dependent? Patients with type 1 diabetes, surgical pancreatectomy, and certain other pancreatic diseases require continuous insulin treatment at all times to avoid ketoacidosis.

C. Evaluation of the patient in the ICU with preexisting diabetes

1. Assess cardiac function and peripheral circulation.
2. Occult infections. May include osteomyelitis, cellulitis, cholecystitis, gingivitis, sinusitis, cystitis, or pyelonephritis.
3. Hypertriglyceridemia may cause pancreatitis.
4. Diabetic eye disease. Not a contraindication to anticoagulation, but its severity should be documented before instituting therapy.
5. Assessment of kidney function should include a test for proteinuria.
6. Autonomic neuropathy. Predisposes to orthostasis, tachyarrhythmias, and intestinal motility disorders; should be suspected in patients with a sluggish pupillary response to light or absence of heart rate deceleration during exhalation or Valsalva (as detected by R-R interval change on an electrocardiogram).

7. Poorly controlled diabetes may imply poor nutrition. Patients with uncontrolled diabetes may be thiamine deficient.

D. Bedside blood glucose monitoring. The accuracy of handheld glucose measurement devices is influenced by hematocrit, creatinine concentration, plasma protein concentration, and arterial Po_2 They are also less accurate at both extremes of the glucose range. Extremely elevated blood glucose concentrations may be above the range accurately measured by the bedside monitor and should be verified with a serum sample sent to the laboratory. In general, therapy should not be delayed by waiting for confirmatory laboratory glucose results.

IV. TREATMENT

A. Why control hyperglycemia in the ICU? Hyperglycemia predisposes to disturbances in electrolyte concentrations, is known to impair innate and adaptive immunity, and is associated with endothelial dysfunction and poor wound healing. Even minimal hyperglycemia (plasma glucose concentration >110 mg/dL) is predictive of increased in-hospital mortality and the risk of congestive heart failure in patients with acute myocardial infarction.

B. Target blood glucose concentration. While there is general agreement that hyperglycemia in the ICU should be controlled, the ideal level of glycemic control remains controversial. In one study performed in a surgical ICU, intensive insulin therapy with a target plasma glucose concentration <110 mg/dL appeared to reduce in-hospital mortality and morbidity. However, several randomized controlled trials in various ICU settings have not documented a comparable benefit and a consensus target has not been agreed upon. It is hoped that several ongoing clinical trials will provide evidence-based recommendations and goals in the near future. Pending the outcome of those studies, we suggest the following guidelines for ICU hyperglycemia management. As implemented at our institution, we recommend:

1. All critically ill or surgical patients with a plasma glucose concentration >140 mg/dL be treated to lower that concentration.
2. Thereafter, plasma glucose concentration should be maintained as close to the normal range as is safely possible. At our institution the target range is 80 to 140 mg/dL.
3. In general, initial management of hyperglycemia in patients in the ICU should be based on intravenous insulin infusion therapy.
4. Avoid glucose concentrations <80 mg/dL because they pose the hazard of hypoglycemia and might contribute to mortality.
5. Institution of an intensive insulin program of this kind requires strong institutional commitment. It is a team effort in which physicians, nurses, pharmacy, and administrative staff must all participate and agree on both the targets and the means by which they can be achieved with local resources.

C. Intravenous insulin infusion therapy. The insulin infusion algorithm that we recommend was developed by a multidisciplinary team to achieve a target blood glucose concentration of 80 to 140 mg/dL. It is shown in Table 87-1. This protocol determines the rate of infusion of regular insulin based on *both* the absolute value *and* the rate of change of the plasma glucose concentration. Glucose concentration is checked hourly until it is in the target range and every 2 hours thereafter. Rapid acting semisynthetic insulin can be used when regular insulin is unavailable.

1. Adjustment of the insulin infusion rate

a. The insulin requirement for a given patient in the ICU will depend in large part on the degree of insulin resistance induced by the primary illness and its treatment and by the patient's body mass index. An *escalating* insulin requirement is a sensitive indicator of increasing

TABLE 87-1 Guidelines for the Titration of Insulin Infusions in the Intensive Care Units (ICUs)

Change in glucose concentration since last measurement					
Current glucose (mg/dL)	**Rising or unchanged**	**Falling *slowly* (change ≥ 10%)**	**Falling *moderately* (change >10%)**	**Falling *rapidly* (see subsequent text)**	
>350	↑ by 4 units/h	↑ by 2 units/h	↑ by 2 units/h	*If BG has fallen by ≥100 mg/dL*	Notify MD/LIP and decrease insulin rate by 50%, resume glucose measurements at least every 1 h
251–350	↑ by 3 units/h	↑ by 2 units/h	↑ by 2 units/h		
201–250	↑ by 2 units/h	↑ by 1 unit/h	↑ by 1 unit/h		
161–200	↑ by 2 unit/h	↑ by 1 unit/h	↑ by 0.5 unit/h	*If BG has fallen by ≥75 mg/dL*	
141–160	↑ by 1 unit/h	↑ by 0.5 unit/h	↑ by 0.5 unit/h		
121–140	↑ by 0.5 unit/h	No change	No change	*If BG has fallen by ≥50 mg/dL*	
80–120	No change	↓ by 0.5 unit/h	↓ by 0.5 unit/h		
70–79	↓ by 1 unit/h		↓ by 1 unit/h	*If BG has fallen by ≥50 mg/dL*	Stop infusion; resume glucose measurements at least every 1 h. Resume insulin at 50% of previous rate when glucose rises above 100 mg/dL
Notify MD/LIP if glucose <70 mg/dL					
40–69	Stop infusion; give 12.5 g D50W (½ amp); resume glucose measurements at least every 1 h Resume insulin at 50% of previous rate when glucose rises above 100 mg/dL				
<40	Stop infusion; give 25 g D50W (1 amp); resume glucose measurements at least every 1 h Resume insulin at 50% of previous rate when glucose rises above 100 mg/dL				

Protocol used at UMass Memorial Healthcare, Worcester, MA. Regular insulin is preferred. Note that "Stop infusion" instructions are accompanied by instructions on infusion resumption. The "Stop infusion" instruction is not an instruction to discontinue the infusion.
BG, blood glucose; LIP, licensed provider; D50W, dextrose 50% in water.

insulin resistance and requires careful reevaluation of the patient's overall metabolic status. We recommend that insulin infusion rates not be increased beyond 20 units/hour (480 U/day) without first decreasing any exogenous carbohydrate loads, especially in patients who are obese. A *decreasing* insulin requirement in the ICU usually represents an increase in insulin sensitivity that can be due to improvement in underlying illnesses, changes in medication (particularly glucocorticoids and pressors), and reductions in enteral or parenteral feeding. Occasionally, hepatic failure, renal failure, or adrenal insufficiency leads to a decreased insulin requirement.

b. When plasma glucose concentration approaches 80 mg/dL, a common response is to discontinue insulin completely. For patients with type 1 diabetes, this is always inappropriate because discontinuation of insulin can precipitate hyperglycemia and ketosis within hours. The proper response is to reduce the insulin infusion rate to 1 or even 0.5 units/hour and, if necessary, to give glucose in the form of dextrose 5% in water (D5 W) (Table 87-1). We recommend the same strategy for most other hyperglycemic patients in the ICU as well, namely, treat hyperglycemia with continuous intravenous insulin until the patient demonstrates clear improvement in overall clinical status and stability of glycemic control.

c. When plasma glucose concentration is <70 mg/dL or <80 mg/dL and has been falling rapidly, it is appropriate to stop the insulin infusion ***but only temporarily***. As shown in Table 87-1, the protocol must have built-in criteria to guide the resumption of the infusion. This is particularly critical for patients with type 1 diabetes.

2. Transition to other forms of therapy

a. When a patient in the ICU has improved to such an extent that continuous insulin infusion is no longer needed, subsequent therapy will depend on the cause of the hyperglycemia. All patients with type 1 and most with type 2 diabetes will transition to subcutaneous insulin. In nearly all cases, this will include an intermediate- or long-acting insulin.

b. It is not uncommon for glycemic control to deteriorate during the transition from intravenous to subcutaneous insulin therapy. It is essential that the intravenous infusion of regular insulin be continued for 2 to 3 hours after the first subcutaneous insulin is injected. The initial dose of subcutaneous intermediate or long-acting insulin can be estimated from the intravenous insulin requirement. We recommend basing the initial dose of subcutaneous insulin on the average hourly insulin infusion requirement during the 6 hours preceding the transition.

c. Patients who are eating should also receive a dose of rapid acting insulin (i.e., lispro, aspart, or glulisine) before meals to avoid postprandial hyperglycemia. Selected patients who are recovering rapidly and desire to do so can resume use of personal insulin infusion pumps while transitioning out of the ICU.

D. Misuse of oral agents and sliding scale insulin in the ICU

1. Oral agents. Oral hypoglycemic agents should not be used in the ICU. In particular, metformin (Glucophage) should be discontinued because of the risk of lactic acidosis and thiazolidinediones (Actos, Avandia) should be discontinued because of the increased risk of congestive heart failure.

2. "Sliding scale" insulin. Periodic boluses of insulin that are not part of an overall ICU glucose management protocol amplify the risk of both hypoglycemia and hyperglycemia and should not be used as the primary tool for managing hyperglycemia in the critically ill patient.

V. COMPLICATIONS

A. Surgery in the critically ill patient with diabetes. Treatment of hyperglycemia patients who are being prepared for urgent surgery in the emergency department can be initiated with either subcutaneous short-acting insulin or, preferably, a continuous insulin infusion, as described earlier. Critically ill patients with hyperglycemia should be treated with an insulin infusion during surgery. The patient in the ICU with hyperglycemia who requires surgery should be sent to the operating room or procedure suite with infusions of both insulin and 5% dextrose in water or half-normal saline. Frequent monitoring of blood glucose is essential. Anesthetic agents may exacerbate hyperglycemia. Regional and local anesthetics are preferable when appropriate.

B. Hyperalimentation and hyperglycemia. If insulin is added to parenteral nutrition formulations, the dose should be limited to <50% of the patient's anticipated total insulin requirement for the duration of the feeding. Any additional insulin should be administered by intravenous infusion or subcutaneous injection. This tactic allows rapid adjustment of the insulin dose to meet changing metabolic needs. If an obese patient receiving hyperalimentation develops severe hyperglycemia and a large insulin requirement, consideration should be given to reducing the amount of carbohydrate administered.

1. Pearls: key points and pitfalls

a. Avoid sliding scales! There is no role for arbitrary insulin boluses given only after hyperglycemia has occurred. They do not take into account the rapid changes in status that can occur in the critically ill and usually lead to fluctuating control.

b. Never completely discontinue insulin in patients with type 1 diabetes. Patients with type 1 diabetes whose insulin is withheld until hyperglycemia occurs can quickly become ketoacidotic.

c. Episodic caloric loads are difficult to manage with intravenous insulin. Medications should be mixed in dextrose-free solutions to the extent possible.

d. Patients who are eating: should receive subcutaneous rapid acting insulin to avoid postprandial hyperglycemia.

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DIABETIC COMAS: KETOACIDOSIS AND HYPEROSMOLAR SYNDROME

Samir Malkani, Michael Thompson, John P. Mordes, and Aldo A. Rossini

88

I. GENERAL PRINCIPLES

A. The four "diabetic emergencies"

1. Four conditions related to severely disordered glucose metabolism and often associated with stupor and coma are:
   - **a.** Diabetic ketoacidosis (DKA)
   - **b.** Hyperglycemic hyperosmolar syndrome (HHS)
   - **c.** Alcoholic ketoacidosis
   - **d.** Hypoglycemia
2. These four diagnoses should be considered during the evaluation of any patient with altered mental status.

II. DIABETIC KETOACIDOSIS

A. Pathophysiology.

DKA is caused by the total or near-total absence of circulating insulin. Without insulin, glucose cannot enter most types of cells. Glucagon secretion is increased and hepatic glucose production increases without restraint. These events lead to severe hyperglycemia. Stress-responsive hormones accelerate catabolism. Lipolysis accelerates and large quantities of free fatty acids are metabolized to ketone bodies. The large amounts of ketones generated result in accumulation of hydrogen ions. Hyperglycemia causes an osmotic diuresis resulting in a loss of free water and depletion of electrolytes.

B. Diagnosis

1. **Clinical presentation.** Any person with diabetes can develop ketoacidosis. It most often occurs in patients with type 1 diabetes who have either omitted their insulin or have an intercurrent infection. It occurs in patients with type 2 diabetes who have intercurrent severe infection, trauma, or myocardial infarction. Among individuals with type 2 diabetes, African Americans and ethnic minorities seem to be more prone to DKA than are whites. Most patients in DKA are lethargic; approximately 10% are comatose. Postural hypotension is common, but shock is rare. Patients have rapid, deep (Kussmaul) respiration, and their breath has a sweet, fruity odor. Patients in DKA are not febrile unless some other intercurrent disorder is present. The rare cases of hypothermia in DKA are associated with sepsis. Abdominal pain is common and may be accompanied by guarding and diminished bowel sounds. Patients with DKA may be nauseated and vomit guaiac-positive, coffee grounds–like material. Pleuritic chest pain may be present. Hepatic enlargement with fatty infiltration may occur.
2. **Laboratory**
   - **a. Plasma glucose.** Plasma glucose concentration in the range of 400 to 800 mg/dL is typical in DKA. Occasional younger patients present with a blood glucose concentration <300 mg/dL.
   - **b. Electrolytes**
     - **i. Sodium.** Serum sodium concentration can vary; decreases occur due to osmotic diuresis and dilution by the osmotic effect of large amounts of extracellular glucose. For every 100 mg increase in

glucose the dilutional effect accounts for a 1.6 mEq/L drop in sodium concentration. The "corrected" serum sodium in a patient with a measured concentration of 135 mEq/L and a glucose concentration of 600 mg/dL is 1.6 × (600 − 100) + 135, or 143 mEq/L. Hypertriglyceridemia can cause a factitiously low sodium concentration.

ii. **Potassium.** All patients with DKA are at risk for life-threatening hypokalemia during treatment. This is true despite the fact that the serum potassium concentration is usually elevated at presentation. A total body potassium deficit in the range of 200 to 700 mEq is typical. A normal or low concentration of potassium early in ketoacidosis often signals a very severe potassium deficit.

iii. **Phosphorus.** Elevated serum phosphate concentrations are common in untreated DKA. After therapy, there is a precipitous decline to subnormal levels.

c. **Anion gap acidosis.** Arterial blood gas and pH measurements are essential in the management of severe DKA. Uncomplicated DKA presents as an anion gap acidosis. More chronic ketoacidotic states may be associated with hyperchloremic acidosis, probably as a consequence of the loss of neutralized ketone body salts. Rare cases of DKA are complicated by intercurrent metabolic alkalosis, most often from severe vomiting.

d. **Plasma ketones.** Plasma ketone levels do not necessarily reflect the full extent of ketogenesis because the nitroprusside test measures only acetoacetate (AcAc) and acetone. β-Hydroxybutyrate (BOHB), a "ketone body" produced from AcAc, is actually an acid alcohol and is not measured by this test. Normally, the BOHB:AcAc ratio is 3:1, but acidosis increases the ratio to 6:1 or even 12:1 as pH decreases. Ketone body measurements may initially rise due to conversion of BOHB back to AcAc. BOHB levels can be estimated by some laboratories. Clearance occurs slowly; measurement more often than every 12 hours is generally unnecessary.

e. **Mixed anion gap acidosis.** A mixed anion gap acidosis may occur in patients with DKA. This can be due, for example, to intercurrent lactic acidosis or salicylate intoxication. To determine whether a nonketone body anion is complicating DKA, multiply the highest positive ketone dilution by 0.1 mM/L to estimate AcAc concentration. Multiply the AcAc concentration by 3 to 6 (depending on the pH) to estimate the BOHB concentration. If the anion gap is greater than the estimated concentrations of AcAc plus BOHB, the presence of an additional unmeasured anion should be considered (e.g., lactate, salicylate, uremic compounds, methanol, ethylene glycol).

f. **Other laboratory findings**

i. **Renal.** The blood urea nitrogen (BUN) of patients with DKA is typically elevated due to prerenal azotemia and increased ureagenesis. AcAc interferes with some creatinine assays.

ii. **Hematology.** The hematocrit and hemoglobin are usually high. Low values suggest preexisting anemia or acute blood loss. Leukocytosis with a left shift often occurs in the absence of intercurrent illness.

iii. **Lipids.** There is marked elevation of serum triglyceride concentrations; this reverses with insulin therapy.

iv. **Other.** Serum amylase, lipase, and creatine phosphokinase (CPK) concentrations are sometimes elevated. Uric acid concentrations may be elevated. Ketone bodies interfere with certain transaminase assays.

III. TREATMENT. Treatment of DKA should be directed at four main problems: hypovolemia, electrolyte disturbances, insulin, and identification of the precipitating event.

A. Correction of hypovolemia. Patients in DKA are always hypovolemic. Fluid and electrolyte therapy always takes precedence over insulin therapy, which shifts salt and water from the extracellular (and intravascular) compartments to the intracellular space. The free water deficit generally ranges between 5 and 11 L, typically approximately 100 mL/kg. Initial fluid resuscitation should be with an infusion of 0.9% saline. Approximately 2 L should be given during the first hour to restore blood volume, stabilize blood pressure, and establish urine flow. Another liter of 0.9% saline can typically be given during the next 2 hours. During the first 24 hours, 75% of the estimated total water deficit should be replaced. Urine flow should be maintained at approximately 30 to 60 mL/hour. After the first 2 L, consider changing to hypotonic 0.45% saline if hypernatremia is present.

B. Electrolytes

1. Sodium, chloride, and potassium. Sodium and chloride are replaced in conjunction with free water as just described. Because serum potassium concentration does not accurately reflect total body potassium, replacement should be initiated early in treatment. Replacement of potassium should begin as soon as the serum potassium concentration is <5.5 mEq/L. The rate of repletion depends on the severity of the hypokalemia.

The typical rate is 20 mEq/hour as KCl or K_3PO_4, and in severe hypokalemia 40 mEq/hour may be required. Typical potassium deficits in DKA are 3 to 5 mEq/kg, but if hypokalemia or normokalemia is present at the time of admission, the deficit may be much higher, up to 10 mEq/kg. If a patient in mild DKA is alert and able to tolerate liquids, potassium should be given orally.

For a variety of reasons, potassium concentration often falls precipitously after starting therapy. Insulin shifts K^+ to the intracellular space. As acidemia resolves, buffered intracellular H^+ exchanges for extracellular K^+. If a nasogastric tube is in place, electrolyte losses resulting from gastric suctioning must also be considered. A sudden reduction in serum potassium concentration can cause flaccid paralysis, respiratory failure, and life-threatening cardiac arrhythmias.

2. Phosphate. Initially the concentration of phosphate is elevated, but levels may decrease to <1 mM/L within 4 to 6 hours of starting insulin treatment. Persistent severe hypophosphatemia can cause neurologic disturbances, arthralgias, muscle weakness with respiratory failure, rhabdomyolysis, and liver dysfunction. The solution of potassium phosphate contains 93 mg phosphorus and 4 mEq potassium/mL. It is rarely necessary to administer more than one 5-mL ampule of potassium phosphate to a patient in DKA. The hazards of parenteral phosphate administration include hypocalcemia and metastatic calcification. Unless hypophosphatemia is severe (<1.0 mg/dL) and persistent, there is generally no need for treatment.

3. Bicarbonate. Most authorities concur that there is no need for the routine use of bicarbonate therapy in DKA. Fluid and electrolyte replacement alone will ameliorate acidosis, and bicarbonate therapy may produce adverse effects. These include severe acute hypokalemia, late respiratory alkalosis due to paradoxical cerebrospinal fluid acidosis, a shift of the oxygen dissociation curve to the left that results in tissue hypoxia and lactic acidosis, and increased hepatic ketogenesis. In children, bicarbonate therapy may increase the risk of cerebral edema. We recommend bicarbonate therapy (a) when the pH is persistently <7.1 after 2 to 3 hours of treatment, (b) in cases complicated by depressed respiratory drive, and (c) when hypotensive shock is unresponsive to rapid fluid replacement. Even

in these circumstances, bicarbonate can only "buy time" until metabolic treatment reverses the acidosis. Administer sodium bicarbonate by adding to intravenous fluids, typically two ampoules (2 × 44 mEq, or 2 × 50 mEq) added to 1 L of D5W. When the pH is >7.2, treatment should be stopped.

4. **Magnesium.** Hypermagnesemia may occur early in the course of DKA. Mg^{2+} concentration generally returns to normal without treatment. In some patients, Mg^{2+} stores may be depleted and in rare instances lead to cardiac arrhythmia.

C. Insulin. Insulin therapy in DKA should be instituted only after fluid and electrolyte resuscitation is under way. For adults, we recommend a bolus of 10 U of short-acting insulin followed by a continuous intravenous infusion starting at 5 to 10 U/hour. In children, the recommended initial bolus is 0.1 U/kg of body weight and the infusion rate is 0.1U/kg/hour. Insulin should be added to 0.45% saline at a concentration of 0.5 U/mL, and the container swirled before use. Typically regular (crystalline) insulin is used for intravenous infusions. Some of the semisynthetic rapid acting insulins have been approved for intravenous use but offer no metabolic advantage. Blood glucose concentration should be measured every 1 to 2 hours after starting the infusion. If the glucose concentration has not decreased by 100 mg/dL, the insulin infusion rate should be doubled. When the glucose concentration has fallen by >150 mg/dL, the infusion rate should be decreased by 50%, but it should never be stopped. The minimum blood glucose concentration during the first 24 hours of treatment should be 200 mg/dL. If it falls below 200 mg/dL, glucose infusion (dextrose 5% in water [D5W]) should be started, and the insulin infusion rate continued to inhibit ketogenesis. Never stop insulin entirely during the treatment of DKA, even if the infusion rate is reduced to only 0.5 U/hour or less. Serum bicarbonate levels should be near normal before transitioning the patient from intravenous insulin to subcutaneous insulin injections.

D. Identification of the precipitating event. DKA may be the first sign of new-onset type 1 diabetes mellitus. Most cases, however, occur in patients known to have diabetes, and it is always necessary to ask why DKA has occurred in this setting. Common underlying causes of DKA include:

1. Omission of insulin therapy
2. Infection
3. Major stressors (e.g., myocardial infarction, trauma)
4. Medication (e.g., high-dose glucocorticoid therapy)

E. Pearls: key points and pitfalls

1. Complications are not infrequent in cases of DKA; some are avoidable.
2. Never stop insulin completely! DKA can recur rapidly, especially in the presence of intercurrent illnesses. Insulin infusions should always be continued, if only at 0.5 to 1 U/hour, until the patient is well enough to be switched to subcutaneous injections of longer-acting insulin. The infusion can be stopped 2 to 3 hours after the first subcutaneous injection of intermediate-acting insulin is given.
3. Recurrent DKA: If ketoacidosis recurs in the ICU despite continued therapy with insulin, severe infection, a severe contrainsulin state (e.g., Cushing's syndrome) or medications (e.g., glucocorticoids) should be suspected.
4. Cerebral edema is a rare complication of DKA in adults, but it occurs occasionally in children. To avoid cerebral edema, the goal of DKA treatment during the first 24 hours is a blood glucose concentration not less than 200 mg/dL.
5. Persistent hypotension should prompt consideration of fluid shifts, bleeding, severe acidosis, arrhythmia, myocardial infarction, cardiac tamponade, sepsis, and adrenal insufficiency.

6. Renal complications include postrenal obstruction, atonic bladder, and acute tubular necrosis secondary to pyelonephritis.
7. Thrombosis of the cerebral vessels and stroke are recognized but uncommon complications of DKA.
8. Hyperchloremic metabolic acidosis with normal anion gap frequently develops after therapy of DKA and corrects spontaneously.

IV. HYPERGLYCEMIC HYPEROSMOLAR SYNDROME

A. Pathophysiology. The pathophysiology of HHS involves three interrelated elements:

1. Insulin deficiency
2. Renal impairment
3. Cognitive impairment

Relative lack of insulin is the fundamental defect. Patients have sufficient insulin to inhibit ketone body formation but not enough to prevent glycogenolysis and gluconeogenesis. The resulting hyperglycemia induces an osmotic diuresis, with resultant fluid and electrolyte losses.

Some degree of renal impairment accompanies all cases of HHS. Typical patients with the HHS syndrome are older and have reduced renal blood flow and glomerular filtration rate (GFR). The underlying renal abnormalities in the HHS syndrome may be prerenal, renal, or postrenal. As a result, affected patients are unable to compensate for the hyperglycemia with an osmotic diuresis.

Invariably, HHS involves acute or chronic impairment of cerebral function. Hyperglycemia leading to an osmotic diuresis and hyperosmolality normally activates a thirst response. A common history for HHS involves an elderly patient with impaired cognitive function due to cerebrovascular disease, dementia, or central nervous system (CNS)-depressant medications. Patients with trauma or burns are also susceptible to HHS.

B. Diagnosis

1. **Clinical presentation.** Patients who develop HHS are typically middle aged or elderly. They often have a history of type 2 diabetes and a prodrome of progressive polyuria and polydipsia lasting days to several weeks. Most patients have intercurrent diseases; renal and cardiovascular disorders are common. Other problems include infection, myocardial infarction, stroke, hemorrhage, and trauma. Additional factors include dialysis, hyperalimentation, and medications (e.g., thiazide diuretics, phenytoin, propranolol, immunosuppressive agents, cimetidine).

   Fever is a common finding in HHS even in the absence of infection, but infection must be rigorously excluded in all cases. Patients may have hypotension and tachycardia due to dehydration, and they frequently hyperventilate. Hyperventilation may reflect intercurrent lactic acidosis. Neurologic manifestations include tremors and fasciculations. Mental status abnormalities range from mild disorientation to obtundation and coma. Up to a third of patients with HHS may seize.

2. **Laboratory**
   - **a. Blood glucose.** Plasma glucose concentrations in HHS are generally higher than in DKA, usually >600 mg/dL. Values as high as 2,000 mg/dL occur.
   - **b. Ketones.** Most patients in HHS are not ketonemic. Serum acetone levels are usually normal or only slightly elevated, seldom exceeding 1:2.
   - **c. Arterial pH.** Occasional patients in HHS will develop an intercurrent metabolic acidosis. Most patients in HHS are only mildly acidotic, the average pH being approximately 7.25 before treatment.
   - **d. Osmolality.** Serum osmolality in comatose patients usually exceeds 350 mOsm/kg. Dehydration induces prerenal azotemia.

e. **Sodium.** The serum sodium concentration in HHS at the time of presentation is variable, ranging between 100 and 180 mEq/L. "Corrected" serum sodium concentration is calculated as for DKA.

f. **Potassium.** Serum potassium concentration in HHS is also variable, ranging from 2.2 to 7.8 mEq/L.

V. **TREATMENT.** Treatment of HHS should be directed at four main problems: hypovolemia, electrolyte disturbances, insulin, and identification of the precipitating event.

A. **Correction of hypovolemia.** Patients with HHS are without exception profoundly dehydrated. Within the first 2 hours, 1 to 2 L of 0.9% saline should be given. Normal saline is recommended, even if hypernatremia is present, to expand the extracellular fluid compartment rapidly. After initial volume expansion and restoration of normotension, subsequent treatment for dehydration in this syndrome emphasizes free water replacement. The average patient requires 6 to 8 L of fluids during the first 12 hours of treatment.

B. **Electrolytes.** As soon as adequate urine flow has been established and the degree of hypokalemia estimated, potassium supplementation should be added to the intravenous fluids. A rapid fall in serum potassium concentration frequently accompanies the initial dose of insulin. Serum potassium concentration should be checked frequently and the electrocardiogram monitored for changes. Cardiac arrhythmias induced by hypokalemia may be irreversible, particularly in the elderly.

C. **Insulin.** Most patients with HHS are more sensitive to insulin than are patients with DKA. In addition, blood glucose concentration in HHS can fall precipitously when urine output is reestablished after volume expansion. Treatment with insulin is essential but should be instituted (i) with careful monitoring and (ii) only after fluid and electrolyte resuscitation is under way. We do not recommend an initial intravenous insulin bolus. For the infusion, we recommend a starting dose of only 1 to 5 U/hour, depending on individual circumstances. Attempt to maintain blood glucose concentration near 250 mg/dL for the first 24 hours. A rapid fall in blood glucose concentration may cause cerebral edema.

D. **Identification of the precipitating event.** HHS may be the first sign of newly recognized diabetes mellitus, but most cases occur in patients known to have glucose intolerance. Regardless of the previous glycemic history, it is always necessary to ask why HHS has occurred. Common and easily recognized underlying causes of HHS include infection and major stressors (e.g., myocardial infarction or trauma). Other precipitating events in the elderly can be subtler. These may include drugs that depress the sensorium and inhibit the response to thirst (e.g., anxiolytics and sedatives), drugs that depress renal function (e.g., diuretics leading to prerenal azotemia), and drugs that promote hyperglycemia (e.g., steroids) and other endocrine disturbances (e.g., hypothyroidism or apathetic thyrotoxicosis).

E. **Pearls: key points and pitfalls.** Patients with HHS may be very sensitive to insulin. Do not be overly aggressive with insulin. Do not give insulin before volume restoration. When insulin is administered to patients with HHS syndrome, glucose shifts from the extracellular to the intracellular compartment. The rapid intracellular movement of free water may precipitate hypotension and shock. Rapid reduction in blood glucose is a major contributor to the development of cerebral edema and a fatal outcome in HHS.

VI. ALCOHOLIC KETOACIDOSIS

A. **Pathophysiology.** Ethanol metabolism consumes nicotinamide adenine dinucleotide (NAD) and generates reduced nicotinamide adenine dinucleotide

(NADH). Sufficient ethanol ingestion can generate an unfavorable NADH:NAD ratio, which in turn impairs gluconeogenesis. Hypoglycemia ensues when glycogen stores are exhausted, explaining the relationship of the disorder to nutritional state. Because of the hypoglycemia, insulin levels are low, which is permissive to the release of free fatty acids from adipose tissue and to the formation of ketone bodies.

B. Diagnosis. The diagnosis depends on the demonstration of hypoglycemia in the setting of ketoacidosis. Definitive demonstration of hypoglycemia has three components: low plasma glucose concentration, neuroglycopenic symptoms (e.g., hunger, headache, confusion, lethargy, slurred speech, seizures, coma) consistent with hypoglycemia, and resolution of those symptoms with administration of glucose.

1. **Clinical presentation.** Patients with this disorder may be stuporous or comatose. They are typically chronically alcoholic, but the disorder can occur after binge drinking in adults or accidental ingestion in children. Adult patients typically have not eaten for days and are prone to nausea, vomiting, and aspiration. Hypothermia and neurologic abnormalities, including trismus, seizures, hemiparesis, and abnormal tendon reflexes, may be observed. Evidence of inebriation is often absent.
2. **Laboratory**
   a. **Hypoglycemia.** Blood glucose concentrations can be as low as 20 mg/dL.
   b. **Anion gap acidosis.** These patients are usually acidotic, with an arterial pH <7.2.
   c. **Ketonemia and ketonuria.** Both ketoacids and lactate contribute to the unmeasured anion pool in this form of acidosis.
   d. **Other.** Liver function tests, amylase, and phosphate are typically normal.

C. Treatment

1. **Fluids and electrolytes.** Rehydration with intravenous fluids as appropriate.
2. **Glucose.** One ampule of dextrose 50% in water (D50W) to correct hypoglycemia, being careful to avoid extravasation.
3. **Parenteral thiamine** (100 mg) to prevent Wernicke's encephalopathy
4. **Pearls: key points and pitfalls**
   a. By the time patients with this disorder are treated, the ethanol has often been metabolized and is no longer detectable.
   b. Administration of sodium bicarbonate is generally not necessary. Treatment with glucose and fluids rapidly reverses the condition by raising the concentration of insulin and thereby inhibiting lipolysis and free fatty acid release.
   c. The presence of urinary ketones in a hypoglycemic patient generally excludes hyperinsulinemia as the cause of the low glucose concentration.
   d. Persons with diabetes treated with insulin or sulfonylurea-class hypoglycemic agents who become intoxicated may develop life-threatening, profound hypoglycemia as a result of the metabolic synergy of ethanol and insulin.

VII. HYPOGLYCEMIC COMA. Hypoglycemic emergencies are discussed in Chapter 92.

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THYROID EMERGENCIES

Alan P. Farwell

89

I. THYROID STORM

A. General principles

1. Thyroid storm is a rare, life-threatening complication of thyrotoxicosis in which a severe form of the disease is usually precipitated by an intercurrent medical problem.
2. Precipitating factors associated with thyroid storm include infections, stress, trauma, thyroidal or nonthyroidal surgery, diabetic ketoacidosis, labor, heart disease, iodinated contrast studies, thyroid hormone overdose and radioiodine treatment (especially if there was no pretreatment with antithyroid drugs).
3. While the cause of the rapid clinical decompensation is unknown, a sudden inhibition of thyroid hormone binding to plasma proteins by the precipitating factor, causing a rise in free hormone concentrations in the already elevated free hormone pool, may play a role in the pathogenesis of thyroid storm.
4. Historically, thyroid storm was frequently associated with surgery for hyperthyroidism but this is rarely seen now.

B. Pathophysiology

1. Symptoms

a. Thyroid storm is primarily a clinical diagnosis, with features similar to those of thyrotoxicosis, but more exaggerated (Table 89-1).
b. Cardinal features include fever (temperature usually >38.5°C), tachycardia out of proportion to the fever, and mental status changes.
c. Tachyarrhythmias, especially atrial fibrillation in the elderly, are common, as are nausea, vomiting, diarrhea, agitation, and delirium.
d. Coma and death may ensue in up to 20% of patients, frequently due to cardiac arrhythmias, congestive heart failure, hyperthermia, or the precipitating illness.

2. Signs

a. Most patients display the classic signs of Graves' disease, including ophthalmopathy and a diffusely enlarged goiter, although thyroid storm has been associated with toxic nodular goiters.
b. In the elderly, severe myopathy, profound weight loss, apathy, and a minimally enlarged goiter may be observed.
c. There are no distinct laboratory abnormalities and thyroid hormone levels are similar to those found in uncomplicated thyrotoxicosis; there is little correlation between the degree of elevation of thyroid hormones and the presentation of thyroid storm.

C. Diagnosis

1. The differential diagnosis of thyroid storm includes sepsis, neuroleptic malignant syndrome, malignant hyperthermia, and acute mania with lethal catatonia, all of which can precipitate thyroid storm in the appropriate setting.
2. Clues to the diagnosis of thyroid storm are a history of thyroid disease, history of iodine ingestion, and the presence of a goiter or stigmata of Graves' disease.

TABLE 89-1 Clinical Features of Thyroid Storm

Fever (as high as 105. 8°C)
Tachycardia/tachyarrhythmias
Delerium/agitation
Mental status changes
Congestive heart failure
Tremor
Nausea and vomiting
Diarrhea
Sweating
Vasodilatation
Dehydration
Hepatomegly
Splenomegly
Jaundice

3. The physician must have a high clinical index of suspicion for thyroid storm, as therapy must be instituted before the return of thyroid function tests in most cases.

D. Treatment

1. Thyroid storm is a major medical emergency that must be treated in an intensive care unit (ICU) (Table 89-2).
2. Treatment includes supportive measures such as intravenous fluids, antipyretics, cooling blankets, and sedation.
3. β-Adrenergic blockers or calcium channel blockers are given to control tachyarrhythmias.
4. Antithyroid drugs are given in large doses, with Propylthiouracil (PTU) being preferred over methimazole due to its additional advantage of impairing peripheral conversion of T4 to T3.
5. PTU and methimazole can be administered by nasogastric tube or rectally if necessary; neither of these preparations is available for parenteral administration.
6. Iodides, orally or intravenously, may be used only after antithyroid drugs have been administered, although the useful radiographic contrast dye iopanoic acid is no longer available in the United States.
7. High-dose dexamethasone is recommended as supportive therapy, as an inhibitor of T4 to T3 conversion and as management of possible intercurrent adrenal insufficiency.
8. Orally administered ion-exchange resins (Colestipol or Cholestyramine) can trap hormone in the intestine and prevent recirculation, and plasmapheresis has also been used in severe cases.
9. Treatment of the underlying precipitating illness is essential to survival in thyroid storm.
10. Once stabilized, the antithyroid treatment should be continued until euthyroidism is achieved, at which point a final decision regarding antithyroid drugs, surgery, or ^{131}Iodine (^{131}I) therapy can be made.

II. MYXEDEMA COMA

A. General principles

1. Myxedema coma is a rare syndrome that represents the extreme expression of severe, long-standing hypothyroidism.

TABLE 89-2 Treatment of Thyroid Storm

Supportive therapy
Treatment of underlying illnesses
Intravenous fluids
Cooling blanket and/or antipyretics
β–Adrenergic blocking drugs
Propranolol — 1 mg IV/min to a total dose of 10 mg, then 40–80 mg PO q6 h, *or*
Esmolol — 500mg/kg/min IV, then 50–100 mg/kg/min, *or*
Metoprolol — 100–400mg PO q12 h, *or*
Atenolol — 50–100 mg PO daily
Antithyroid drugs
Inhibition of thyroid hormone synthesis
Propylthiouracil — 800 mg PO first dose, then 200–300 mg PO q8 h, *or*
Methimazole — 80 mg PO first dose, then 40–80 mg PO q12 h
Block release of thyroid hormones from the gland
SSKI — 5 drops PO q8 h, *or*
Lugol's solution — 10 drops PO q8 h, *or*
Lithium — 800–1,200 mg PO qd — achieve serum lithium levels 0.5–1.5 mEq/L
Block T4 to T3 conversion
Corticosteroids — dexamethasone 1–2 mg PO q6 h
Most β-blockers — propranolol 40–80 mg PO q6 h
Propylthiouracil
Telapaque (iopanoic acid) — no longer available in the United States
Remove thyroid hormones from the circulation
Plasmapheresis, *or*
Peritoneal dialysis, *or*
Cholestyramine — 4 g PO q6 h, *or*
Colestipol — 20–30 mg PO qd

SSKI, saturated solution of potassium iodide.

2. Even with early diagnosis and treatment, the mortality can be as high as 60%.
3. Myxedema coma occurs most often in the elderly and during the late fall and winter months.
4. Other common precipitating factors include pulmonary infections, cerebrovascular accidents, trauma, surgery, and congestive heart failure.
5. The clinical course of lethargy proceeding to stupor and then coma is often hastened by drugs, especially sedatives, narcotics, antidepressants, and tranquilizers, especially in the undiagnosed hypothyroid patient who has been hospitalized for other medical problems.

B. Pathophysiology

1. Symptoms

a. Cardinal features of myxedema coma are hypothermia, respiratory depression, hypotension, and unconsciousness (Table 89-3).

b. Most patients have the physical features of severe hypothyroidism, including bradycardia; macroglossia; delayed reflexes; and dry, rough skin and myxedematous facies, which results from the periorbital edema, pallor, hypercarotinemia, periorbital edema, and patchy hair loss.

c. Hypotonia of the gastrointestinal (GI) tract is common and often so severe as to suggest an obstructive lesion.

d. Urinary retention due to a hypotonic bladder is related but less frequent.

TABLE 89-3 Clinical Features of Myxedema Coma

Mental obtundation
Hypothermia
Bradycardia
Hypotension
Coarse, dry skin
Myxedema facies
Hypoglycemia
Atonic GI tract
Atonic bladder
Pleural, pericardial, and peritoneal effusions

GI, gastrointestinal.

2. Signs

a. Pleural, pericardial, and peritoneal effusions may be present.

b. The thyroid hormone abnormalities are similar to those in uncomplicated hypothyroidism, with >95% of cases due to primary hypothyroidism.

c. Dilutional hyponatremia is common and may be severe.

d. Elevated creatine kinase concentrations, sometimes markedly so, are encountered frequently, suggesting cardiac ischemia; however, in most cases the myocardial band (MB) fraction is normal and an electrocardiogram (ECG) often shows the low voltage and loss of T waves that is characteristic of severe hypothyroidism.

e. Elevated lactate dehydrogenase concentrations, acidosis, and anemia are common findings.

f. Lumbar puncture reveals increased opening pressure and high protein content.

C. Diagnosis

1. The diagnosis of myxedema coma is based on the presence of the characteristic clinical syndrome in a patient with hypothyroidism.

2. Clues to the diagnosis include symptoms related by family and friends, an outdated container of L-T4 discovered with the patient's belongings, previous treatment with radioactive iodine, or there may be a thyroidectomy scar present.

3. Differential diagnosis includes protein-calorie malnutrition, sepsis, hypoglycemia, exposure to certain drugs and toxins, and cold exposure.

4. What distinguishes myxedema coma from other disorders is the combination of laboratory evidence of hypothyroidism, the characteristic myxedema facies with periorbital puffiness, the skin changes, obtundation, and other physical signs characteristic of severe hypothyroidism.

5. The physician must have a high clinical index of suspicion for myxedema coma, as therapy must be instituted before the return of thyroid function tests in most cases.

D. Treatment

1. Myxedema is a medical emergency and must be managed in an ICU setting (Table 89-4).

2. The mainstays of therapy are supportive care, with ventilatory and hemodynamic support, rewarming, correction of hyponatremia and hypoglycemia,

TABLE 89-4 Treatment of Myxedema Coma

Assisted ventilation for hypoventilation
Hemodynamic support for hypotension
Intravenous glucose for hypoglycemia
Water restriction or hypertonic saline for severe hyponatremia
Passive rewarming for hypothermia
Administer thyroid hormone intravenously
L-T4 — 200–300 μg loading dose, up to 500 μg in the first 24 h[a] and/or
L-T3 — 12.5 μg q6 h until awake[a]
Administer hydrocortisone IV (100 mg q8 h)[a]
Treat underlying infection and other illnesses, if present
Avoid all sedatives, hypnotics, and narcotics

[a]Note that dosage must be individualized (see text).

and treatment of the precipitating incident and administration of thyroid hormone.

3. Active heating in myxedema coma should be avoided as it increases oxygen consumption and promotes peripheral vasodilation and circulatory collapse.
   a. An exception is at core temperatures below 28°C, when ventricular fibrillation is a major threat to life—in this case, the rate of rewarming should not exceed 0.5°C/hour until the core temperature is raised to approximately 31°C.
   b. In general, patients should be kept in a warm room and covered with blankets.
4. Sedatives, hypnotics, narcotics, and anesthetics must be minimized or avoided altogether due to their extended duration of action and exacerbation of obtundation in the hypothyroid patient.
5. Because of a 5% to 10% incidence of coexisting adrenal insufficiency in patients with myxedema coma, intravenous steroids are indicated before initiating T4 therapy.
6. Parenteral administration of thyroid hormone is necessary due to uncertain absorption through the gut.
   a. A reasonable approach is an initial intravenous loading dose of 200 to 300 μg L-T4, with another dose of L-T4 given in 6 to 12 hours to bring the total dose during the first 24 hours to 0.5 mg, followed by 50 to 100 μg intravenously every 24 hours until the patient is stabilized.
   b. In the most severe cases, some clinicians recommend using L-T3 at a dosage of 12.5 to 25 μg intravenously every 6 hours until the patient is stable and conscious, followed by a switch to L-T4.
7. Although myxedema coma is associated with a high mortality, many patients can be saved by judicious therapy aimed at correcting the secondary metabolic disturbances and reversing the hypothyroid state in a sustained but gradual fashion, since an effort to correct hypothyroidism too rapidly may completely negate the beneficial effects of the initial treatment.

This chapter is based on the chapters by Safran, M, Abend SL, and Braverman LE, "Thyroid Storm" and Emerson CH, "Myxedema Coma" in *Intensive Care Medicine* 6th Edition (Irwin RS and Rippe JM, eds) Lippincott-Raven (Philadelphia), 2008.

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HYPOADRENAL CRISIS AND THE STRESS MANAGEMENT OF THE PATIENT ON CHRONIC STEROID THERAPY

90

Neil Aronin

I. HYPOADRENAL CRISIS

A. General principles. The adrenal glands secrete five types of hormones, but only two are critical in the intensive care unit (ICU) setting. Mineralocorticoids (primarily aldosterone) have their major effects on electrolyte balance; glucocorticoids (primarily cortisol) promote gluconeogenesis but have many other actions. Mineralocorticoids and glucocorticoids are life maintaining and deficiency of either can result in a hypoadrenal crisis. By contrast, the other three types of adrenal hormones do not play a major role in this disorder.

Hypoadrenal crisis can occur as an acute event in individuals who give little history of previous adrenal problems. A high index of suspicion arises in patients who have inadequate responses to initial therapies. Pathophysiological conditions that contribute to the ICU admission (e.g., sepsis, acute respiratory failure) might interfere with traditional tests of adrenal function. Biochemical diagnosis may have uncertainty, but therapy initiated nonetheless.

1. Etiology. The most common cause of primary adrenal failure, Addison's disease, is autoimmune and is often known before the ICU admission. Other causes of adrenal failure offer a difficult diagnosis in the ICU: overwhelming sepsis, hemorrhage secondary to trauma, circulating anticoagulants or anticoagulant therapy, tuberculosis, fungal disease, amyloidosis, acquired immune deficiency syndrome, antiphospholipid syndrome, infarction, irradiation, metastatic disease and drugs. Critical illness can cause or bring out adrenal insufficiency.

The most common cause of secondary adrenal insufficiency is suppression of corticotrophin (adenocorticotrophic hormone [ACTH]) release by prior glucocorticoid therapy. There are no cut-offs on duration of glucocorticoid therapy, its route of administration, and its dosage that can cause adrenal cortical atrophy and inadequate reserve.

2. Actions of mineralocorticoids and glucocorticoids. The adrenal cortex secretes aldosterone from the zona glomerulosa and cortisol from the zona fasciculata. Aldosterone, which promotes the reabsorption of sodium and the secretion of potassium and hydrogen in the renal tubule, is controlled mainly by the renin-angiotensin system. Glucocorticoid suppression of ACTH and therefore cortisol in the zona fasciculata does not suppress aldosterone in the zona glomerulosa. Glucocorticoids promote gluconeogenesis and protein wasting and increase the excretion of free water by the kidney. In large doses, glucocorticoids bind to mineralocorticoid receptors, thereby increasing sodium reabsorption and potassium and hydrogen ion excretion. Glucocorticoids act on numerous tissues, including the central nervous system, and affect the sense of well-being, appetite, and mood. They inhibit ACTH release through hypothalamic and pituitary actions. Glucocorticoids have direct effects on the cardiovascular system and maintain blood pressure, although mechanisms are not established. Critical illness and glucocorticoid deficiency affect common physiological systems.

Excess glucocorticoids cause lymphopenia, leukocytosis, and eosinopenia, can lead to osteoporosis and reduction of hypercalcemia, and can impair host defenses to infectious diseases.

Aldosterone deficiency results in sodium wasting, with concomitant loss of water and an increase in renal reabsorption of potassium. A decrease in plasma volume and dehydration occurs, with subsequent increases in blood urea nitrogen (BUN) and plasma renin activity.

The decrease in circulating levels of cortisol causes a marked increase in circulating levels of ACTH and a corresponding increase in β-lipotropin, from which melanocyte-stimulating hormone activity increases; in long-standing adrenal insufficiency, the skin, especially creases and scars, develops hyperpigmentation. Orthostatic hypotension can progress to frank shock in a crisis. Hypoglycemia and an increase in sensitivity to insulin are commonplace.

B. Diagnosis

1. **Clinical.** Clinical manifestations that suggest adrenal insufficiency can include a nonspecific history of increasing weakness, lassitude, fatigue, anorexia, vomiting, and constipation (with the hypoadrenal crisis, diarrhea can occur). Patients who present with adrenal hypofunction in crisis are hypotensive (volume depletion) or in frank shock; they generally have a fever, sometimes high, and may be stuporous or comatose. In individuals whose loss of adrenal function occurs as a precipitous event (adrenal hemorrhage during the course of an infection, anticoagulant therapy, trauma, or after surgery), no hyperpigmentation is seen but flank pain is often present. Severely ill patients are often suspected of developing adrenal hypofunction, but actual incidence is not established. To further complicate recognition of adrenal dysfunction, glucocorticoid resistance has been postulated in critical illness.

   In secondary adrenal failure caused by a lack of ACTH, the signs and symptoms are essentially those of glucocorticoid deficiency, especially hypoglycemia. ACTH deficiency generally follows deficiency in other anterior pituitary hormones, so that deficits in overall pituitary secretion can lead to signs of other endocrine gland dysfunctions.

2. **Adrenal function tests.** In critical illness, the diagnosis of hypoadrenal function is less apparent than it is in the ambulatory medicine. In primary adrenal insufficiency, plasma concentrations of cortisol are usually low or in the low normal range and do not rise after ACTH stimulation. This failure to respond to ACTH is the definitive test for primary adrenal hypofunction. Administering 250 μg of cosyntropin (Cortrosyn) (synthetic ACTH 1-24) intravenously (IV) leads to a 10 μg increase of cortisol over baseline at 30 or 60 minutes, or a stimulated cortisol level >20 μg/dL, in an adequate adrenal response.

   Severe illness can interfere with the adrenal response to ACTH. Recognition of the complexity of adrenal hypofunction in critical illness has led to reconsideration of its diagnosis in the ICU. A serum-free cortisol of <9 μg/dL is sufficient to initiate glucocorticoid replacement. However, measurement of free cortisol is currently unavailable in most hospitals, so that a random, total cortisol of <10 μg/dL is used as a threshold for glucocorticoid therapy. The American College of Critical Care considers this recommendation to be weak with moderate quality of evidence. The concept of situational adrenal insufficiency is an idea inchoate, but a threshold concentration of total cortisol provides a guideline for intervention. The term *critical illness-related corticosteroid insufficiency* is preferred in considering adrenal function in severe illness, because of the uncertainties in diagnosis.

   In acute adrenal insufficiency, as a result of adrenal hemorrhage, a computed tomography (CT) scan of the adrenal glands can be a useful diagnostic tool. Individuals with adrenal hypofunction generally show varying degrees

of hyponatremia and hyperkalemia and the sodium:potassium ratio is almost always <30.

C. Treatment. The management of the hypoadrenalism has been vetted by a committee of international experts and the American College of Critical Care Medicine. Recommendations have been provided as guidelines for usefulness of glucocorticoid therapy in hypoadrenal function and critical illness. There is agreement that hypoadrenalism needs to be treated. In critical illness in which primary adrenal function is suspected (e.g., evidence for hemorrhage), a bolus of 100 mg of hydrocortisone should be administered IV and then 100 mg IV over the next 24 hours. After the initial therapy and stabilization of the patient, hydrocortisone can be decreased by 50% each day. Maintenance is 20 to 30 mg/day. Fludrocortisone 0.1 mg/day is started at the maintenance glucocorticoid close.

It is not established whether adrenal insufficiency is a prerequisite for use of glucocorticoids in septic shock or early severe adult respiratory distress syndrome. Two recommendations are based on strong evidence of moderate quality: IV hydrocortisone (50 mg q6 h) is indicated in patients with septic shock and high-dose methylprednisolone (continuous infusion; 1 mg/kg/day) can be useful in acute respiratory distress syndrome. The other strong evidence is that hydrocortisone is preferred to dexamethasone in treatment of septic shock or acute respiratory distress syndrome. Less certainty attends other recommendations on use of glucocorticoids (weak evidence of moderate or low quality): use of the mineralocorticoid fludrocortisones, slow tapering of glucocorticoids, and duration of use of glucocorticoids in septic shock and respiratory failure.

II. GLUCOCORTICOID USE IN STRESSED PATIENTS ON GLUCOCORTICOID TREATMENT

A. General principles. In healthy subjects, the secretion rate of cortisol increases from 10 mg/day to 50 to 150 mg/day during surgical procedures but rarely exceeds 200 mg/day. The degree of response depends, in part, on the extent and duration of surgery.

After the introduction of glucocorticoid therapy, several case reports linked withdrawal of steroids, adrenal suppression, and shock in patients on long-term steroid treatment. The few studies available suggest that hypotension from inadequate adrenal function is uncommon. Therefore, the development of shock in the acutely ill or surgical patient on steroid therapy (or after withdrawal within 1 year) should not be attributed solely to diminished adrenal responsiveness. Adrenal steroids can and should be administered, but other contributing causes of hypotension should be sought. Suppression of the hypothalamic-anterior pituitary-adrenal axis can occur only after 5 days of glucocorticoid treatment. After long-term administration of corticosteroids, the adrenal axis may respond poorly to appropriate stimuli up to 1 year after steroid withdrawal. Adrenal suppression cannot be predicted based on glucocorticoid dosage and duration or a normal basal cortisol.

B. Diagnosis and treatment. Patients on glucocorticoid therapy for at least 4 weeks at either pharmacologic or replacement levels and those who have stopped glucocorticoids within the last year have the highest risk for adrenal suppression. Time permitting, a Cortrosyn test provides information on the adequacy of the adrenal response to stress. An adequate increase in cortisol following corticotrophin administration is interpreted to indicate the presence of an intact hypothalamic-anterior pituitary-adrenal axis, and patients who have a subnormal response to Cortrosyn also have a subnormal cortisol response to stress or surgery. For minor surgical procedures, the patient's usual dose of glucocorticoid is probably sufficient, but a single dose of 25 mg hydrocortisone or its equivalent can be given instead. As the extent and duration of surgery increases, the glucocorticoid dose should be increased from 50 to 75 mg/day

hydrocortisone, or its equivalent for up to 2 days, to 100 mg to 150 mg hydrocortisone or its equivalent for up to 3 days.

Hydrocortisone can be rapidly tapered and the patients returned to their usual dose of glucocorticoid if needed.

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DISORDERS OF MINERAL METABOLISM

Seth M. Arum and Daniel T. Baran

91

I. GENERAL PRINCIPLES

A. Disorders of mineral metabolism (calcium, magnesium, and phosphorus) occur frequently in patients admitted to intensive care units (ICUs). They are rarely the primary cause for admission, but may exacerbate existing medical situations.

B. Calcium, magnesium, and phosphorus metabolism are controlled by the interaction of parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (1,25 D), and calcitonin.

II. CALCIUM DISORDERS

A. Pathophysiology

1. In extracellular fluids, calcium is free and bound to albumin or other anions. The free (ionized) form is biologically active. Measured serum calcium should be corrected for the albumin level with the following equation:

$$\text{Corrected calcium} = \text{Measured calcium} + (0.8 \times [4 - \text{measured albumin}])$$

2. Changes in acid–base balance affect binding of calcium to albumin.

a. Acidosis decreases binding and increases the free form

b. Alkalosis increases binding and decreases the free form

3. Calcium balance depends on bone resorption and formation, intestinal absorption, and renal excretion.

a. Persistent PTH exposure increases bone resorption and renal calcium reabsorption

b. 1,25 D enhances intestinal calcium absorption

c. Calcitonin inhibits bone resorption and increases renal calcium excretion

B. Diagnosis of hypercalcemia

1. Signs and symptoms

a. Mental manifestations vary from stupor to coma

b. Neurologic effects include reduced muscle tone and reflexes

c. Intestinal and urologic signs include vomiting, polyuria, polydipsia, and constipation

d. Cardiovascular effects include shortening of the QT interval increasing the potential for arrhythmias

2. Differential diagnoses can be divided into PTH-independent and PTH-dependent

a. PTH-independent (PTH level will be suppressed) is more common in ICU

i. Malignancy—especially lung, head and neck, breast, hematologic (myeloma and lymphoma), and renal

ii. Granulomatous disease

iii. Immobilization

iv. Thyrotoxicosis

v. Vitamins D or A intoxication
vi. Addison's disease
vii. If PTH is suppressed (PTH-independent), then thyroid stimulating hormone levels, urine/serum protein electrophoreses, and bone scan can help establish the diagnosis

b. PTH-dependent (PTH level will be high or normal) is more common as outpatient
i. Hyperparathyroidism from adenoma, hyperplasia, carcinoma
ii. Familial hypocalciuric hypercalcemia (FHH)

C. Treatment of hypercalcemia
1. Hydration
a. Pivotal because response is rapid. Aim is to achieve a urine output of 3 to 5 L/24 hours, usually requiring 200 to 500 mL/hour of normal saline.
b. Furosemide (Lasix) 20 to 40 mg intravenously (IV) once rehydration has been achieved—prevents fluid overload and inhibits renal calcium reabsorption. Electrolyte measurement is mandatory.
2. Calcitonin
a. Inhibits bone resorption when a rapid decrease is required.
b. Dose is 4 to 8 IU/kg body weight subcutaneously or intramuscularly every 12 hours with hydration.
c. Decrease in serum calcium 2 hours after dose and lasts 6 to 8 hours. Average decrease is 9% and lasts 5 to 8 days (tachyphylaxis occurs).
3. Bisphosphonates
a. Inhibit bone resorption and provide a more prolonged calcium decrease
b. Pamidronate (Aredia) 60 to 90 mg IV over 2 hours, with hydration
c. Zoledronate (Zometa) 4 mg IV over not less than 15 minutes, with hydration
i. Calcium normalizes in 60% to 90% of patients with significant decreases within 4 days and duration of response between 1 and 3 weeks.
ii. Renal function needs to be monitored.
iii. Retreatment after a minimum of 7 days to allow full response to initial dose. Dose and manner of retreatment identical to initial treatment.

D. Diagnosis of hypocalcemia
1. Signs and symptoms
a. Neurologic manifestations include hyperreflexia and tetany
b. Chvostek's sign—facial muscle spasm by tapping the facial nerve
c. Trousseau's sign—carpal spasm elicited with a blood pressure cuff inflated above systolic pressure for 3 minutes.
2. Differential diagnosis
a. Hypoparathyroidism
b. Vitamin D deficiency
c. Hyperphosphatemia
d. Magnesium deficiency
3. PTH, 25-hydroxyvitamin D, magnesium, and phosphorus levels (measured before IV calcium) usually identify the cause

E. Treatment of hypocalcemia
1. Depends on severity and chronicity. Symptomatic patients should receive IV calcium.
2. Calcium gluconate 1 to 2 g administered in 100 mL 5% dextrose in water over 30 to 60 minutes. Can be repeated every 6 hours until ionized calcium is 4.5 mg/dL or the total calcium is 7 mg/dL. Total calcium should be maintained between 8 and 8.5 mg/dL and not higher to avoid hypercalciuria.

3. Vitamin D
   a. Ergocalciferol 50,000 to 100,000 U/day by mouth (PO). Slow onset but wide safety margin.
   b. 1,25 D (Rocaltrol) 0.25 to 2.0 μg/day PO. More rapid and potent than ergocalciferol, but narrower safety margin—can cause hypercalciuria or hypercalcemia.

III. MAGNESIUM DISORDERS

A. Pathophysiology
1. Magnesium circulates in the free form (60%) and bound to albumin (40%). Albumin needs to be measured to interpret magnesium levels.
2. Magnesium levels depend on intestinal absorption and renal excretion.
   a. Decreased renal excretion (e.g., renal failure) increases magnesium levels.
   b. Increased renal excretion (e.g., osmotic diuresis or drugs [ethanol, aminoglycosides, cisplatin]) decreases magnesium levels.
   c. Decreased intestinal absorption (e.g., accompanying fat malabsorption) decreases magnesium levels.

B. Diagnosis of hypermagnesemia
1. Signs and symptoms
   a. Central nervous system depression (e.g., decreased reflexes, flaccid paralysis, stupor, coma).
2. Etiology
   a. Most common cause is renal failure, aggravated by use of magnesium-containing antacids.
   b. The hypermagnesemia associated with diabetic ketoacidosis usually reflects dehydration and masks total body magnesium depletion.

C. Treatment of hypermagnesemia
1. Dialysis for the symptomatic patient when renal function is impaired.
2. If renal function is not impaired, magnesium excretion can be increased by furosemide 20 to 40 mg IV every 1 to 2 hours. Electrolytes must be monitored.
3. Neuromuscular depressant effects of magnesium in the symptomatic patient can be acutely antagonized by calcium gluconate 1 to 2 g administered in 50 to 100 mL 5% dextrose in water over 5 to 10 minutes. Serum calcium levels must be monitored.

D. Diagnosis of hypomagnesemia
1. Signs and symptoms
   a. Central nervous system excitability which in part may be caused by hypocalcemia. Low magnesium impairs PTH secretion and peripheral responsiveness to PTH which may result in hypocalcemia.
2. Etiology
   a. Increased renal excretion due to osmotic diuresis or medications (see Section III.A.2.b) is the most common cause.
   b. Frequently present in patients with malabsorption.
   c. Often encountered in the alcoholic patient due to poor dietary intake and increased renal excretion.

E. Treatment of hypomagnesemia
1. Symptomatic patient usually has a total body magnesium deficit of 1 to 3 mEq/kg body weight.
2. Magnesium oxide (Mag-Ox 400) 1 to 2 tablets PO daily (241 mg [19.86 mEq] of magnesium per tablet).
3. In the symptomatic patient who cannot take oral medications, magnesium sulfate (100 mg [8 mEq] magnesium per vial) IV can be used. Administer 64 mEq magnesium in 5% dextrose in water or normal saline over the first 24 hours. Then 32 mEq infused daily for 3 days. Monitor serum magnesium levels. Reduce by 75% if renal failure is present.

IV. PHOSPHORUS DISORDERS

A. Pathophysiology

1. Most phosphorus is found intracellularly. Because of shifts between intra- and extracellular compartments, serum phosphorus does not reflect body stores.

a. Acidosis causes shift of phosphorus from within cells to the extracellular compartment. Serum phosphorus levels may be normal in the acidotic patient despite depletion of total body stores due to this shift. As the acidosis is corrected, serum phosphorus levels may fall.

b. Low serum phosphorus stimulates renal production of 1,25 D.

B. Diagnosis of hyperphosphatemia

1. Signs and symptoms: No clinical signs or symptoms of byperphosphatemia *per se*. Hyperreflexia and tetany may occur due to accompanying hypocalcemia.

2. Differential diagnosis: Most often encountered in patients with renal failure or hypoparathyroidism. In both clinical situations, hyperphosphatemia results from impaired renal excretion. Can also be seen from cellular lysis such as rhabdomyolisis and tumor lysis syndrome.

C. Treatment of hyperphosphatemia

1. Restriction of dietary phosphorus intake

2. Correction of accompanying hypocalcemia

3. Phosphate binders

a. Calcium acetate 667 mg, 2 tablets PO with meals

b. Sevelamer 800 mg, 1 to 2 tablets PO with meals is preferred in patients with elevated calcium × phosphate products

D. Diagnosis of hypophosphatemia

1. Signs and symptoms—muscle weakness, rhabdomyolysis

2. Differential diagnosis

a. Impaired intestinal absorption (e.g., malnutrition or use of phosphate-binding antacids.

b. Increased renal excretion (e.g., hyperparathyroidism, vitamin D deficiency [due to secondary hyperparathyroidism], hyperglycemic states [due to osmotic diuresis], impaired renal handling of phosphorus [vitamin D resistant rickets]).

E. Treatment of hypophosphatemia

1. Severe hypophosphatemia (<1.5 mg/dL) requires parenteral therapy

a. Sodium phosphate 15 mmol IV over 2 hours. Can repeat up to three times in the first 24 hours until phosphate levels normalize.

b. Hypercalcemic patients or patients with renal failure should receive less (e.g., 0.08 mmol sodium phosphate/kg body weight)

2. Mild hypophosphatemia: Potassium phosphate (K-phos neutral) 1 to 4 g phosphorus/day PO in divided doses. Diarrhea is the most common side effect of oral therapy.

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92 HYPOGLYCEMIA

John P. Mordes, Michael J. Thompson, and Aldo A. Rossini

I. GENERAL PRINCIPLES. Hypoglycemia is frequently encountered in emergency departments and must be excluded in every patient with stupor or coma. Cases of refractory and prolonged hypoglycemia of unknown etiology require admission to an intensive care unit (ICU). Severe hypoglycemia can lead to permanent neurologic damage. Hypoglycemia is also a common occurrence in critically ill patients and is associated with adverse outcomes.

No specific blood glucose concentration defines hypoglycemia, but the serum glucose is typically <50 mg/dL (2.8 mM). The physiological definition of hypoglycemia is a blood glucose concentration sufficiently low as to cause the release of counterregulatory hormones (e.g., catecholamines) and impair the function of the central nervous system. Specifically, "Whipple's triad" defines hypoglycemia as (a) documentation of a low blood glucose concentration, (b) concurrent symptoms of hypoglycemia, and (c) resolution of those symptoms after administration of glucose.

II. PATHOPHYSIOLOGY. Hypoglycemia can be divided into fasting and nonfasting categories. Nonfasting, postprandial, and "reactive" hypoglycemic states are not usually life-threatening and do not require intensive management. A recently recognized exception is the case of postprandial hypoglycemia that may occur in patients who have undergone gastric bypass surgery. Hypoglycemia in such cases can be severe. It may result from a combination of postsurgical gastric dumping and inappropriately increased insulin secretion. Fasting hypoglycemia subsumes several subcategories: (a) states of overinsulinization, (b) states of impaired counterregulation, (c) states of inadequate endogenous glucose production, and (d) states in which gluconeogenic substrates are unavailable. Physiologically, most medication-induced hypoglycemia presents as fasting hypoglycemia.

A. Hypoglycemia due to excess insulin

1. Insulin overdose

a. Insulin overdose is the most common cause of hypoglycemia. In the outpatient setting, the overdose is usually inadvertent, the consequence of a missed meal or increased intensity of exercise. Patients with long-standing diabetes may be at increased risk of hypoglycemia due to increased sensitivity to short-acting insulins and defective counterregulatory responses. Intentional overdoses occur in both diabetic and nondiabetic individuals. Self-induced hypoglycemia should be suspected in anyone with access to insulin or oral hypoglycemic agents who experiences unexplained hypoglycemia.

i. Insulin infusion–induced hypoglycemia is not infrequent in ICU patients, particularly when glycemic targets are low. The risk of hypoglycemia is a barrier to intensive insulin therapy in critical care and its avoidance is dependent on frequent glucose monitoring and appropriate and timely responses to glucose concentrations that are trending downward.

b. Hypoglycemia is often more severe among patients with long-standing type 1 diabetes because they develop defective counterregulatory

responses. Impaired glucagon secretory responses are common, and epinephrine responses can also be inadequate. When counterregulation is impaired, adrenergic warning signals (e.g., tremor, diaphoresis, and tachycardia) may not occur and neuroglycopenic symptoms (e.g., confusion, combativeness, seizure, coma) can develop rapidly. Inadequate counterregulatory responses can also delay spontaneous recovery from insulin-induced hypoglycemia.

2. Hypoglycemia due to hypoglycemic and antidiabetic agents.
   a. Noninsulin agents used to treat type 2 diabetes fall into two classes. Hypoglycemic agents enhance insulin secretion and can cause hyperinsulinemic hypoglycemia. The sulfonylureas and meglitinides belong to this class. Antidiabetic agents promote normoglycemia through other mechanisms. When given as monotherapy they rarely cause hypoglycemia, but they can amplify the glucose-lowering activity of both insulin and oral hypoglycemic agents. Many subclasses of antidiabetic agents are now in use. These include thiazolidinediones, biguanides, incretin mimetics, gliptins, amylin mimetics, and α-glucosidase inhibitors. All of these drugs are oral agents except for the incretin and amylin mimetics, which are injectable peptides. The oral agents are used only to treat type 2 diabetes; the injectables are used in both type 1 and type 2 diabetes. In addition, many drugs not used for the treatment of diabetes can also amplify the glucose-lowering activity of all of these agents, and a complete medication history can be critical in the diagnosis of hypoglycemia.
   b. Hypoglycemic agents
      i. **Sulfonylureas.** This class of oral hypoglycemic agents enhances insulin secretion by pancreatic β cells. Sulfonylurea overdose is the leading cause of hypoglycemia in diabetic persons older than 60 years. It typically occurs in the setting of acute or chronic starvation superimposed on mild to moderate liver or kidney failure. Severe hypoglycemia has resulted from inadvertent substitution of an oral hypoglycemic agent for a different medication (e.g., chlorpropamide for chlorpromazine).
      ii. Meglitinides: Like sulfonylureas, repaglinide (Prandin) and nateglinide (Starlix) increase endogenous insulin secretion, but both are rapidly eliminated, have a limited toxicity profile, and are uncommonly associated with hypoglycemia.
   c. Antidiabetic agents
      i. Biguanides: Oral hypoglycemic drugs of the biguanide class induce hypoglycemia much less often than do sulfonylureas. They act by inhibiting gluconeogenesis, impairing gut glucose absorption, and increasing insulin sensitivity. Metformin is the only biguanide currently available in the United States.
      ii. Thiazolidinediones: Pioglitazone (Actos) and rosiglitazone (Avandia) are currently the only drugs of this class available in the United States. They do not cause hypoglycemia when used as monotherapy but can potentiate hypoglycemia when coadministered with insulin or a sulfonylurea. They act by increasing insulin sensitivity.
      iii. Incretin mimetics: Drugs in this class are synthetic peptides that mimic the effects of endogenous gut incretins. They promote normoglycemia by inducing glucose-dependent insulin secretion. Exenatide (Byetta) is currently available in the United States. Monotherapy with exenatide does not cause hypoglycemia, but coadministration with either metformin or, especially, a sulfonylurea can lead to serious hypoglycemia.
      iv. Gliptins: Members of this class of small molecules are inhibitors of the enzyme (dipeptidyl peptidase-4 [DPP-4]) responsible for

degrading endogenous incretins. They amplify the effects of endogenous incretins, leading to enhanced glucose-dependent insulin secretion. Sitagliptin (Januvia) is currently available in the United States. Sitagliptin monotherapy has not been reported to cause hypoglycemia.

v. Amylin mimetics: Amylin is a peptide cosecreted with insulin by β cells. Synthetic analogs of amylin are used to control postprandial hypoglycemia in persons with diabetes. Pramlintide (Symlin) is available in the United States. It does not cause hypoglycemia when used as monotherapy, but can cause severe hypoglycemia when coadministered with insulin.

vi. α-Glucosidase inhibitors: Acarbose (Precose) and miglitol (Glyset) inhibit the digestion of complex carbohydrates. They do not cause hypoglycemia when used as monotherapy. Insulin or sulfonylurea-induced hypoglycemia in patients who are also taking α-glucosidase inhibitor may not respond to oral administration of complex sugars but should respond to monomeric glucose.

3. Hypoglycemia due to other drugs: Several medications can cause hypoglycemia by increasing circulating insulin concentration. Some of them are listed in Table 92-1. Several of them have been reported to synergize with antidiabetic medications to cause hypoglycemia.
4. Insulinomas and other tumors: Insulin-secreting pancreatic islet cell tumors are very rare. They classically cause fasting hypoglycemia. Paraneoplastic hypoglycemia may be caused by tumors that secrete insulin-like growth factors. Another unusual cause of hypoglycemia due to insulin is nesidioblastosis. In children this is known as *nonmalignant islet cell adenomatosis*. In adults nesidioblastosis occurs only rarely.
5. Autoimmune- or antibody-mediated hypoglycemia: A rare condition in which endogenous autoantibodies bind to and activate the insulin receptor.
6. Familial hyperinsulinemic hypoglycemia.

B. Hypoglycemia associated with deficiencies in counterregulatory hormones

1. Adrenal disease: Glucocorticoid deficiency commonly causes hypoglycemia in children but not in adults.
2. Pituitary disease: Patients with hypopituitarism may develop hypoglycemia because of deficiencies of growth hormone and/or thyroid hormone.
3. Glucagon: Glucagon deficiency is the rarest cause of hypoglycemia of endocrine origin.

C. Hypoglycemia due to inadequate production of endogenous glucose

1. Liver disease: Hypoglycemia due to abnormal liver function generally does not occur until hepatic injury is severe. Hepatotoxins that can impair gluconeogenesis and cause hypoglycemia include carbon tetrachloride, the *Amanita phalloides* mushroom toxin, and urethane. Hepatic congestion due to severe congestive heart failure rarely causes hypoglycemia.
2. Kidney disease: Symptomatic hypoglycemia occurs in many diabetic patients undergoing dialysis. The cause may involve increased glucose-stimulated insulin release due to the high glucose concentration in the dialysate and impaired clearance of insulin due to the underlying renal disease. Spontaneous fasting hypoglycemia has been reported to occur in nondiabetic patients with end-stage renal disease.
3. Ethanol-induced hypoglycemia (alcoholic ketoacidosis): Ethanol inhibits gluconeogenesis and the hepatic uptake of gluconeogenic precursors. Hypoglycemia can occur more than a day after the ingestion of ethanol. Ketonuria and ketonemia are usually present. Children and chronic alcohol abusers are most susceptible. This condition most commonly occurs in the setting

TABLE 92-1 Drugs and Toxins Associated with Hypoglycemia

Drugs that increase circulating insulin concentrations	Drugs that impair gluconeogenesis	Unknown mechanism of action
Direct stimulants of insulin secretion	*Hepatotoxins (Amaitatoxin)*	Acetazolamide (Diamox)
Acetohexamide (Dymelor)	Acetaminophen (Tylenol, Tempra)	Acetylsalicylic acid (Aspirin)
Chloroquine (Aralen)	Propoxyphene (Darvon)	Aluminum hydroxide (Dialume)
Chlorpropamide (Diabinese)	*Agents that decrease activity of gluconeogenic enzymes*	Captopril (Capoten)
Disopyramide (Norpace)	Metoprolol (Lopressor)	Chlorpromazine (Thorazine)
Glimepiride (Amaryl)	Nadolol (Corgard)	Cimetidine (Tagamet)
Glipizide (Glucotrol)	Phenformin	Diphenhydramine (Benadryl)
Glyburide (Micronase, Diabeta, Glynase, Glibenclamide)	Metformin (Glucophage)	Doxepin (Sinequan, Adapin)
Pentamidine (Pentam)	Pindolol (Visken)	Enalapril (Vasotec)
Quinidine	Propranolol (Inderal)	Ethylenediaminetetraacetic acid (EDTA, Versene)
Quinine	*Hypoglycin*	Haloperidol (Haldol)
Ritodrine (Yutopar)	*Ethanol*	Isoxsuprine
Terbutaline (Brethine, Bricanyl)		Lidocaine (Xylocaine)
Tolazamide (Tolinase)		Lithium (Eskalith)
Tolbutamide (Orinase)		Oxytetracycline (Terramycin)
Trimethoprim/ Sulfamethoxazole (Bactrim, Septra)		Para-aminobenzoic acid (PABA)
Agents that enhance the action of sulfonylureas		Para-aminosalicyclic acid (PASA)
Bishydroxycoumarin (Dicoumarol)		Phenytoin (Dilantin)
Imipramine (Tofranil)		Ranitidine (Zantac)
Phenylbutazone (Butazolidine)		Sulfadiazine
Exenatide (Byetta)		Sulfisoxazole (Gantrisin)
		Warfarin (Coumadin)

A sampling of common trade names is shown in parenthesis: the enumeration of trade names is not exhaustive. Data for some listed agents may be very limited.
(Adapted from Seltzer HS. Drug-induced hypoglycemia: a review of 1418 cases. *Endocrinol Metab Clin North Am* 1989:18:163–183.)

of poor food intake and depleted glycogen stores. More information can be found in Chapter 88.

4. Drugs: Some of the many drugs and poisons that do not increase circulating insulin but nonetheless cause hypoglycemia are listed in Table 92-1. β-Blockers prevent the normal glycogenolytic and gluconeogenic responses to hypoglycemia and may mask adrenergic symptoms. Salicylate intoxication causes hypoglycemia commonly in children but only very rarely in adults. Hypoglycemia associated with angiotensin-converting enzyme inhibitors has been reported in patients with diabetes.
5. Sepsis: Sepsis has occasionally been implicated as a cause of hypoglycemia. Septic hypoglycemic patients are often acidotic, and the fatality rate is high.
6. Congenital enzymatic deficiencies: Typically produce hypoglycemia in the context of glycogen storage disease or impaired hepatic gluconeogenesis. These uncommon conditions usually present in infancy.

D. Fasting hypoglycemia due to the unavailability of gluconeogenic substrate. The prototypic disease in which substrate deficiency leads to hypoglycemia is nonketotic hypoglycemia of childhood. The hallmark of the disease is a low basal blood concentration of the gluconeogenic precursor alanine.

III. DIAGNOSIS

A. Clinical presentation

1. Adrenergic signs and symptoms: Caused by counterregulatory hormones (catecholamines) released in response to hypoglycemia. The most prominent symptoms and signs are weakness, palpitations, anxiety, diaphoresis, tachycardia, peripheral vasoconstriction, and widening of the pulse pressure. These findings may be absent in patients taking sympatholytic drugs (e.g., prazosin, clonidine, and β-blockers) and in patients with long-standing diabetes (see subsequent text).
2. Neurologic signs and symptoms: Symptoms and signs of neuroglycopenia include hunger, headache, confusion, slurred speech, and other nonspecific behavioral changes. These can progress to lethargy, obtundation, seizures, and coma.
3. Cardiac manifestations: In the ICU setting, hypoglycemia and the sympathoadrenal response to it can be associated with supraventricular and ventricular tachycardias, atrial fibrillation, and junctional dysrhythmias. Electrocardiographic abnormalities include T-wave flattening, increased Q-T interval, ST segment depression, and repolarization abnormalities. Bradycardias have rarely been attributed to hypoglycemia.
4. Prolonged hypoglycemia: Can be associated with hypothermia, hypokalemia, hypophosphatemia, and respiratory failure.

B. Laboratory.

Obtain blood and urine samples from comatose hypoglycemic patients when they are first seen. This will allow appropriate assays for sulfonylureas or insulin to be performed later, if indicated.

1. Blood glucose concentration: The normal plasma glucose concentration is 60 to 120 mg/dL (3.3 to 6.7 mM). Whole blood glucose and capillary fingerstick glucose levels are 15% to 20% lower. Fingerstick blood glucose determinations can be inaccurate at lower glucose concentration. Symptoms of hypoglycemia generally occur when the glucose concentration is <50 mg/dL (2.8 mM) in plasma or <40 mg/dL (2.2 mM) in whole blood. After approximately 48 hours of starvation, however, many individuals, particularly women, have a plasma glucose concentration <50 mg/dL (2.8 mM). After 72 hours of fasting, the plasma glucose concentration may approach 40 mg/dL (2.2 mM) in asymptomatic individuals. Comparably "low" plasma glucose concentrations also occur in pregnancy, during which the normal fasting plasma glucose concentration is 60 mg/dL or less (3.3 mM). Factitious hypoglycemia may occur as a result of storing blood samples at room temperature before testing. Glucose concentration in the test tube may decline at a rate of approximately 7% per hour. The effect is enhanced if large numbers of white blood cells are present as the result of severe leukocytosis or leukemia.
2. Ketonuria: Low plasma glucose concentrations are associated with low circulating insulin levels that in turn promote lipolysis and ketogenesis. Hypoglycemia associated with ketonuria is unlikely to be due to overinsulinization.
3. Detection of drugs and toxins: If oral agent abuse is suspected, serum and urine should be screened for sulfonylurea compounds. Not automatically available as part of toxic screens, testing for sulfonylurea drugs must be requested specifically.
4. Detection of surreptitiously injected insulin: When nontherapeutic insulin self-administration is suspected, obtain simultaneous insulin and C-peptide blood concentrations during a hypoglycemic episode. Insulin and C-peptide are normally cosecreted by the pancreas in equimolar quantities, but the latter is not present in commercial insulin. Insulinomas are often small and difficult to visualize radiographically. In patients with suspected insulinoma, fasting insulin (in μU/mL) and glucose (in mg/dL) measurements should be

obtained. If the insulin/glucose ratio is >0.3, the insulin concentration may be inappropriately high. Another useful test is the serum concentration of proinsulin, which is typically elevated to >30% of the insulin concentration in cases of insulinoma.

5. Other: Additional tests should be ordered as appropriate. In general, these should always include studies of hepatic and renal function. A cosyntropin test may be performed if adrenal insufficiency is suspected.

IV. TREATMENT

A. Specific therapies

1. Glucose: Treat presumed or documented hypoglycemia in the patient with stupor or coma with an intravenous injection of 50 mL of D50W over 3 to 5 minutes. The treatment is lifesaving in the presence of hypoglycemic coma and harmless when given to patients with coma due to other causes. Avoid subcutaneous extravasation; the solution is hypertonic and can cause local tissue damage and pain. Treatment with D50W usually leads to improved mental status within minutes, but patients who are elderly or who have had very prolonged hypoglycemia may respond slowly. Most cases of hypoglycemia in the ICU can be treated with glucose alone.

   If a patient is sufficiently alert and cooperative, oral carbohydrates (e.g., sucrose in orange juice, glucose tablets) may be given. Hypoglycemia in patients taking α-glucosidase inhibitors should be treated with monomeric glucose (e.g., glucose tablets) or fructose (e.g., fruit juice) because these drugs delay absorption of complex sugars including sucrose.

   The most common error in management is inadequate treatment leading to recurrence of symptoms. After the first bolus of D50W is given, an infusion of D5W or D10W glucose should be started in any patient whose hypoglycemic episode is not due to exogenous short- or intermediate-acting insulin. Severe cases of unexplained hypoglycemia require intensive care monitoring. Blood glucose should be monitored every 1 to 3 hours and the serum glucose concentration maintained at a target level of at least 100 mg/dL.

   To determine whether parenteral glucose is no longer needed, the infusion should be discontinued and blood glucose concentration measured every 15 minutes. If a patient is unable to maintain a blood glucose concentration >50 mg/dL (2.8 mM) or if the patient becomes symptomatic, reinstitution of glucose therapy is necessary.

   When the cause of hypoglycemia is sulfonylurea ingestion, the patient should usually be admitted to the hospital because continuous intravenous glucose is mandatory. The biological half-life of many drugs in this class is >24 hours. Meals should be provided if the patient can eat. It is particularly important that glucose infusions be continued while patients recovering from a sulfonylurea overdose are asleep. Patients with this condition may require 2 to 3 days of intravenous glucose therapy. The somatostatin analog octreotide, which inhibits insulin secretion, may be used as an adjunct to the treatment of severe oral agent overdosage.

2. Glucagon: Parenteral glucagon injection is a useful treatment for hypoglycemia, particularly in out-of-hospital treatment of hypoglycemia. It is useful in the emergency department or ICU if hypoglycemic coma occurs in a patient without intravenous access. It is most effective in patients with ample liver glycogen stores.
3. Agents that block insulin secretion: When refractory hypoglycemia is due to an insulinoma or nesidioblastosis, it may rarely be necessary to supplement glucose infusion therapy with drugs that inhibit insulin secretion. These include diazoxide and the somatostatin analog octreotide. Hypoglycemia

due to nesidioblastosis can reportedly be treated with calcium-channel blockers such as nifedipine.

4. Consider efforts to prevent drug absorption and increase elimination. Activated charcoal adsorbs sulfonylureas, and urinary alkalinization may enhance excretion of drugs in this class. Charcoal hemoperfusion is probably not indicated except in the setting of renal failure and massive overdose.
5. Steroids: When the etiology of severe, refractory hypoglycemia is obscure, adrenocortical steroids may be given to increase gluconeogenic substrates and inhibit insulin action in the periphery.

B. Pearls (key points and pitfalls): Manage the precipitating factor. Glucose corrects hypoglycemia but not its cause. The commonest cause of hypoglycemia is inadvertent insulin overdosage due to changes in diet, increases in exercise, or injection of the wrong kind of insulin. Other causes of hypoglycemia include drugs and intercurrent illnesses including renal or hepatic failure. A patient should not be discharged until one of these processes, outlined in the section on pathophysiology, is identified or an appropriate follow-up plan is formulated.

1. Think about drugs: Many drugs cause hypoglycemia. In particular, persons with diabetes who become intoxicated may develop life-threatening, profound hypoglycemia because of the metabolic synergy of ethanol and insulin.
2. Measure urinary ketones: The presence of urinary ketones in a hypoglycemic patient generally excludes hyperinsulinemia as the cause of the low glucose concentration and can quickly refocus the differential diagnosis.
3. Beware of recurrent hypoglycemia. Many sulfonylurea-class oral hypoglycemic agents have a very long duration of action. Prolonged treatment is often required in cases of sulfonylurea overdose.
4. Be alert for "hypoglycemia unawareness." Patients with diabetes may fail to perceive the symptoms of hypoglycemia, especially when it occurs precipitously. Hypoglycemia unawareness can be due to frequent hypoglycemic episodes and due to medicines that interfere with recovery from hypoglycemia (e.g., β-blockers). Patients who have had diabetes for many years experience blunting of the normal counterregulatory response to hypoglycemia. They may also become exquisitely sensitive to short-acting insulins and can therefore become hypoglycemic very rapidly.

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SICK EUTHYROID SYNDROME IN THE INTENSIVE CARE UNIT

93

Alan P. Farwell

I. GENERAL PRINCIPLES

A. Critical illness causes multiple nonspecific alterations in thyroid hormone concentrations in patients who have no previously diagnosed intrinsic thyroid disease that relate to the severity of the illness.

B. There is an ongoing debate whether such alterations are a physiologic adaptation or a pathologic perturbation. Because to the complexity of many patients with the sick euthyroid syndrome, it is likely that both physiologic and pathologic effects play a role.

C. Despite abnormalities in serum thyroid hormone parameters, there is little evidence that critically ill patients have clinically significant thyroid dysfunction. While some investigators have proposed otherwise, there is no current evidence to support thyroid hormone therapy in the management of the sick euthyroid syndrome.

D. While a wide variety of illnesses tend to result in the same changes in serum thyroid hormones, these changes are rarely isolated and often are associated with alterations in other endocrine systems, such as reductions in serum gonadotropin and sex hormone concentrations and increases in serum adrenocorticotropic hormone (ACTH) and cortisol.

E. The sick euthyroid syndrome should not be viewed as an isolated pathologic event but as part of a coordinated systemic reaction to illness that involves both the immune and endocrine systems.

II. PATHOGENESIS

A. While the cause of the alterations in thyroid hormone economy in critical illness is largely unknown, cytokines, such as tumor necrosis factor α, interleukin 1, and interleukin 6, have been shown to reproduce many of the features of the sick euthyroid syndrome in both animal and human studies when administered in pharmacologic doses.

B. Whether the sick euthyroid syndrome results from activation of the cytokine network or simply represents an endocrine response to systemic illness resulting from the same mediators that trigger the cytokine cascade remains to be determined.

III. PATHOPHYSIOLOGY

A. Alterations in peripheral metabolic pathways

1. The major pathway of metabolism of thyroxine (T_4) is by sequential monodeiodination by type 1 (D1) or type 2 deiodinase (D2) to generate triiodothyronine (T_3) (activating pathway) or type 3 deiodinase (D3) to generate rT_3 (inactivating pathway).

2. One of the first alterations in thyroid hormone metabolism in acute illness is inhibition of D1 in peripheral tissues, which is affected by a wide variety of factors (Table 93-1) and subsequent impairment in T_4 to T_3 conversion.

3. Because >80% of T_3 is derived from deiodination of T_4 in peripheral tissues, T_3 levels fall soon after the onset of acute illness. D1 also deiodinates rT_3, so degradation is impaired and levels of this inactive hormone rise in proportion to the fall in T_3 levels.

TABLE 93-1 Factors that Inhibit Thyroxine (T_4) to Triiodothyronine (T_3) Conversion in Peripheral Tissues

Acute and chronic illness
Caloric deprivation
Malnutrition
Glucocorticoids
β-Adrenergic blocking drugs (e.g., propranalol)
Oral cholecystographic agents (e.g., iopanoic acid[a], sodium ipodate[a])
Amiodarone
Propylthiouracil
Fatty acids
Fetal/neonatal period
Selenium deficiency
Cytokines (Il-1, Il-6)

[a]Currently unavailable or limited availability.
Il, interleukin.

4. In general, D3 is unaffected by acute illness so inner ring deiodination of T_4 to produce rT_3 is unchanged. However, recent studies have suggested that D3 may be increased in certain tissues, leading to increased T_3 disposal within those tissues.
5. D2, a deiodinase abundant in the brain, has also been found to be abundant in skeletal muscle in humans and levels may be increased in critical illness. The significance of these findings is uncertain at present.

B. Alterations in the pituitary–thyroid axis

1. Synthesis and secretion of thyroid hormone is under the control of the anterior pituitary hormone, thyrotropin (thyroid stimulating hormone [TSH]), in a classic negative feedback system.
2. While serum TSH levels are usually normal early in acute illness, levels often fall as the illness progresses due to the effects of a variety of inhibitory factors that are common in the treatment of the critically ill patient (Table 93-2).
3. The use of dopamine, increased levels of glucocorticoids, either endogenous or exogenous, and inhibitory signals from higher cortical centers also may play a role in decreasing TSH secretion, as well as certain thyroid hormone metabolites that are increased in nonthyroidal illness.

C. Alterations in serum-binding proteins

1. Both T_4 (99.97% bound) and T_3 (99.7% bound) circulate in the serum bound primarily to thyroxine-binding protein (TBG), and the binding of thyroid hormones to TBG is affected by a variety of factors in acute illness (Table 93-3).
2. Since only the unbound hormone has any metabolic activity (free hormone concept), changes in the concentrations of, or binding to, TBG would have major effects on the total serum hormone levels but minimal changes in the free hormone concentrations, and, thus, overall thyroid function, are actually seen.

D. Stages of the sick euthyroid syndrome

1. **Low T_3 state**
   a. Common to all of the abnormalities in thyroid hormone concentrations seen in critically ill patients is a substantial depression of serum T_3 levels, which can occur as early as 24 hours after the onset of illness and affects over half of the patients admitted to the medical service.

TABLE 93-2 Factors that Alter Thyroid Stimulating Hormone (TSH) Secretion

Increase	Decrease
Chlorpromazine	Acute and chronic illness
Cimetidine	Adrenergic agonists
Domperidine	Caloric restriction
Dopamine antagonists	Carbamazapine
Haloperidol	Clofibrate
Iodide	Cyproheptadine
Lithium	Dopamine and dopamine agonists
Metoclopramide	Endogenous depression
Sulphapyridine	Glucocorticoids
X-ray contrast agents	IGF-1
	Metergoline
	Methylsergide
	Opiates
	Phenytoin
	Phentolamine
	Pimozide
	Somatostatin
	Serotonin
	Surgical stress
	Thyroid hormone metabolites

IGF-1, insulin-like growth factor-1.

TABLE 93-3 Factors that Alter Binding of Thyroxine (T_4) to Thyroxine-Binding Protein (TBG)

	Increase binding	Decrease binding
Drugs		
	Estrogens	Glucocorticoids
	Methadone	Androgens
	Clofibrate	L-asparaginase
	5-Fluorouracil	Salicylates
	Heroin	Mefenamic acid
	Tamoxifen	Antiseizure medications (phenytoin, tegretol)
	Raloxifene	Furosemide
		Heparin
Systemic factors		
	Liver disease	Inherited
	Porphyria	Acute illness
	HIV infection	Nonesterified free fatty acids
	Inherited	

HIV, human immunodeficiency virus.

b. The decrease in serum T_3 levels can be explained solely by inhibition of D1 and subsequent impairment of peripheral T_4 to T_3 conversion.
c. Clinically, these patients appear euthyroid, although mild prolongation in Achilles reflex time is found in some patients.
d. This stage is common in patients with congestive heart failure and with acute cardiac injury. In patients with cardiac disease, serum T_3 concentrations are a negative prognostic factor and inversely proportional to mortality.

2. High T_4 state
a. Serum T_4 levels may be elevated early in acute illness due to either the acute inhibition of T_4 to T_3 conversion or increased TBG levels.
b. Increased serum T_4 levels are seen most often in the elderly and in patients with psychiatric disorders.
c. As the duration of illness increases, nondeiodinative pathways of T_4 degradation increase and return serum T_4 levels to the normal range.

3. Low T_4 state
a. As the severity and the duration of the illness increases, serum total T_4 levels may decrease into the subnormal range as a result of a decrease in the binding of T_4 to TBG, a decrease in serum TSH levels leading to decreased production of T_4, and an increase in nondeiodinative pathways of T_4 metabolism.
b. The decline in serum T_4 levels correlates with prognosis in noncardiac ICU patients, with mortality increasing as serum T_4 levels drop below 4 μg/dL and approaching 80% in patients with serum T_4 levels <2 μg/dL.
c. Despite marked decreases in serum total T_4 and T_3 levels to the hypothyroid range, the free hormone levels are often normal; therefore, the low T_4 state is more likely a marker of multisystem failure in these critically ill patients than a true hormone-deficient state.

4. Recovery state
a. The alterations in thyroid hormone concentrations resolve as the illness resolves.
b. This stage may be prolonged and is characterized by the modest increases in serum TSH levels.
c. Full recovery, with restoration of thyroid hormone levels to the normal range, may take up to several months after the patient is discharged from the hospital.

IV. DIAGNOSIS

A. The routine screening of an ICU population for the presence of thyroid dysfunction is not recommended due to the high prevalence of abnormal thyroid function tests and low prevalence of true thyroid dysfunction.
B. Whenever possible, it is best to defer evaluation of the thyroid–pituitary axis until the patient has recovered from his/her acute illness.
C. When thyroid function tests are ordered in a hospitalized patient, it should be with a high clinical index of suspicion for the presence of thyroid dysfunction.
D. Because every test of thyroid hormone function can be altered in the critically ill patient, no single test can definitively rule in or rule out the presence of intrinsic thyroid dysfunction (Table 93-4).

E. Thyroid function tests

1. TSH assays
a. While the sensitive TSH assay is currently the best screening test for thyroid dysfunction in the healthy, ambulatory patient, this does not hold true for the ill patient.

TABLE 93-4 Tests of Thyroid Function in the Intensive Care Unit (ICU)

Tests	Typical normal range	Use	Limitation in acute illness
TSH	0.4–5.0 mU/L	Best initial test to determine thyroid status in healthy patients	Loss of specificity, abnormal in up to 20% of hospitalized patients
Total T_4	4–12 μg/dL	Measures bound and free hormone in serum	Affected by alterations in serum-binding proteins
T_4- or T_3-resin uptake	25%–35%	Estimate of the serum protein–binding sites	Affected by alterations in serum-binding proteins
THBR	0.8–1.15	Estimate o f the serum protein–binding sites	Affected by alterations in serum-binding proteins
FTI	1–4 (if use resin uptake) 4–12 (if use THBR)	Estimate of free T_4 concentrations	Affected by alterations in serum-binding proteins
Free T_4, analog method	0.7–2.1 ng/dL	Direct measurement of free T_4 concentrations	May not be any more reliable than FTI
Free T_4, equilibrium dialysis method	0.7–2.1 ng/dL	Gold standard for measurement of free T_4 concentrations	Expensive, time-consuming to perform, not readily available
Total T_3	75–180 ng/dL	Measures bound and free hormone in serum	Levels fall in all hospitalized patients, never a first-line test
Free T_3	200–400 pg/dL	Direct measurement of free T_3 concentrations	No advantage to Total T_3
Thyroid autoantibodies (anti-Tg, anti-TPO)	Negative	Determines presence of autoimmune thyroid disease	Second-line test, may help predict presence of thyroid dysfunction

TSH, thyroid stimulating hormone; T_4, thyroxine; T_3, triiodothyronine; THBR, thyroid hormone binding ratio; FTI, free T_4 index; Tg, thyroglobulin; TPO, thyroid peroxidase.

b. Abnormal TSH values have been reported in up to 20% of hospitalized patients, over 80% of whom have no intrinsic thyroid dysfunction on follow-up testing when healthy.

c. Abnormal TSH values require additional biochemical and clinical evaluation before a diagnosis of thyroid dysfunction can be made.

2. Free T_4 concentrations

a. Total T_4 measurements alone are of little use in the acutely ill patient since abnormalities in binding to serum proteins are commonplace.

b. Measurement of true serum free T_4 concentrations is time-consuming and expensive; therefore, estimates of the free T_4 concentrations are obtained by either the free T_4 index (FTI) or the free T_4 by analog measurement.

3. Total T_3

a. There is no indication for the routine measurement of serum T_3 levels in the initial evaluation of thyroid function in the critically ill patient, since serum T_3 concentrations are affected to the greatest degree by the alterations in thyroid hormone economy resulting from acute illness.

b. The only setting where serum T_3 levels may be helpful is in the presence of a suppressed sensitive TSH value where an elevated serum T_3 concentration will differentiate between thyrotoxicosis and the sick euthyroid syndrome.

4. Thyroid autoantibodies

a. The presence of thyroid autoantibodies (antithyroglobulin and antithyroid peroxidase) determines the presence of autoimmune thyroid disease but does not necessarily indicate thyroid dysfunction.

b. Thyroid autoantibodies do add to the specificity of abnormal TSH and FTI values in diagnosing intrinsic thyroid disease.

F. Diagnostic approach

1. A reasonable initial approach is to obtain both FTI (or FT_4) and TSH measurements in patients with a high clinical suspicion for intrinsic thyroid dysfunction.

2. Assessment of these values in the context of the duration, the severity, and the stage of illness of the patient will allow the correct diagnosis in most patients.

3. If the diagnosis is still unclear, measurement of thyroid antibodies may be helpful as a marker of intrinsic thyroid disease.

4. Only in the case of a suppressed TSH and a mid-normal to high FTI, the measurement of serum T_3 levels is indicated.

G. Treatment

1. Starvation/undernutrition

a. L-T_3 treatment results in increased protein breakdown and increased nitrogen excretion in fasting normal and obese patients.

2. General ICU patients

a. No benefit of L-T_4 on general medical patients, burn patients, patients with acute renal failure or renal transplant

3. Premature infants

a. No benefit of L-T_4 on developmental indices of premature infants at 26 to 28 weeks gestation

b. Possible beneficial effect of L-T_4 on infants of at 25 to 26 weeks gestation but possible deleterious effects on infants of 27 to 30 weeks gestation

c. No benefit of L-T_3

d. Meta-analysis shows no significant effects of thyroid hormone treatment of premature infants

4. Cardiac surgery patients

a. Small studies suggest improved hemodynamic parameters with L-T_3

b. Large trials show no benefit of L-T_3 noted in patients undergoing cardiac bypass

c. Possible improvement in hemodynamic parameters and hospital stay with L-T_3 in children undergoing cardiac

5. Cardiac donors

a. Variable results on the effects of L-T_3 in preserving function of normal hearts in brain-dead cardiac donors before transplantation.

b. Possible benefits of L-T_3 in improving function of impaired hearts before transplant, potentially increasing the pool of organs available for transplantation.

c. Consensus conferences recommend the use of L-T_3 as part of the hormonal resuscitation in donors whose cardiac ejection fraction is <45%.

6. Congestive heart failure

a. Small uncontrolled study suggested short-term L-T_4 therapy increased cardiac output and functional capacity and decreased systemic vascular resistance.

b. Improved hemodynamic parameters and neurohumerol profiles with short-term intravenous L-T_3 infusion, possibly requiring supraphysiologic concentrations.

This chapter is based on the chapter by Farwell AP, "The sick euthyroid syndrome in the Intensive Care Unit." in *Intensive Care Medicine*, 6th Edition (Irwin RS, Cerra FB, Rippe JM, eds) (2008) Lippincott Williams & Wilkins, Philadelphia, PA.

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Hematologic Problems in the Intensive Care Unit

VIII

DISORDERS OF HEMOSTASIS

94

Adam Cuker and Suman L. Sood

I. THE BLEEDING PATIENT: BASIC PRINCIPLES

A. Etiology

1. Bleeding disorders (Table 94-1) may be secondary to
   - **a.** Defects in the activity of platelets
   - **b.** Defects in the activity of one or more coagulation factors (coagulopathy)
   - **c.** Congenital causes
   - **d.** Acquired causes
2. Hematology consultation is often necessary if the cause of bleeding is not immediately apparent and/or if specialized laboratory testing is required for diagnosis.

B. Clinical presentation

1. Site of bleeding
   - **a.** Platelet disorders tend to cause mucocutaneous bleeding (e.g., epistaxis, oral, gastrointestinal [GI], genitourinary [GU], ecchymosis)
   - **b.** Coagulopathies (i.e., deficiencies in the activity of coagulation factors) tend to cause deep soft tissue bleeding (e.g., into joints and muscles)
   - **c.** Bleeding from a single site (e.g., a surgical site, GI tract, etc.) warrants evaluation for an anatomic cause of bleeding

TABLE 94-1 Selected Congenital and Acquired Bleeding Disorders

Mechanism	Congenital	Acquired
Defects in platelet activity[a]	Qualitative platelet disorders von Willebrand disease[b]	Medications Renal disease Myelodysplasia Myeloproliferative disorders
Defects in coagulation	Hemophilia A Hemophilia B Other factor deficiencies	Vitamin K deficiency Liver disease Exposure to anticoagulants DIC, Trauma Acquired factor inhibitors

[a] For defects in platelet function due to thrombocytopenia, see Chapter 95.
[b] Deficiency of von Willebrand factor leads to reduced binding of platelets to sites of vascular injury and to one another.
DIC, disseminated intravascular coagulation.

2. Personal and family bleeding history
   a. Congenital disorders: life-long history of bleeding, positive family history
      i. Exceptions are possible (e.g., mild hemophilia)
   b. Acquired disorders: often no previous history of bleeding, no family history
3. Physical examination
   a. Skin: ecchymosis, petechiae, nonpalpable purpura
   b. Hemarthrosis: warm, swollen joints
   c. Mucosal surfaces (e.g., nasal or oral pharyngeal mucosa)

C. Laboratory studies

1. Initial testing
   a. Complete blood count (exclude thrombocytopenia, assess for anemia)
   b. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) (to exclude coagulopathy; see Fig. 94-1 and Table 94-2)
      i. Prolonged PT
         (a) May indicate defect in tissue injury (also known as *extrinsic*) pathway of coagulation
      ii. Prolonged aPTT
         (a) May indicate defect in contact (also known as *intrinsic*) pathway of coagulation
   c. Prolonged PT and aPTT
      i. May indicate single defect in common pathway of coagulation, or multiple defects
2. Specialized testing
   a. Mixing study (1:1 mix of patient and normal plasma)
      i. Indication: prolonged PT or aPTT
         (a) If prolongation completely corrects with mixing → suggests factor deficiency
         (b) If prolongation does not completely correct with mixing → suggests inhibitor (either specific to an individual coagulation factor or nonspecific, such as a lupus anticoagulant)
   b. Individual coagulation factor levels
      i. aPTT prolongation: send factors VIII, IX, XI
      ii. PT prolongation: send factors II, V, VII, X, fibrinogen
      iii. von Willebrand factor (VWF) levels (see Section III.B)

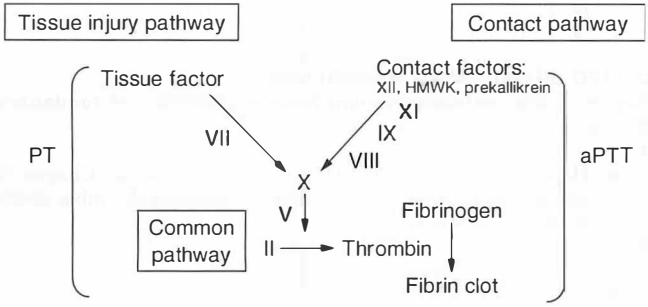

Figure 94-1. The coagulation cascade may not fully represent the process of coagulation *in vivo*, where activation of coagulation usually is initiated through the **tissue injury** (also known as *extrinsic*) **pathway of coagulation**, which subsequently can activate the **contact** (also known as *intrinsic*) **pathway** through thrombin-mediated activation of factors VIII and XI (not shown). The tissue injury system involves binding of activated factor VII to tissue factor and activation of factor X, whereas the contact system involves activation of factor XI by contact factors such as factor XII and subsequent activation of factor IX, which in conjunction with activated factor VIII subsequently activates factor X. The **common pathway** involves the activated factor X-mediated cleavage of factor II to yield thrombin, which cleaves fibrinogen to form fibrin clot. The fibrin clot is strengthened through the cross-linking action of factor XIII (not shown). aPTT, activated partial thromboplastin time; PT, prothrombin time.

TABLE 94-2 Selected Causes of a Prolonged Activated Partial Thromboplastin Time (aPTT) and/or Prothrombin Time (PT)[a]

Isolated prolonged aPTT	Isolated prolonged PT	Prolonged aPTT and PT
Heparin exposure	Warfarin exposure[d]	DIC
Lupus anticoagulant[b]	Vitamin K deficiency	Liver synthetic dysfunction
Deficiency (or inhibitor) of factors VIII, IX, or XI	Liver synthetic dysfunction	Supratherapeutic warfarin or heparin
Deficiency of contact factors (XII, HMWK, or prekallikrein) [b]	Congenital deficiency of factor VII	Exposure to direct thrombin inhibitors (argatroban >> lepirudin)
von Willebrand disease[c]	Mild DIC	Congential deficiency of factors II, V, or X
		Hypo- or dysfibrinogenemia
		Superwarfarin exposure[e]

[a] Bleeding disorders that typically do not feature a prolongation in the aPTT or PT include, but are not limited to: von Willebrand disease, FXIII deficiency, antiplasmin deficiency, disorders of the vasculature or integument (e.g., Ehlers–Danlos, Osler–Weber–Rendu, scurvy).
[b] Conditions not associated with bleeding.
[c] VWD (especially type 1) also may feature a normal aPTT.
[d] Supratherapeutic warfarin also can lead to prolonged aPTT.
[e] Superwarfarin pesticides include brodifacoum, bromodiolone, coumafuryl, and difenacoum
DIC, disseminated intravascular coagulation; HMWK, high molecular weight kininogen.

iv. Platelet function studies (see Section III.C)
v. FXIII levels (see Section III.D)

II. ACQUIRED DISORDERS OF HEMOSTASIS

A. Heparin-, low-molecular-weight heparin (LMWH)-, or fondaparinux-induced

1. Pathophysiology
   a. Heparins (including LMWH) and fondaparinux (see Chapter 96) bind and potentiate antithrombin, which inactivates thrombin and/or other activated clotting factors
2. Diagnosis
   a. Compatible clinical history
   b. Unfractionated heparin (UFH)
      i. Prolonged aPTT
      ii. Prolongation corrects with treatment of laboratory sample with heparin neutralizing agent
   c. LMWH or fondaparinux
      i. aPTT not usually prolonged
3. Treatment
   a. Clinically insignificant bleeding
      i. Discontinue or reduce dose of anticoagulant and observe patient closely
   b. Clinically significant bleeding requiring urgent reversal of anticoagulant effect
      i. UFH
         (a) Intravenous (IV) UFH
            (1) Give protamine, 1 mg/100 units heparin remaining in the circulation (see Table 94-3 for calculation of protamine dose)
            (2) Infuse protamine slowly (≤20 mg/minute; ≤50 mg over any 10-minute period) due to low risk (<1%) of anaphylaxis

TABLE 94-3 [a]**Calculation of Protamine Dose**

Time of administration of UFH (h)	Dose of UFH (units)	Bolus/ infusion	UFH remaining at 1 h[b,c] (units)	UFH remaining at 2 h[b,c] (units)	UFH remaining at 3 h[b,c] (units)	Protamine required to reverse (mg)[d]
0	6,400	Initial bolus	3,200	1,600	800	8
0	1,440	Infusion	1,440	720	360	3.6
1	1,440	Infusion	(0)	1,440	720	7.2
2	1,440	Infusion	(0)	(0)	1,440	14.4
Approximate dose of protamine required to reverse heparin remaining in circulation →						**33.2**

[a] This illustration presumes an 80-kg patient who was given 80 units UFH/kg (=6,400 units) IV bolus at time zero, then 18 units/kg/h (=1,440 units/h) continuous IV infusion for 3 h, then developed clinically significant bleeding requiring reversal.
[b] This model assumes a half-life of UFH of 1 h.
[c] Calculated amounts of UFH remaining at one hour following initiation of a *continuous infusion* may be overestimated in this model.
[d] Administer no more than 20 mg of protamine per minute and no more than 50 mg over any 10-min period.
UFH, unfractionated heparin; IV, intravenous.

(3) Send aPTT to ensure adequate reversal of anticoagulant effects of UFH
(b) Subcutaneous (SC) UFH
(1) Repeated administration of smaller doses of protamine may be required
ii. LMWH
(a) Protamine less effective for reversal than for UFH
(b) Only 30% of LMWH molecules may be neutralized by protamine
(c) Give protamine, 1 mg/100 units LMWH given at last dose
(1) *Example*: Bleeding patient receiving enoxaparin, 60 mg q 12 hours subcutaneously: 1 mg enoxaparin = 100 units → protamine dose = 60 mg → give 50 mg protamine (60 mg would exceed maximum dose of 50 mg).
(2) If LMWH was given >8 hours ago, halve calculated dose of protamine (using example above: 60 ÷ 2=30 mg protamine).
(3) Infuse protamine slowly (≤20 mg/minute, ≤50 mg over any 10-minute period) due to low risk (<1%) of anaphylaxis.
iii. Fondaparinux
(a) No reversal agent available
(b) Supportive care
(c) Use of recombinant human factor VIIa (rhVIIa) (NovoSeven) in a single patient has been reported

B. Warfarin-induced

1. Pathophysiology
   a. Warfarin inhibits production of vitamin K-dependent clotting factors (II, VII, IX, X)
2. Diagnosis
   a. Compatible clinical history
   b. Prolonged PT/international normalized ratio (INR)
      i. Corrects with mixing
      ii. aPTT may also be prolonged in the context of supratherapeutic warfarin
   c. Decreased levels of clotting factors II, VII, IX, X (vitamin K-dependent)
   d. When necessary, can be differentiated from vitamin K deficiency by measuring warfarin level in the blood
3. Treatment
   a. Dependent on degree of INR elevation and presence or absence of bleeding (Table 94-4)

C. Vitamin K deficiency

1. Pathophysiology
   a. Inadequate dietary intake of vitamin K
   b. Malabsorption of fat-soluble dietary vitamin K
   c. Decreased production of vitamin K by intestinal flora (which may be destroyed by antibiotics)
2. Diagnosis
   a. Compatible clinical scenario
   b. Prolonged PT (corrects with mixing)
   c. Decreased levels of clotting factors II, VII, IX, X (vitamin K-dependent)
3. Treatment
   a. Phytonadione (vitamin K_1) administration
   b. May be given PO or IV at a dose of 1 to 10 mg/day
      i. IV dosing associated with small risk of anaphylaxis
         (a) Administer over 30 minutes with close monitoring
         (b) Smaller doses (e.g., 1 mg) advised
      ii. SC dosing not preferred due to erratic absorption

TABLE 94-4 Reversal of Warfarin-Induced Anticoagulation

Clinical situation	INR	Actions
No significant bleeding	<5.0	■ Hold warfarin ■ Check INR in 24 h to ensure declining INR
	5.0 to 9.0	■ Hold warfarin ■ Patients with high bleeding risk: Give vitamin K_1 2.5 to 5 mg PO $\times 1$[a] ■ Check INR in 24 h to ensure declining INR
	≥9.0	■ Hold warfarin ■ Give vitamin K_1 2.5–5 mg PO $\times$ 1 (may repeat in 24 h if INR not reduced)[a] ■ Check INR in 24 h to ensure declining INR
Serious or life-threatening bleeding	Any prolongation in INR due to warfarin administration	■ Hold warfarin ■ Give vitamin K_1 10 mg slow IV push (over 30 min); may repeat in 12–24 h if INR not reduced[a] ■ Give FFP, PCC[b], or rhVIIa[b] for acute reversal[c] ■ Initially, plan to follow INR frequently (every 1–4 h), and at least twice daily as long as bleeding risk remains, until INR within normal range and stable

[a] Oral vitamin K_1 is available as 5 mg tabs; may split 5 mg tab if 2.5 mg dose desired. Not available in 1 mg tablets. Higher doses of vitamin K_1 (e.g., 10 mg) may lead to warfarin resistance for up to 7 days.
[b] PCC or rhVIIa use associated with a small risk of thrombosis and/or DIC.
[c] Usual initial doses: FFP, 3–5 units per treatment initially; PCC (e.g., Bebulin VH), 50 units/kg $\times$ 1 IV push; rhVIIa (NovoSeven), 15–90 μg/kg $\times$ 1 IV push. Effects of FFP or PCC on INR are transient (4–6 h); vitamin K_1 must be administered concurrently to achieve durable reduction in INR. INR reduction may not correlate with clinical responsiveness to rhVIIa.
INR, international normalized ratio; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; rhVIIa, recombinant human factor VIIa.

   c. Treatment may be given empirically without confirmatory laboratory studies
      i. PT should begin to normalize within 12 hours of IV administration of vitamin K_1

D. Coagulopathy of liver disease

1. Pathophysiology
2. Deficiency of hepatically synthesized clotting factors including the vitamin K-dependent factors (II, VII, IX, X) and factors V, XI, XII, and fibrinogen
   a. Owing to any cause of liver disease that impairs synthetic function
3. Diagnosis
   a. Compatible clinical history
   b. Prolonged PT
      i. aPTT may also be prolonged
   c. Decreased levels of factors II, V, VII, X, and fibrinogen (IX and XI also may be decreased)
      i. Decreased factor V level distinguishes from pure vitamin K deficiency, which typically features a normal factor V level

- **d.** Other laboratory evidence of liver disease (e.g., decreased albumin, elevated alanine aminotransferase (ALT)/aspartate aminotransferase (AST), etc.)

4. Treatment
   - **a.** Blood products
     - **i.** Should be administered only if bleeding, at high risk of bleeding, or invasive procedure required
     - **ii.** Isolated mildly-moderately prolonged clotting times without bleeding not sufficient grounds for treatment
     - **iii.** Ongoing treatment may be required until liver synthetic deficiency is resolved (e.g., by definitive treatment, such as liver transplantation, or recovery following shock liver)
   - **b.** Fresh frozen plasma (FFP)
     - **i.** Usual dose: infusions of approximately 10 to 15 mL/kg (usually 3 to 5, 250 mL units)
     - **ii.** Severe hepatic failure and ongoing bleeding: consider continuous infusion ("FFP drip")
     - **iii.** Goal: cessation in bleeding
       - **(a)** A target INR of ≤ 1.5 is often cited, but may be difficult to achieve
     - **iv.** Beware of volume overload
   - **c.** Cryoprecipitate
     - **i.** Usual dose: 10 units per infusion
       - **(a)** Goal: cessation in bleeding and/or fibrinogen of ≥ 80 to 100 mg/dL
   - **d.** Follow aPTT, PT, fibrinogen, complete blood count every 3 to 6 hours if actively bleeding or every 6 to 12 hours if not actively bleeding

E. Disseminated intravascular coagulation (DIC)

1. Pathophysiology
   - **a.** Uncontrolled activation of coagulation, which paradoxically may lead to bleeding due to consumptive deficiencies of multiple clotting factors and platelets
2. Etiology
   - **a.** Sepsis
   - **b.** Malignancy (e.g., acute promyelocytic leukemia, Trousseau's syndrome)
   - **c.** Obstetrical complications (e.g., placental abruption; hemolysis, elevated liver enzymes, and low platelet count [HELLP] syndrome; amniotic fluid embolism)
   - **d.** Tissue damage (trauma, burns)
   - **e.** Vascular abnormalities (e.g., abdominal aortic aneurysm, giant hemangioma)
   - **f.** Toxic procoagulant molecules (e.g., snake bite)
   - **g.** Fat embolism (e.g., fracture of long bones, sickle cell crisis)
3. Diagnosis
   - **a.** Compatible clinical scenario
   - **b.** Laboratory testing
     - **i.** Decreased fibrinogen (due to consumption)
     - **ii.** PT/aPTT may be prolonged (due to consumption of clotting factors)
     - **iii.** Thrombocytopenia may be present (due to accelerated platelet consumption)
     - **iv.** Increased D-dimer, a measure of cross-linked fibrin degradation products (due to accelerated fibrin degradation)
     - **v.** Red blood cell fragments (schistocytes) may be present on blood smear
4. Treatment
   - **a.** Treatment of underlying cause (e.g., antibiotics for sepsis, delivery of baby for pregnancy related)

TABLE 94-5 [a]Management of Disseminated Intravascular Coagulation (DIC): Blood Products

Component	Typical dose	Associated laboratory parameter[b]	Target laboratory parameter: No clinically significant bleeding	Target laboratory parameter: Clinically significant bleeding
Platelets	1 dose[c]	Platelet count	>10 K/μL	>20–50 K/μL
Cryoprecipitate	10 units	Fibrinogen	>80–100 mg/dL	>80–100 mg/dL
FFP	3–5 units	aPTT/PT	—	<1.5 × upper limit normal reference range

[a]Transfuse blood products only if clinically significant bleeding or high risk of bleeding.
[b]Before transfusion, establish baseline platelet count, PT, aPTT, D-dimer, fibrinogen. Follow laboratory parameters every 4–6 h until DIC resolves and underlying condition successfully treated.
[c]One dose of platelets is equal to 1 unit of single donor platelets or a 4- or 6-pack of pooled random donor platelets.
FFP, fresh frozen plasma; aPTT, activated partial thromboplastin time; PT, prothrombin time.

- **b.** Hemostatic therapy (for dosing, see Table 94-5)
  - **i.** Should be given only to patients with high risk for bleeding, clinically significant bleeding, or in need of invasive procedures
    - **(a)** Platelet transfusion
    - **(b)** Cryoprecipitate
    - **(c)** FFP
    - **(d)** Coagulation tests (PT, aPTT, fibrinogen, platelet count) should be monitored frequently to assess response to hemostatic therapy
  - **ii.** For refractory bleeding (e.g., mucocutaneous oozing, ongoing bleeding from catheter exit sites) despite above measures, consider low-dose heparin
    - **(a)** Typical dose: 5 to 10 units/kg/hour (*no* bolus)
    - **(b)** Avoid in intracranial/GI bleeding, placental abruption, imminent surgery

F. Trauma-induced coagulopathy

1. Clinical features
   - **a.** Persistent bleeding from mucosal and serosal surfaces and wound and vascular access sites following major trauma
2. Pathophysiology
   - **a.** Major contributor is massive volume resuscitation with fluids or packed red blood cells (PRBCs), which are deficient in clotting factors and platelets, leading to thrombocytopenia and coagulopathy
   - **b.** Other possible contributing factors
     - **i.** Acidemia (impairs activity of clotting cascade)
     - **ii.** Hypocalcemia (impairs activity of calcium-dependent clotting factors)
     - **iii.** Hypothermia (impairs platelet function)
     - **iv.** Concurrent DIC
3. Diagnosis
   - **a.** Compatible clinical scenario
   - **b.** Thrombocytopenia
   - **c.** Prolonged PT and aPTT (correct with mixing; deficiencies of multiple clotting factors can be demonstrated but rarely is necessary)
   - **d.** Hypofibrinogenemia

4. Treatment
   a. Liberal transfusion of platelets, FFP, and cryoprecipitate
      i. Goals: aPTT/PT ≤1.5 × upper limit of normal; fibrinogen ≥100 mg/dL; platelets >50,000/uL
   b. Body and fluid warming to treat hypothermia
   c. Correction of electrolyte and acid–base disturbances
   d. Consider recombinant factor VIIa (rhFVIIa) in otherwise uncontrolled bleeding (further studies warranted)

G. Acquired hemophilia

1. Pathophysiology
   a. Neutralizing autoantibodies (typically immunoglobulin G [IgG]) against endogenous coagulation factor VIII, producing factor VIII deficiency
2. Epidemiology
   a. Incidence: approximately 1 case per million people per year
   b. More common in women and in the elderly
3. Associated conditions
   a. Malignancy
   b. Autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosus [SLE])
   c. Postpartum state
   d. Idiopathic (50% of cases)
4. Diagnosis
   a. Prolonged aPTT (does not correct with mixing)
   b. Low or unmeasurable factor VIII activity level
   c. Inhibitor titer using the Bethesda assay; reported in Bethesda units ("B.U.")
5. Treatment
   a. Control of bleeding
      i. Low-titer inhibitors (<5 B.U.): give high doses of factor VIII concentrate
      ii. High-titer inhibitors (>5 B.U.) or severe bleeding
         (a) Give inhibitor bypassing agent (Table 94-6)
            (1) Activated prothrombin complex concentrates (aPCCs) (e.g., Factor VIII Inhibitor Bypassing Activity [FEIBA]): 50 to 100 units/kg IV every 8 to 12 hours initially
            (2) rhFVIIa (NovoSeven): 90 μg/kg IV every 2 hours initially
   b. Inhibitor eradication
      i. Prednisone (typically 1 mg/kg orally daily) initially
      ii. Cyclophosphamide (typically 2 mg/kg orally) added if inhibitor persists after 3 weeks of prednisone
         (a) Some centers advocate initial concurrent use of prednisone and cyclophosphamide

TABLE 94-6 Bypassing Agents for the Treatment of Bleeding due to an Inhibitor

Bypassing agent	Description	Initial dose/schedule
FEIBA	Activated prothrombin complex concentrate (plasma-derived)	50–100 IU/kg q 8–12 h IV
rhFVIIa (NovoSeven)	Human activated factor VII (recombinant)	90 μg/kg q 2 h IV

FEIBA, factor VIII inhibitor bypassing activity; rhVIIa, recombinant human factor VIIa.

TABLE 94-7 Mechanisms of Antiplatelet Agents

Drug/class	Mechanism	Duration of action
Aspirin	Inhibit synthesis of thromboxane, a promoter of platelet aggregation	Days
NSAIDs		Hours
Clopidogrel, ticlopidine	Block ADP-mediated platelet activation	Days
GPIIb/IIIa inhibitors	Block the fibrinogen-binding site on platelets	Hours
Dipyridamole	Inhibits breakdown of cyclic AMP	Hours

NSAIDs, nonsteroidal anti-inflammatory drugs; ADP,adenosine diphosphate; GPIIb/IIIa, glycoprotein IIb/IIIa; AMP,adenosine monophosphate.

- **(b)** Second- or third-line immunomodulatory agents: rituximab, cyclosporine, azathioprine

c. Prognosis
- **i.** More than one third of patients achieve complete remission within 1 year of presentation
- **ii.** Relapse rate after first remission: approximately 20%

H. Acquired platelet disorders

1. Medication related (Table 94-7)

a. Irreversible antiplatelet agents
- **i.** Impair platelet function for the lifespan of the platelet (~7 days)
- **ii.** *Examples*: aspirin, clopidogrel, ticlopidine

b. Reversible antiplatelet agents
- **i.** Impair platelet function for hours
- **ii.** *Examples*: Nonsteroidal anti-inflammatory drugs (NSAIDs), glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, dipyridamole

c. Other agents reported to affect platelet function in some patients (e.g., omega-3-fatty acids (fish oils), selective serotonin reuptake inhibitors)

d. Diagnosed by abnormal platelet function testing (rarely necessary)

e. Treatment
- **i.** Stop antiplatelet agent(s)
- **ii.** Consider platelet transfusion (especially for patients on aspirin, clopidogrel, ticlopidine)

2. Renal failure/uremic platelets

a. Pathophysiology: Uremic toxins impair platelet function in some patients with kidney disease

b. Diagnosed by abnormal platelet function testing (rarely necessary)
- **i.** Note: degree of azotemia not correlated well with risk of bleeding

c. Treatment
- **i.** Desmopressin acetate (DDAVP) (for dosing, see Table 94-8)
- **ii.** Correction of anemia
  - **(a)** Target hematocrit ≥30%
    - **(1)** May improve platelet function by facilitating interaction of platelets with vessel wall
    - **(2)** Accomplished acutely by red cell transfusion and chronically by administration of erythropoietin
- **iii.** Hemodialysis
- **iv.** Severe/refractory cases
  - **(a)** High-dose conjugated estrogens

TABLE 94-8 Treatment of von Willebrand Disease

Agent	Mechanism	Dose/frequency	Comments
DDAVP	Releases VWF and FVIII from endothelial cells into circulation	0.3 μg/kg in 50 mL normal saline (NS) IV[a] over 20 min; may repeat in 12–24 h, maximum 2–3 doses	Fluid restrict (≤750 mL in the 24 h after dosing) and limit doses to reduce likelihood of hyponatremia Tachyphylaxis occurs after 2–3 doses
VWF-containing factor VIII concentrate (Humate-P, Alphanate)	Direct replacement of deficient VWF and factor VIII activity	For major bleeding or procedures: 60–80 RCoF[b] units/kg IV bolus q 12 h initially followed by 40–60 RCoF units/kg q 12 h once hemostasis has been established	Goal VWF and FVIII levels are >80–100% for major bleeding or procedures Trough levels should be performed to ensure adequate dosing
Epsilon-Aminocaproic acid (Amicar)	Inhibits fibrinolysis	IV: 5 g (in 250 mL NS) bolus followed by 1 g/h continuous infusion Oral: 4–6 g every 4–6 h Max. dose (IV or PO) is 24 g/24 h	For VWD, adjunctive to either DDAVP- or VWF-containing factor VIII concentrate for treatment of mucosal bleeding Avoid if active hematuria, DIC

[a] Intranasal formulation (Stimate) also available; dose for adults weighing >50 kg is 150 μg (one spray) in *each* nostril.
[b] RCoF, Ristocetin cofactor, a measure of VWF activity.
DDAVP, desmopressin acetate; VWF, von Willebrand factor; RCoF, ristocetin cofactor; VWD, von Willebrand disease; DIC, disseminated intravascular coagulation.

(1) Short-term (i.e. ≤7 days) use only
(2) Typically 50 mg orally daily

v. Cryoprecipitate

3. Myeloproliferative disorders/myelodysplastic syndrome (MPDs)/(MDS)
   a. Pathophysiology
      i. MPDs and MDS lead to production of abnormal blood cells, including platelets
      ii. MPDs include polycythemia vera, essential thrombocythemia, primary myelofibrosis
   b. Diagnosis
      i. Laboratory evidence of MPDs or MDS (e.g., abnormal blood cell counts, abnormal blood cell morphology on blood smear or bone marrow examination, and/or genetic mutations or karyotypic abnormalities)
      ii. Platelet function testing may be required to establish a qualitative defect, as distinguished from decreased platelet function due to thrombocytopenia (as commonly occurs in MDS and spent-phase MPD)

TABLE 94-9 Bleeding Phenotypes in Hemophilia by Factor Level

Severity of hemophilia	Factor level	Usual manifestation of bleeding
Severe	<1%	Spontaneous; often manifests in infancy/childhood
Moderate	1–5%	Spontaneous or trauma-induced
Mild	5–20%	Trauma-induced only

- **c.** Treatment
  - **i.** Treat underlying disorder
  - **ii.** Consider platelet transfusions for clinically significant bleeding

III. CONGENITAL DISORDERS OF HEMOSTASIS

A. Hemophilia

1. Pathophysiology
   - **a.** Congenital deficiency of a coagulation factor due to a mutation in gene for factor VIII (hemophilia A) or factor IX (hemophilia B)
   - **b.** X-linked inheritance
     - **i.** Males only affected
       - **(a)** Family history usually shows affected males but some patients are affected by *de novo* mutations, leading to negative family history
     - **ii.** Females typically are asymptomatic carriers
       - **(a)** Owing to variable lyonization, some females are symptomatic carriers
2. Clinical presentation
   - **a.** Bleeding phenotype determined by level of residual clotting factor activity (Table 94-9)
   - **b.** Bleeding into soft tissues (joints and muscles) is most common
     - **i.** Bleeding at any site, however, is possible
     - **ii.** Bleeding may be life- or limb-threatening (Table 94-10)
3. Diagnosis
   - **a.** Laboratory studies
     - **i.** Prolonged aPTT (corrects with mixing)
     - **ii.** Reduced or unmeasurable activity level of factor VIII (hemophilia A) or factor IX (hemophilia B)
4. Treatment (Table 94-11)
   - **a.** If clinical suspicion for limb- or life-threatening bleeding, administer factor before completing radiographic/diagnostic work-up
   - **b.** Factor VIII and IX concentrates
     - **i.** Contain much higher concentrations of factor than FFP or cryoprecipitate (use of both should be avoided if possible due to large volume required and lack of viral inactivation)
     - **ii.** Both plasma-derived and recombinant products available
     - **iii.** Administered by IV push (Table 94-11)
   - **c.** DDAVP (for dosing, see Table 94-8)
     - **i.** Effective in some cases of mild hemophilia A only
   - **d.** ε-Aminocaproic acid (for dosing, see Table 94-8)
     - **i.** Useful for mucosal bleeding or procedures involving mucosa
     - **ii.** Usually given for 3 to 7 days
   - **e.** Transfusion of PRBCs (if anemic)

TABLE 94-10 Limb- or Life-Threatening Bleeding Syndromes in Hemophilia

Site	Clinical presentation	Diagnostic testing
Intracranial	Head trauma, severe headache, mental status changes	Stat head CT
Retroperitoneal	New back pain	Stat CT of abdomen/pelvis
Retropharyngeal	Stridor	Lateral x-ray of neck, ENT evaluation
Compartment syndrome	Recent intramuscular bleed; disproportionate pain, neurovascular findings	Serial neurovascular examinations, vascular surgery evaluation, ultrasound, CT/MRI

CT, computed tomography; ENT, ear nose throat; MRI, magnetic resonance imaging.

5. Complications
   - **a.** Inhibitor formation
     - **i.** Alloantibody directed against deficient coagulation factor
     - **ii.** Occurs in 25% of patients with severe hemophilia A; less common in hemophilia B and mild/moderate hemophilia A
     - **iii.** Causes bleeding and poor response to infusion of factor concentrate
     - **iv.** Treatment
       - **(a)** Low-titer inhibitors (<5 B.U.) may be overcome by high doses of factor concentrate

TABLE 94-11 Treatment of Bleeding in Hemophilia

Disorder	Subtype	Treatment for minor bleeding[a]	Treatment for major bleeding[b]	Treatment periprocedurally
Hemophilia A	Mild	DDAVP[c] or FVIII 25 units/kg initially[d]	FVIII concentrate, 50 units/kg IV initially[e]	DDAVP[c], or FVIII concentrate, 50 units/kg IV pre-op[e]
	Moderate/ severe	FVIII concentrate: 25 units/kg IV initially[d]	FVIII concentrate, 50 units/kg IV initially[e]	FVIII concentrate, 50 units/kg IV pre-op[e]
Hemophilia B	Any	FIX concentrate, 50 to 60 units/kg IV initially[e]	FIX concentrate,100 to 120 units/kg IV initially[e]	FIX concentrate, 100 to 120 units/kg IV pre-op[e]

[a] For example, typical hemarthrosis or intramuscular hemorrhage, epistaxis.
[b] For example, intracranial, retroperitonal, or gastrointestinal bleeding.
[c] For dose of DDAVP, see Table 94-8.
[d] May repeat in 12–24 h if ongoing symptoms.
[e] Follow initial dose with 25 units/kg (FVIII concentrate) or 50–60 units/kg (FIX concentrate) IV every 8–12 h to maintain factor activity ≥50% for 3–10 d or as long as bleeding is present. Consider adjunctive Epsilon-aminocaproic acid for mucosal bleeding or procedures involving mucosa. Less invasive procedures (e.g., endoscopy with biopsy) may require less intensive factor replacement.
DDAVP, desmopressin acetate.

(b) High-titer inhibitors: treat with agents that bypass the inhibitor (Table 94-6)
b. Blood-borne viral infection
i. High rate of infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV) acquired through tainted blood products in 1970s and 1980s
ii. Currently available factor products in developed countries undergo viral inactivation or are recombinant, greatly reducing risk
c. Hemophilic arthropathy
i. Chronic joint damage due to recurrent hemarthroses

B. von Willebrand disease (VWD)

1. Pathophysiology
a. Deficiency or dysfunction of VWF
b. Normal function of VWF
i. Tethers platelets to the subendothelium
ii. Bridges platelets
iii. Serves as carrier for factor VIII, protecting it from accelerated clearance
2. Epidemiology
a. Most common congenital bleeding disorder
3. Classification
a. Type 1 (70% to 80% of cases): mild to moderate quantitative deficiency of VWF
b. Type 2 (20% to 30% of cases): functional (qualitative) deficiency of VWF
c. Type 3 (rare): severe quantitative deficiency of VWF
4. Diagnosis
a. Decreased VWF antigen
b. Decreased VWF activity
i. Usually measured by ristocetin cofactor assay
c. Decreased factor VIII activity
i. aPTT may be prolonged if factor VIII activity sufficiently decreased, but frequently is normal
d. VWF multimer electrophoresis can help distinguish among types
5. Treatment (Table 94-8)
a. DDAVP
i. Synthetic analog of vasopressin
ii. Primarily effective in type 1 VWD, some type 2 VWD
(a) Patients should have previously undergone therapeutic challenge to assess responsiveness
(b) If not previously performed or data unavailable, must measure postinfusion VWF and factor VIII activities to ensure hemostatic levels, or administer VWF-containing factor VIII concentrate (see below) instead of DDAVP
iii. May worsen thrombocytopenia in patients with type 2B VWD
b. VWF-containing factor VIII concentrate
c. ε-Aminocaproic acid (Amicar)
i. Primarily adjunctive
ii. Useful for mucosal bleeding or invasive procedures involving the mucosa

C. Congenital qualitative platelet disorders

1. Pathophysiology
a. Mutations in genes encoding proteins responsible for platelet activation, aggregation, or secretion
b. Poorly defined in most cases

2. Specific disorders:
   a. Bernard–Soulier: very rare, autosomal recessive; deficiency of the VWF-binding site on platelets
   b. Glanzmann's thrombasthenia: very rare, autosomal recessive; deficiency of the fibrinogen-binding site on platelets
   c. Storage pool disorders: rare, heterogeneous group of disorders with deficient or abnormal platelet granules
   d. Others (e.g., defects of platelet signaling; more common)
3. Diagnosis
   a. Abnormal platelet aggregation studies or platelet function analyzer (PFA-100) results
4. Treatment (if clinically significant bleeding or requirement for invasive procedure)
   a. DDAVP and ε-aminocaproic acid (for dosing, see Table 94-8)
   b. Platelet transfusion
   c. rhVIIa (NovoSeven) may be useful in patients with Glanzmann's thrombasthenia

D. Other coagulation factor deficiencies

1. Pathophysiology
   a. Mostly autosomal recessive inheritance
2. Incidence: very rare
3. Treatment
   a. Deficiencies of factors II, V, X, and XI usually treated with infusion of FFP
      i. Platelet transfusion may also be used to treat factor V deficiency if refractory bleeding
      ii. PCC may be used to treat deficiencies of factor II or factor X
   b. Deficiencies of factor XIII and fibrinogen usually treated with cryoprecipitate
   c. Deficiency of factor VII usually treated with rhVIIa

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THROMBOCYTOPENIA IN THE CRITICAL CARE PATIENT

95

Terry B. Gernsheimer

I. OVERVIEW

A. Definition
- **1.** <150,000/μL, generally not significant until <100,000/μL
- **2.** Relative—acute drop from a higher platelet count may be pathologic (Table 95-1)

B. Pathophysiology
- **1.** Decreased production
- **2.** Increased destruction or consumption
- **3.** Increased sequestration in enlarged spleen
- **4.** Dilutional—effect of massive transfusion and fluid resuscitation
- **5.** States with multiple causes of thrombocytopenia
  - **a.** Cirrhosis with portal hypertension
  - **b.** Hepatitis
  - **c.** Human immunodeficiency virus (HIV)
  - **d.** Other viral illnesses
  - **e.** Patients with multiple medical problems on multiple drugs

C. Diagnosis
- **1.** Complete blood count with examination of peripheral smear
  - **a.** Rule out pseudothrombocytopenia due to platelet clumping
  - **b.** Review for erythrocyte abnormalities such as schistocytes, teardrops, nucleated red blood cells
- **2.** Coagulation testing
  - **a.** Identify associated coagulation abnormalities
- **3.** Additional blood tests, if required
  - **a.** Viral titers and antibody (e.g., for HIV, hepatitis C virus [HCV] infection)
  - **b.** Autoimmune disorders (e.g., collagen vascular disease)—antibody testing
  - **c.** Other disorders—see specific disorders
- **4.** Radiologic
  - **a.** Abdominal ultrasound—evaluation of spleen size
  - **b.** Computed tomography (CT) scanning—evaluation for lymphoproliferative disease
- **5.** Indications for bone marrow examination
  - **a.** Unclear pathophysiology
  - **b.** Multiple cytopenias
  - **c.** Suspected infiltrative process

D. Therapy
- **1.** Transfusion therapy indications
  - **a.** Bleeding or necessary invasive procedures
  - **b.** Prophylactic—very severe (<10,000/μL) thrombocytopenia
  - **c.** Other blood components as indicated to correct coagulation abnormalities
  - **d.** Platelet transfusion relatively contraindicated
    - **i.** Thrombotic thrombocytopenic purpura (TTP) unless bleeding present (worsened thrombotic tendency reported)

TABLE 95-1 [a]Target Platelet Count Values in Selected Clinical Scenarios

Platelet count ($\times 10^9$/L)	Clinical scenario
>10	Prevention of spontaneous bleeding in critically ill patient
>20–50	Insertion of central venous catheters[b]
>30–50	Administration of therapeutic anticoagulation
>50–60	Secondary prevention of serious bleeding (e.g., gastrointestinal) due to severe thrombocytopenia
>50–80	Minor surgery and some invasive procedures[c]
>80–100	Major surgery
>100	Secondary prevention of intracranial hemorrhage, microvascular bleeding

[a]The values provided are suggestions only; management must be individualized with respect to the underlying cause of thrombocytopenia, presence of bleeding, and other relevant clinical factors.
[b]Nontunneled catheters may be inserted with platelet counts in the lower end of the specified range.
[c]Representative procedures include needle biopsies and endoscopy with biopsy; skin biopsy and bone marrow biopsy typically may be performed at lower platelet counts than the specified range.

- **ii.** Immune thrombocytopenia unless bleeding present (due to poor- or short-lived response)
- **iii.** Heparin-induced thrombocytopenia (HIT) without bleeding—unknown

2. Primary thrombocytopenia—depends on specific disorder (see subsequent text)
3. Secondary thrombocytopenias—direct therapy at underlying cause(s)

E. Decreased platelet production
1. Isolated thrombocytopenia
- **a.** Drugs, ethyl alcohol (ETOH), viral (e.g., HIV, HCV)
- **b.** Decreased thrombopoietin (liver disease)
- **c.** Amegakaryocytic thrombocytopenia

2. Multiple cytopenias
- **a.** Marrow toxins
  - **i.** Drugs, alcohol, radiation
- **b.** Nutritional (B_{12} or folate deficiency)
- **c.** Metabolic (e.g., thyroid disorders)
- **d.** Primary marrow disorders
  - **i.** Hematopoietic stem cell disorders
  - **ii.** Marrow infiltration
- **e.** Hemophagocytic syndrome

3. Diagnosis
- **a.** Peripheral blood smear
  - **i.** Bizarre forms (e.g., abnormal granulation)—suggests myelodysplasia
  - **ii.** Red blood cell abnormalities
    - **(a)** Teardrops, nucleated red blood cells—suggests marrow infiltrative diseases
    - **(b)** Macrocytosis—suggests B_{12} or folate deficiency, myelodysplasia
  - **iii.** White blood cell abnormalities
    - **(a)** Immature forms—suggests leukemia
    - **(b)** Hyperlobulated neutrophils, bizarre forms—suggests B_{12} or folate deficiency, myelodysplasia

4. Therapy
   a. Direct at underlying or associated disorder

F. Increased splenic sequestration
   1. Etiology
      a. Portal hypertension
      b. Myeloproliferative disease
      c. Lymphoma
      d. Storage and infiltrative diseases of spleen
      e. Chronic hemolysis
      f. Granulomatoses (e.g., tuberculosis, sarcoidosis)
   2. Diagnosis
      a. Imaging—abdominal ultrasound, CT
      b. Biopsy of apparently pathologic tissue, bone marrow
   3. Treatment
      a. Direct at underlying cause

G. Disorders of increased platelet destruction
   1. Characterized by shortened platelet lifespan (normal—10 days)
   2. Immune—autoimmune or alloimmune
   3. Nonimmune—isolated or combined platelet consumption
   4. Autoimmune thrombocytopenias
      a. Etiology
      b. Primary (idiopathic)—immune thrombocytopenic purpura (ITP)
      c. Secondary
         i. Associated with other autoimmune disease (e.g., systemic lupus)
         ii. Associated with malignancy (e.g., lymphoproliferative disease)
         iii. May be a complication of infection with HIV, HCV, hepatitis B virus (HBV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and others
         iv. Drug-associated thrombocytopenia

II. ITP

A. General principles
   1. Acute ITP may present with any degree of thrombocytopenia, including severe thrombocytopenia (<5,000/μL)
   2. Initial presentation typically abrupt in onset
   3. Petechiae, bruising, mucosal bleeding are the most common manifestations

B. Epidemiology
   1. Adults—chronic relapsing disorder in 90%
   2. Children—acute, self-resolving disorder in 90%
   3. Female predominance (F:M = 3:2) except in children, elderly

C. Etiology
   1. Idiopathic—may present following acute viral illness
   2. May be initial presentation of connective tissue disease, lymphoproliferative malignancy, HIV infection (i.e., secondary ITP)
   3. May be associated with antiphospholipid antibody syndrome

D. Pathophysiology
   1. Antibody against glycoproteins on platelet membrane
   2. Reticuloendothelial, especially splenic, platelet clearance
   3. Inadequate platelet production response

E. Diagnosis
   1. Diagnosis of exclusion
   2. Clinical—presentation; therapeutic response
   3. Laboratory testing
      a. Other peripheral blood and hemostatic measurements normal unless the patient has been bleeding
      b. Rule out associated disorders when indicated by history or clinical presentation
      c. Antiplatelet antibodies generally not helpful in diagnosis

- **d.** Bone marrow examination
  - **i.** Not required unless diagnosis uncertain or age older than 60 years
  - **ii.** Normal to increased numbers of megakaryocytes without other abnormalities

F. Treatment

1. Give treatment only if severe thrombocytopenia (< 30,000/uL) or clinically significant bleeding; all others perform periodic platelet count monitoring as clinically indicated

2. Acute

- **a.** Immune globulin therapy—usually produces rapid response
  - **i.** Anti-D immune globulin (WinRho)
    - **(a)** Appropriate only in Rh-positive patients who have not undergone splenectomy
    - **(b)** Dose: 50 to 75 μg/kg IV
    - **(c)** Complications: fever, chills, acute intravascular hemolysis, disseminated intravascular coagulation (DIC)

  Or

  - **ii.** Immune globulin
    - **(a)** Dose: 2 g/kg IV administered over 2 to 5 days (e.g., 1 g/kg daily × 2 days)
    - **(b)** Complications: severe headache, renal failure, aseptic meningitis
  - **iii.** Corticosteroids
    - **(a)** Usual—prednisone dose 1 to 2 mg/kg
    - **(b)** Acute emergency—up to 1 g methylprednisolone IV
  - **iv.** Serious or life-threatening bleeding with severe thrombocytopenia
    - **(a)** Platelet transfusion: markedly decreased survival of transfused platelets
    - **(b)** Epsilon aminocaproic acid (Amicar): Antifibrinolytic; starting dose—1 g PO/IV q 6 hours. Increase as needed up to 24 g total daily dose. Contraindication—urinary tract bleeding, DIC

3. Chronic

- **a.** Options for patients who relapse after immune globulin therapy or prednisone taper include splenectomy, pulse–dose corticosteroids, monoclonal antibody (e.g., rituximab), alkylating agents, immunosuppressive agents, thrombopoietin mimetic agents and others

4. Complications

- **a.** Therapeutic complications may interfere more with quality of life and be more severe than bleeding risk in mild or moderately thrombocytopenic patients (30 to 100,000/μL)
- **b.** Chronic steroid therapy and immunosuppression: severe osteoporosis, infections, and other complications

5. Prognosis

- **a.** Severe refractory ITP: 10% to 25% risk of significant bleed during the course of disease

III. DRUG-ASSOCIATED AUTOIMMUNE THROMBOCYTOPENIA

A. General principles

1. Numerous drugs implicated

2. Most common offenders: quinine and derivatives, antibiotics, thiazide diuretics, platelet glycoprotein IIb/IIIa inhibitors

3. HIT: treated differently; see Section IV

B. Diagnosis

1. History of exposure to possibly offending drug

2. Laboratory testing
   a. Drug-dependent platelet autoantibody
   b. No other blood or hemostatic abnormalities identified
3. Contraindicated: readministration of suspected drug as diagnostic challenge

C. Therapy
1. Discontinue suspected offending agent(s)
2. Intravenous gammaglobulin therapy: administer as for ITP
3. Platelet transfusion may be indicated for bleeding
4. Plasma exchange in severe refractory cases

IV. HIT

A. General principles
1. Immune reaction to heparin
2. May be associated with life-threatening prothrombotic state
3. Discontinue all heparin therapy (including low–molecular-weight heparin [LMWH], flushes) while considering the diagnosis

B. Pathophysiology
1. Heparin binds to platelet factor 4 (PF4), creates antigenic complex
2. Antibody bound to PF4 in the presence of heparin causes platelet activation, aggregation, thrombin generation
3. Thrombin generation further activates platelets
4. Large and small venous- and arterial-vessel thrombosis may occur

C. Diagnosis
1. Clinical
   a. Exposure to any type of heparin (e.g., unfractionated heparin [UFH], LMWH)
      i. Unfractionated > low molecular weight
      ii. Intravenous > subcutaneous
   b. A > 50% fall in platelet count more important than absolute thrombocytopenia
   c. Onset commonly 4 to 14 days after initial heparin exposure
2. Laboratory
   a. PF4 ELISA (enzyme-linked immunosorbent assay) (sensitive, may be nonspecific)
   b. Serotonin release assay (specific, specialized laboratories only)
   c. Heparin—platelet aggregation studies (specialized laboratories only)

D. Treatment
1. Discontinue all heparin exposure
2. Rule out thrombosis—Doppler studies
3. Anticoagulation with direct thrombin inhibitors
   a. Lepirudin—renal clearance
   b. Argatroban—hepatic clearance
   c. Bivalirudin—patients with renal and hepatic failure

E. Prognosis
1. Associated with up to 50% thrombosis rate, leading to serious morbidity and mortality, without administration of direct thrombin inhibitor and ongoing anticoagulation for ≥30 days

V. ALLOIMMUNE THROMBOCYTOPENIAS

A. Antibodies against foreign platelet antigens (PLAs) encountered through transfusion or pregnancy

B. Include
1. Posttransfusion purpura (PTP)

2. Human leukocyte antigen (HLA) alloimmunization and refractoriness to transfused platelets
3. Neonatal alloimmune thrombocytopenia (NATP)

VI. PTP

A. General principles
1. Severe thrombocytopenia
2. Typically occurs 5 to 10 days posttransfusion of cellular blood components
3. Most common in multiparous women

B. Pathophysiology
1. Alloimmunization occurs through pregnancy or transfusion to common PLA
2. Allogeneic platelet destruction with recall of antibody
3. Mechanism of associated autologous platelet destruction poorly understood

C. Diagnosis
1. Laboratory—strong serum antibody, immunoglobulin G (IgG) or IgM class, most commonly against PLA-1

D. Treatment
1. Immune globulin 2 g/kg administered IV over 2 to 5 days
2. Plasma exchange in refractory cases
3. Poor responses to platelet transfusion

VII. NONIMMUNE THROMBOCYTOPENIA

A. Combined consumption—DIC
1. Associated with fibrinogen deposition and consumption
2. Sepsis, malignancy, obstetric complications, massive tissue injury, snake bite

B. Diagnosis
1. Peripheral blood smear
   a. Bands, toxic granulations, Dohle bodies (sepsis)
   b. May see red cell fragmentation (schistocytes)
2. Abnormal coagulation tests
   a. Increased prothrombin time (PT), partial thromboplastin time (PTT), thrombin time
   b. Falling fibrinogen level
   c. Increased D-dimers

C. Treatment
1. Direct at underlying cause
2. Support with transfusion therapy for bleeding

VIII. ISOLATED PLATELET CONSUMPTION

A. Vascular injury, high shear flow (e.g., vasculitis, intravascular prosthetic devices)

B. Microangiopathic hemolysis
1. Includes TTP, hemolytic-uremic syndrome (HUS) (see Section XI)

IX. MICROANGIOPATHIC HEMOLYTIC ANEMIAS

A. General principles
1. Isolated platelet consumption associated with intravascular hemolysis
2. Patients present with end-organ signs and symptoms due to microvascular thrombosis

B. Etiology
1. TTP
2. HUS
3. *Escherichia coli* 0157:H7 or *Shigella* species infection

4. Malignant arterial hypertension
5. Drug-induced (cyclosporine, mitomycin C, pentostatin, and others)
6. Pregnancy
   a. Pre-eclampsia associated
   b. May be associated with elevated liver enzymes (hemolysis, elevated liver enzymes, and low platelet count [HELLP] syndrome)
7. HIV

C. Diagnosis
1. Peripheral blood smear—red cell fragmentation (schistocytes)
2. Elevated parameters of intravascular hemolysis—lactic dehydrogenase (LDH), indirect bilirubin
3. Compensatory reticulocytosis often present
4. Normal coagulation tests

D. Treatment
1. Discontinue offending agents, if any
2. Treat underlying disorder
   a. Pregnancy associated—requires emergency delivery
3. HUS, TTP: see Sections X and XI

X. TTP

A. General principles
1. Acute presentation of severe-to-moderate thrombocytopenia
2. May present with fever, neurologic signs or symptoms, and/or renal abnormalities
   a. The complete pentad of signs/symptoms (i.e., thrombocytopenia, microangiopathic hemolytic anemia, fever, and neurologic and renal abnormalities) is present in fewer than 25% of cases

B. Etiology
1. Autoimmune
   a. May be HIV-associated
2. Congenital

C. Pathophysiology
1. Deficiency of von Willebrand factor–cleaving enzyme (ADAMTS-13) results in persistence of large multimeric forms and increased platelet adhesion
   a. Autoimmune (i.e., idiopathic) TTP: Autoantibody forms against ADAMTS-13
   b. Congenital TTP: Familial decrease in production of functional ADAMTS-13
2. Formation of platelet thrombi in microvasculature leads to tissue ischemia and end-organ disease
3. Intravascular hemolysis by increased shearing forces

D. Diagnosis
1. Laboratory
   a. Thrombocytopenia
   b. Red cell fragments on peripheral blood film
   c. Elevated LDH
   d. Indirect bilirubin may be elevated
   e. Hemostasis parameters otherwise normal
   f. Creatinine may be increased, hematuria may be present
   g. Usefulness of ADAMTS-13 level and antibody for diagnosis controversial

E. Treatment
1. Medical emergency; >90% mortality without treatment
2. Institute immediate plasma exchange; replacement fluid must be plasma

   a. Continue daily plasma exchange until LDH and platelet count have normalized for 2 to 3 days, then begin to taper frequency of plasma exchange
3. Infuse fresh frozen plasma (4 to 6 units in an adult) if plasma exchange delayed
4. Corticosteroids—role unclear
5. Patients with renal failure—hemodialysis
6. Refractory cases—splenectomy, vincristine, rituximab, immunosuppression

F. Prognosis
1. 90% mortality without rapid institution of therapy
2. Relapses after reduction/discontinuation of plasma exchange occur in a minority of patients

XI. HUS

A. Pathophysiology
1. Deposition of platelet thrombi in small- and medium-sized vessels
2. No deficiency of ADAMTS-13
3. Especially in children, antecedent gastrointestinal illness and exposure to bacterial toxins may precede illness ("endemic HUS")

B. Treatment
1. Primarily supportive (e.g., dialysis)
2. Plasma exchange of value in some patients
3. Most cases resolve with supportive care

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Review of platelet alloantigen systems and related immune thrombocytopenias.

ANTITHROMBOTIC THERAPY IN CRITICALLY ILL PATIENTS

96

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I. ANTIPLATELET AGENTS (Table 96-1 for dosing information)

A. Acetylsalicylic Acid (Aspirin)

1. General principles

a. Aspirin is a prodrug of salicylic acid

b. Generally well absorbed from the gastrointestinal (GI) tract, erratic rectal absorption (60% to 76% bioavailability)

c. Aspirin is available in several combination products, total aspirin exposure should be monitored

2. Mechanism of action

a. Inhibition of cyclooxygenase resulting in decreased prostaglandin synthesis and inhibition of platelet function

3. Reversal of antiplatelet effect

a. Antiplatelet effect lasts for life span of platelet (7 to 10 days)

b. Platelet transfusion(s) for clinically significant bleeding

B. Thienopyridine derivatives (Table 96-2)

1. General principles

a. Generally well absorbed from GI tract, can be taken with or without food

b. Prodrugs requiring hepatic activation

2. Mechanism of action

a. Inhibits platelet aggregation by irreversibly inhibiting the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent activation of ADP-mediated glycoprotein IIb/IIIa (GPIIb/IIIa) complex

3. Reversal of antiplatelet effect

a. Antiplatelet effect lasts for life of platelet (7 to 10 days)

b. Platelet transfusion(s) for clinically significant bleeding

C. Glycoprotein IIb/IIIa inhibitors (Table 96-3)

1. General principles

a. Abciximab is Fab component of human-murine monoclonal antibody that irreversibly blocks platelet glycoprotein IIb/IIIa receptor.

b. Eptifibatide is a heptapeptide causing competitive glycoprotein IIb/IIIa receptor blockade

c. Tirofiban is a nonpeptide causing competitive glycoprotein IIb/IIIa receptor blockade

2. Mechanism of action

a. Inhibition of platelet aggregation by blocking the glycoprotein IIb/IIIa receptor, the major surface receptor involved in platelet aggregation (i.e., fibrinogen receptor)

3. Reversal of antiplatelet effect

a. Platelet transfusion(s) for clinically significant bleeding.

b. Duration of effect is agent specific and is influenced by its binding (i.e., abciximab irreversible up to 10 days) and renal function/elimination (i.e., for tirofiban and eptifibatide, 2 to 4 hours)

D. Dipyridamole (Table 96-4)

1. General principles

TABLE 96-1 Aspirin and Aspirin-Containing Products

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions	Contraindications
Acetylsalicylic acid (Aspirin)	Treatment of acute coronary syndromes	Load 162–325 mg orally Initial dosing for stents 162–325 mg orally/d: Bare metal 1 mo Sirolimus 3 mo Paclitaxel 6 mo Maintenance: 81–325 mg/d orally	■ CBC ■ Signs and symptoms of bleeding ■ Blood pressure ■ Liver function ■ Renal function	■ Thrombocytopenia ■ Bleeding disorders ■ Alcohol use (three or more drinks/d) ■ Pregnancy (third trimester) ■ Gastrointestinal disorders ■ Renal failure ■ Severe hepatic insufficiency ■ Concomitant antithrombotic medication use ■ Alcohol consumption	■ Hypersensitivity to salicylates ■ Children and teenagers with chickenpox or flu symptoms (risk of Reye's syndrome)
	Primary and secondary prevention of myocardial infarction (MI) in patients with chronic stable angina, previous MI, or unstable angina	81–325 mg/d orally			
	Secondary prevention in patients with stroke and TIA	75–325 mg/d orally			
	Acute thrombotic stroke	160–325 mg/d, initiated within 48 h (in patients who are not candidates for thrombolytics and are not receiving systemic anticoagulation)			
	Secondary prevention in CABG, carotid endarterectomy patients	75–325 mg/d starting 6 h following procedure; if bleeding prevents administration at 6 h after CABG, initiate as soon as possible			

CBC, complete blood count; TIA, transient ischemic attack; CABG, coronary artery bypass graft

TABLE 96-2 Thienopyridine Derivatives

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions	Contraindications
Clopidogrel (Plavix)	Treatment of acute coronary syndromes +/– percutaneous intervention	Load 300 mg X1 PCI Load: 300– 600 mg x1 Maintenance 75 mg/d orally Drug-eluting stents: duration of clopidogrel ideally 12 mo following drug-eluting stent Bare Metal Stent 1 mo	■ Signs of bleeding, especially with concomitant antithrombotic agents ■ CBC with differential ■ Bleeding time ■ Hepatic function ■ Lipid panel (Ticlopidine)	■ Interruption of clopidogrel may cause in-stent thrombosis with subsequent fatal and nonfatal myocardial infarction (MI) ■ Indwelling epidural catheter ■ Combination of aspirin and clopidogrel in patients with recent TIA or stroke ■ Liver disease ■ Thrombotic thrombocytopenic purpura may occur (rare) ■ Recent trauma, surgery/ biopsy, or other pathological condition ■ Underlying hematologic disorders ■ Discontinue if ANC $<1,200/mm^3$ or platelet count $<80,000/mm^3$ (Ticlopidine) ■ Elevated triglycerides (Ticlopidine)	■ Hypersensitivity to clopidogrel, ticlopidine, prasugrel, or any component of their product ■ Severe active bleeding (such as peptic ulcer or intracranial hemorrhage) ■ Neutropenia/ thrombocytopenia ■ Severe liver impairment
	Primary and secondary prevention of MI in patients with chronic stable angina, previous MI, or unstable angina Cerebrovascular accident Arteriosclerotic vascular disease Peripheral arterial occlusive disease	75 mg orally once daily			
Ticlopidine (Ticlid)	Placement of stent in coronary artery Secondary prevention in thromboembolic stroke	250 mg orally twice a day			
Prasugrel (Effient)[a]	Treatment of acute coronary syndromes +/– percutaneous intervention	Load 60 mg X1 Maintenance: 10 mg/d orally			

PCI, percutaneous coronary intervention; CBC, complete blood count; TIA, transient ischemic attack; ANC, absolute neutrophil count.
[a] Agent currently not approved by U.S. Food & Drug Administration (FDA)

TABLE 96-3 Glycoprotein IIB/IIIA Inhibitors

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions	Contraindications
Eptifibatide (Integrilin)	Treatment of acute coronary syndromes +/− percutaneous coronary intervention (PCI)	IV bolus 180 μ/kg actual body weight (AjBW) (maximum 22.6 mg) as soon as possible, followed by 2 μg/kg AjBW/min (maximum 15 mg/h) infusion until discharge or CABG surgery, up to 72 h If undergoing PCI, administer a second 180 μg/kg IV bolus 10 min after the first and continue the infusion up to discharge, or for up to 18–24 h after procedure, whichever comes first, allowing for up to 96 h of therapy Renal adjustment: Creatinine clearance (CrCl) <50 mL/min, 180 μg/kg AjBW (maximum 22.6 mg) IV bolus	■ Baseline hematocrit (HCT) or Hgb, platelet count, serum creatinine (SCr), prothrombin time (PT), activated partial thromboplastin time (aPTT) ■ Acute coronary syndrome: aPTT while on heparin ■ PCI: activated clotting time (ACT) during PCI and before sheath removal ■ Signs of bleeding	■ Concomitant use of thrombolytics, anticoagulants, antiplatelet agents, and nonsteroidal anti-inflammatory agents ■ Indwelling epidural catheter ■ Do not remove arterial sheath unless aPTT is <45 s or ACT <150 s and heparin discontinued for 3 to 4 h ■ Platelet count below 150,000/mm^3 ■ Renal insufficiency (Eptifibatide) ■ Severe renal insufficiency, chronic hemodialysis (Tirofiban) ■ Readministration of abciximab may result in hypersensitivity, thrombocytopenia, or	■ Active internal bleeding ■ Abnormal bleeding within the previous 30 d or a history of bleeding diathesis ■ Concomitant or planned administration of other parenteral glycoprotein IIb/IIIa inhibitors ■ Hypersensitivity to active ingredient or any other product component ■ Hypersensitivity to abciximab or murine proteins ■ Major surgery (within the previous 6 wk) ■ Stroke (within previous 30 d ■ Severe hypertension (systolic pressure over 180–200 mm Hg or diastolic pressure above 110 mm Hg)

		as soon as possible, followed by 1 μg/kg/min (maximum 7.5 mg/h) infusion	diminished benefit due to formation of human antichimeric antibodies ■ Hemorrhagic retinopathy	■ History or clinical suspicion of intracranial bleeding, tumor, arteriovenous malformation, or aneurysm ■ Pericarditis
Abciximab (Reopro)	Treatment of acute coronary syndromes +/− PCI	Initial, 0.25 mg/kg IV bolus (over 5 min), followed by 0.125 μg/kg/min (maximum 10 μg/min) IV infusion for 12 h in combination with fibrinolytic treatment or after PCI, unless complications No adjustment required for renal dysfunction		■ Aortic dissection ■ Thrombocytopenia following prior tirofiban administration
Tirofiban (Aggrastat)	Treatment of acute coronary syndromes	0.4 μg/kg/min IV for 30 min, then 0.1 μg/kg/min for 12–24 h after PCI Severe renal impairment (SCr <30 mL/min): give half the usual dose — 0.2 μg/kg/min IV for 30 min then 0.05 μg/kg/min		

TABLE 96-4 Phosphodiesterase Inhibitors

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions	Contraindications
Dipyridamole (Persantine)	Radionuclide myocardial perfusion study Thromboembolism prophylaxis after heart valve replacement	0.142 mg/kg/min IV for 4 min (0.57 mg/kg total) before thallium; maximum 60 mg With concomitant warfarin therapy: 75–100 mg orally four times daily	■ Coagulation panel ■ IV for study: ECG and vital signs during infusion, 10 to 15 min after infusion ■ Angina, hypotension, abnormal ECG ■ Hepatic function	■ Aminophylline injection should be readily available for relieving adverse effects such as chest pain and bronchospasm ■ Hypotension ■ Severe coronary artery disease, abnormal cardiac rhythm	■ Hypersensitivity to dipyridamole and any components of the product
Dipyridamole extended release/ aspirin (Aggrenox)	Secondary prevention in stroke and TIA patients	200 mg dipyridamole, 25 mg aspirin (1 capsule) orally twice daily Patients with intolerable headache 200 mg dipyridamole, 25 mg aspirin orally daily at bedtime, with 81 mg of aspirin in the morning Return to usual dose as soon as tolerance to headache develops (usually within 1 wk)	■ Coagulation panel ■ CBC ■ Blood pressure ■ Fecal occult blood test ■ Liver function ■ After initiation of NSAID therapy and every 6–12 mo thereafter, more frequently in patients at risk for hepatic, renal, cardiac, or gastrointestinal toxicity (e.g., age older than 60, high-dose NSAID therapy, concurrent corticosteroids or anticoagulants, history of cardiac, renal, or hepatic disease)	■ Avoid in patients with severe hepatic insufficiency ■ Avoid in patients with severe renal failure (glomerular filtration rate <10 mL/min) ■ Severe coronary artery disease ■ Coagulation abnormalities	■ Hypersensitivity to dipyridamole, salicylates, or any components of the product

Cilostazol (Pletal)	Intermittent claudication	100 mg orally twice a day	■ Blood pressure ■ Heart rate ■ CBC ■ Coagulation panel ■ Renal function ■ Signs and symptoms of bleeding or CHF	■ Severe renal impairment	■ CHF of any severity ■ Hemostatic disorders or active pathological bleeding (bleeding peptic ulcer or intracranial bleeding) ■ Hypersensitivity to Cilostazol or any of its components

ECG, electrocardiogram; TIA, transient ischemic attack; CBC, complete blood count; NSAID, nonsteroidal anti-inflammatory drug; CHF, congestive heart failure

2. Mechanism of action
   a. Dipyridamole's exact mechanisms of action is not fully understood, but may involve its ability to increase endogenous concentrations of adenosine, a coronary vasodilator and a platelet aggregation inhibitor, and of cyclic adenosine monophosphate (cAMP), which decreases platelet activation.
3. Agents available
   a. Dipyridamole immediate release (Persantine)
   b. Dipyridamole extended release/acetylsalicylic acid (Aggrenox)
4. Reversal of anticoagulation effect
   a. Platelet transfusion for clinically significant bleeding

E. Cilostazol (Table 96-4)
1. General principles
2. Mechanism of action
   a. Phosphodiesterase inhibition and suppression of cAMP degradation increases cAMP in platelets and blood vessels. This causes reversible inhibition of platelet aggregation induced by various stimuli, including thrombin, ADP, collagen, arachidonic acid, epinephrine, and shear stress.
   b. Cilostazol produces nonhomogenous vasodilation, with greater dilation in femoral beds than in vertebral, carotid, or superior mesenteric arteries, but without effect in renal arteries.
3. Reversal of antiplatelet effect
   a. Platelet transfusion(s) for clinically significant bleeding

II. ANTICOAGULANTS

A. Unfractionated heparin (UFH) (Table 96-5)
1. General principles
   a. Natural glycosaminoglycan that is extracted from porcine intestinal mucosa.
   b. Intravenous (IV) administration results in immediate onset of action with a $t_{1/2}$ of 60 to 90 minutes. Liver and renal disease results in prolonged $t_{1/2}$.
   c. Subcutaneous (SC) administration results in a longer onset of action (20 to 60 minutes)
   d. *Heparin resistance* is a term used to describe patients who require unusually high doses of heparin (>35,000 U/day), to achieve a therapeutic activated partial thromboplastin time (aPTT), and can be attributable to antithrombin deficiency, increased heparin clearance, elevations in heparin-binding proteins, elevations in factor VIII, and elevations of fibrinogen
   e. Heparin protocols are more effective in achieving goal anticoagulation than an *ad hoc* approach
2. Mechanism of action
   a. When combined with antithrombin (heparin cofactor), thrombosis is blocked through inactivation of activated factor II, IX, X, XI and XII. Heparin also binds to platelets, both inhibiting and promoting their function.
3. Reversal of anticoagulation effect (see also Chapter 94)
   a. Protamine
      i. Dose required decreases rapidly as time from heparin administration elapses.
         (a) Immediately recent UFH administration: give 1 mg protamine/100 units of heparin administered
         (b) Thirty to 60 minutes since UFH administration: 0.5 to 0.75 mg protamine for every 100 units of heparin

TABLE 96-5 Unfractionated Heparin

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions	Contraindications
Unfractionated Heparin	Treatment of VTE	80 U/kg bolus 18 U/kg/h infusion adjusted per local heparin nomogram	■ aPTT: at least 4 h after initiation, then at least once daily ■ Anti Xa Levels (alternative if available, consider in patients with heparin resistance) ■ CBC ■ Heparin-induced thrombocytopenia (HIT) antibody testing (not warranted in the absence of thrombocytopenia, thrombosis, heparin-induced skin lesions, or other signs pointing to a potential diagnosis of HIT ■ Signs and symptoms of bleeding	■ Allergic or hypersensitivity-type reactions ■ Congenital or acquired bleeding disorders ■ Indwelling epidural catheter ■ Gastrointestinal ulceration and ongoing tube drainage of the small intestine or stomach ■ Hepatic disease with impaired hemostasis ■ Hereditary antithrombin III deficiency and concurrent use of antithrombin ■ Menstruation ■ Neonates and infants weighing <10 kg ■ Premature infants weighing <1 kg ■ Risk of delayed onset of HIT and heparin-induced thrombocytopenia and thrombosis (HITT)	■ Uncontrollable active bleeding, except when due to disseminated intravascular coagulation ■ Instances in which blood coagulation tests cannot be performed at necessary intervals ■ Severe thrombocytopenia ■ Positive test for immune-mediated HIT ■ Patients with a remote history of HIT (>100 d) could be considered for a rechallenge with heparin provided a negative antibody test
	Treatment of ACS	IV bolus: 60 U/kg (max 4,000 U) 12 U/kg/h (max 1,000 U) +/− fibrin specific adjusted to maintain aPTT 1.5 to 2 times control or per local heparin nomogram			
	Bridge therapy for atrial fibrillation, cardioversion	IV infusion: 60–80 U/kg bolus Target aPTT, 60 s, range, 50 to 70 s)			
	Prophylaxis of VTE in the medically ill or surgical population	5,000 U SC q8 h			
	Prophylaxis of VTE in pregnancy (with prior VTE)	7,500–15,000 U SC every 12 h			

VTE, venous thromboembolism; aPTT, activated partial thromboplastin time; ACS, acute coronary syndrome; IV, intravenous; SC, subcutaneous; CBC, complete blood count

Heparin Dose-Adjustment Nomogram

Variables	Adjustment
Initial dose	80 U/kg bolus, then 18 U/kg/h
aPTT <35 s	80 U/kg bolus, then increase 4 U/kg/h
aPTT 35–45 s	40 U/kg bolus, then increase 2 U/kg/h
aPTT 46–70 s	No change
aPTT 71–90 s	Decrease infusion rate by 2 U/kg/h
aPTT >90 s	Hold infusion 1 h, then decrease infusion rate by 3 U/kg/h

aPTT, activated partial thromboplastin time
Adapted from Raschke R, Gollihare B, Peirce J. The effectiveness of implementing the weight-based heparin nomogram as a practice guideline. *Arch Intern Med* 1996; 156:1645–1649

ii. Administer slowly with no more than 50 mg in a 10-minute period.
iii. Perform postinfusion aPTT to verify response to reversal.

B. Low molecular weight heparin (LMWH) (Table 96-6)
1. General principles
a. Produced from UFH, with improved bioavailability and more predictable dose response.
b. SC administration results in onset of action of 20 to 60 minutes with a $t_{1/2}$ of 3 to 6 hours.
c. Primarily cleared through the kidneys.
d. Antifactor Xa to antithrombin activity ratio of approximately 3:1 versus 1:1 with heparin, but ratio varies amongst different products.
e. Doses based upon actual body weight, but doing on adjusted body weight (AjBW) for obese patients may be necessary.
i. AjBW = LBW + CF × (TBW – LBW)
ii. CF = correction factor = 0.4
iii. LBW = (height – 150 cm) × 0.9 + 45 kg (female) *or* LBW = (height – 150 cm) × 0.9 + 50 kg (male)
iv. Where LBW = lean body weight; TBW = total body weight; cm = centimeters
2. Mechanism of action
a. Anti–factor Xa activity and antithrombin (anti–factor IIa) activity
b. For LMWH, anti–factor Xa effect predominates
3. Reversal of anticoagulation effect (see also Chapter 94)
a. Protamine
i. Provides partial reversal of LMWH products
ii. Protamine 1 mg neutralizes 100 anti-Xa units *or* 1 mg protamine neutralizes 1 mg of LMWH (e.g., enoxparin) administered
b. Discontinuation should be considered 12 to 24 hours before procedure or surgery

C. Pentasaccharides (Fondapariux) (Table 96-7)
1. General principles
a. SC administration results in rapid and complete absorption, with a $t_{1/2}$ of 17 to 21 hours (in normal renal function)
b. Excreted unchanged in urine
c. Clearance reduced in patients with renal impairment

TABLE 96-6 Low Molecular Weight Heparins

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions	Contraindications
Enoxaparin (Lovenox)	Treatment of VTE	1 mg/kg SC q12 h *or* 1.5 mg/kg SC q24 h CrCl <30 mL/min: 1 mg/kg SC q24 h	■ Anti Xa level in with significant renal impairment, those experiencing bleeding or abnormal coagulation parameters, pregnant patients, obese or low-weight patients, and children ■ CBC ■ Serum creatinine ■ Heparin-induced thrombocytopenia (HIT) antibody testing (not warranted in the absence of thrombocytopenia, thrombosis, heparin-induced skin lesions, or other signs pointing to a potential diagnosis of HIT ■ Signs and symptoms of bleeding	■ Indwelling epidural catheter ■ Recent spinal or ophthalmologic surgery ■ History of recent major bleed (GI, intracranial, etc.) ■ Congenital or acquired bleeding disorders ■ Bacterial endocarditis ■ History of HIT ■ Liver disease ■ Renal impairment (CrCl <30 mL/min), consider UFH ■ Concomitant use of antithrombotic drugs ■ Diabetic retinopathy ■ Uncontrolled hypertension	■ Severe active bleeding ■ Hypersensitivity to enoxaparin, dalteparin, tinzaparin, heparin, or pork products, sulfites (tinzaparin) ■ Hypersensitivity to benzyl alcohol (multidose formulation) ■ Positive test for immune-mediated HIT ■ Patients within a remote history of HIT (>100 d) could be considered for a rechallenge with heparin provided a negative antibody test
	Treatment of acute coronary syndrome (ACS) [–]	30 mg bolus IV followed by 1 mg/kg SC q12 h *with* tenecteplase CrCl <30 mL/min: not recommended			
	Prophylaxis/bridge therapy for atrial fibrillation/ cardioversion	1 mg/kg SC q12 h *or* 1.5 mg/kg SC q24 h CrCl <30 mL/min: 1 mg/kg SC q24 h			
	Prophylaxis of VTE in the medically ill or surgical population	40 mg SC q24 h CrCl <30 mL/min: 1 mg/kg SC daily			
	Prophylaxis of VTE in the trauma patients	30 mg SC q12 h *or* 40 mg SC q24 h			
Dalteparin (Fragmin)	Treatment of VTE	<56 kg: 10,000 IU daily 57–68 kg: 12,500 IU daily 69–82 kg: 15,000 IU daily 83–98 kg: 18,000 IU daily >99 kg: 18,000 IU daily			
	ACS	120 IU/kg SC every 12 h (*max* 10,000 international units/dose)			

(continued)

TABLE 96-6 Continued

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions	Contraindications
	Prophylaxis of VTE after hip or other major surgery (first month)	Initial dose: 2,500 IU once Maintenance: 2,500 to 5,000 IU SC q24 h			
	Prophylaxis of VTE in the medically ill or surgical population	5,000 IU SC every 24 h			
Tinzaparin (Innohep)	Treatment of DVT	175 international units anti-Xa/kg SC daily			

VTE, venous thromboembolism; SC, subcutaneous; CrCl, creatinine clearance; IV, intravenous; DVT, deep venous thrombosis; CBC, complete blood count; GI, gastrointestinal; UFH, unfractionated heparin

TABLE 96-7 Pentasaccharides

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions	Contraindications
Fondaparinux (Arixtra)	Treatment of VTE Treatment is for 5–9 d; continue treatment until a therapeutic oral anticoagulant effect is established	<50 kg: 5.0 mg SC daily 50–100 kg: 7.5 mg SC daily >100 mg kg: 10 mg SC daily Renal impairment: Creatinine clearance (CrCl) 50–80 mL/min – 25% reduction in total clearance; consider empiric dosage reduction CrCl 30–50 mL/min – 40% reduction in total clearance; consider empiric dosage reduction CrCl <30 mL/min – contraindicated	■ CBC ■ Serum creatinine ■ Signs and symptoms of bleeding ■ Anti-Xa level in with significant renal impairment, those experiencing bleeding or abnormal coagulation parameters, pregnant patients, obese or low-weight patients, and children ■ Hepatic function	■ Indwelling epidural catheter ■ Recent spinal or ophthalmologic surgery ■ History of recent major bleed (GI, intracranial, etc.) ■ Congenital or acquired bleeding disorders	■ Severe active bleeding ■ Bacterial endocarditis ■ Body weight <50 kg for prophylactic therapy of hip fracture, hip replacement or knee replacement surgery, or abdominal surgery; increased risk for major bleeding episodes ■ Fondaparinux-related thrombocytopenia ■ Hypersensitivity to fondaparinux ■ CrCl <30 mL/min
	Treatment of STEMI and NSTEMI[a]	2.5 mg SC qd			
	Prophylaxis of VTE in major surgery and acute medically ill[a]	2.5 mg SC qd			

[a] *Indicates off label use of medication*

VTE, venous thromboembolism; SC, subcutaneous; CBC, complete blood count; STEMI, ST-elevated myocardial infarction; NSTEMI, non-ST-elevated myocardial infarction; GI, gastrointestinal

2. Mechanism of action
   a. Selectively binds to antithrombin, resulting in neutralization of factor Xa, which inhibits thrombin formation and thrombus development
3. Reversal of anticoagulation effect
   a. Hold agent, duration of effect is dependent upon renal function/clearance and can range from 13 to 21 hours in healthy persons
   b. No pharmacologic reversal agent available; in select patients, rFVIIa (NovoSeven) may be effective

D. Direct thrombin inhibitors (Table 96-8)
1. General principles
   a. Currently only available in IV formulations
   b. Available agents exhibit wide variability in pharmacokinetic parameters such as metabolism and clearance
2. Mechanism of action
   a. Direct, selective, and reversible binding to the active site of thrombin, leading to inhibition of thrombin-catalyzed or induced reactions, including fibrin formation; activation of coagulant factors V, VIII, and XIII and protein C; and platelet aggregation
3. Reversal of anticoagulant effect
   a. Hold agent, no specific reversal agent available

E. Vitamin K antagonists (VKAs) (Table 96-9)
1. General principles
   a. Well absorbed from GI tract and 99% bound to plasma albumin.
   b. Metabolized in the liver by the cytochrome P450 (CYP) family of enzymes (mostly 2C9).
   c. Average half-life is approximately 40 hours but is extremely variable (range: 20 to 60 hours).
   d. Wide range of dosing required to maintain therapeutic international normalized ratio (INR).
   e. CYP2C9 and VKORC1 genetic variation influences patient response to initial and maintenance therapy and increase the risk of bleeding.
   f. Lower dosing is often required for the elderly and patients with comorbidities.
   g. Both dietary and drug interactions (Table 96-10) can influence dosing, frequent monitoring of INR may be required.
2. Mechanism of action
   a. Inhibits conversion of vitamin K to its active form, thereby blocking the synthesis of all vitamin K–dependent clotting factors (II, VII, IX, X, protein C and S)
3. Reversal of anticoagulant effect due to warfarin (also see Chapter 94)
   a. Hold warfarin, duration of effect could last up to several days in the absence of reversal agent administration
   b. Vitamin K (Phytonadione)
      i. INR >5.0 but <9.0 with or no significant bleeding: omit next two doses of warfarin and evaluate INR, give 1 to 2.5 mg of oral vitamin K if increased risk of bleeding
      ii. INR >9.0 with or no significant bleeding: hold warfarin and give 2.5 to 5 mg of oral vitamin K
      iii. Serious/life-threatening bleeding at any INR: hold warfarin and administer vitamin K 10 mg by slow IV infusion
      iv. Supplement with immediate reversal agent
         (a) Fresh frozen plasma (FFP), or
         (b) Prothrombin complex concentrate (PCC), or
         (c) Recombinant factor VIIa (NovoSeven)

TABLE 96-8 Direct Thrombin Inhibitors

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions	Contraindications
Bivalirudin (Angiomax)	Percutaneous coronary intervention (with or without GPIIb/IIIa)	0.75 mg/kg IV bolus dose, followed by an infusion of 1.75 mg/kg/h for the duration of the procedure CrCl <30 mL/min, a reduction of initial infusion rate to 1 mg/kg/h should be considered; no bolus dose reduction is necessary	■ CBC ■ aPTT ■ ACT ■ PT/INR (false elevation while on infusion) ■ Blood pressure ■ Heart rate ■ ECG ■ Renal function (Bivalirudin and lepirudin) ■ Hepatic function (argatroban)	■ Indwelling epidural catheter ■ Recent major, spinal or ophthalmologic surgery ■ History of recent major bleed (GI, intracranial, etc.) ■ Congenital or acquired bleeding disorders ■ Recent cerebrovascular accident ■ Repeat lepirudin courses may require more frequent monitoring due to antibody formation ■ Renal dysfunction (Bivalirudin and lepirudin) ■ Hepatic Impairment (Argatroban)	■ Hypersensitivity to bivalirudin, argatroban, lepirudin, or formulation excipients ■ Severe active bleeding
	Treatment of ACS[a]	Initial IV bolus dose of 0.1 mg/kg, followed by 0.25 mg/kg/h; titration to aPTT 1.5 to 2 times control			
	Treatment and prophylaxis of HIT and HITT[a]	0.1–0.2 mg/kg/h, titration to aPTT 1.5 to 2 times control			
Argatroban	Treatment and prophylaxis of HIT and HITT	0.5–1.2 μ/kg/min continuous IV infusion to start titration to goal aPTT between 50–85 s Begin VKA therapy, measure INR daily; stop Argatroban when INR >4; repeat INR in 4–6 h, if INR is below desired range then resume Argatroban infusion			
	Treatment ACS	Bolus: 100 μg/kg Initial infusion: 1–3 μg/kg/min for 6–72 h; maintain aPTT between 50–85 s			

(continued)

TABLE 96-8 Continued

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions	Contraindications
Lepirudin (Refludan)	Treatment and prophylaxis of HIT and HITT ■ aPTT ratio target: between 1.5 and 2.5; begin monitoring aPTT 4 h after initiation of infusion and daily thereafter; recheck aPTT 4 h after any dosage changes ■ aPTT >2.5: discontinue infusion for 2 h, decrease infusion rate by 50% when reinstated ■ aPTT <1.5: increase infusion rate in 20% increments until target aPTT is achieved	Bolus: 0.4 mg/kg IV (up to 44 mg) Initial infusion: 0.05–0.15 mg/kg/h (up to 16.5 mg/h) for 2–10 d, adjust infusion rate according to aPTT ratio Renal impairment CrCl <60 mL/min): bolus: 0.2 mg/kg IV Initial infusion: 0.001–0.01 mg/kg/h (up to 16.5 mg/h) for 2–10 d, adjust infusion rate according to aPTT ratio			

[a] *Indicates off label use of medication*

GP, glycoprotein; IV, intravenous; CBC, complete blood count; CrCl, creatinine clearance; ACS, acute coronary syndrome; aPTT, activated partial thromboplastin time; HITT, heparin-induced thrombocytopenia/thrombosis; VKA, vitamin K antagonists; INR, international normalized ratio; ACT, activated clotting time; GI, gastrointestinal; PT, prothrombin time; ECG, electrocardiogram

TABLE 96-9 Vitamin K Antagonism: Warfarin

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions	Contraindications
Warfarin (Coumadin)	Treatment of VTE	Initial dosing: 2.5– 10 mg q24 h (see precautions) titrated to range INR: 2.0–3.0; target of 2.5	■ Signs and symptoms of bleeding ■ CBC ■ PT/INR	■ Lower initial dosing (<5 mg may be warranted in patients who are debilitated, are malnourished, have congestive heart failure (CHF), have liver disease, have had recent major surgery, or are taking medications known to increase sensitivity to warfarin ■ Cerebrovascular disease ■ Coronary disease ■ CYP2C9 and VKORC1 genetic variation ■ Moderate to severe hypertension ■ Malignancy ■ Renal impairment ■ Recent trauma ■ Malignancy ■ Collagen vascular disease ■ Conditions that increase risk of hemorrhage, necrosis, and/or gangrene, preexisting	■ Hypersensitivity to warfarin or any component of the product ■ Pregnancy, known or suspected ■ Spinal puncture and other procedures with potential for uncontrollable bleeding ■ Pericarditis and pericardial effusion ■ Bleeding tendencies of the gastrointestinal, genitourinary, or respiratory tract ■ Gastrointestinal, genitourinary, or respiratory tract ulcerations or overt bleeding ■ Cerebrovascular hemorrhage
	Atrial fibrillation	Initial dosing: 2.5–10 mg q24 h (see precautions) titrated to range INR: 2.0–3.0; target of 2.5			
	s/p MI	Initial dosing: 2.5–10 mg q24 h (see precautions) titrated to range INR: 2.0–3.0; target of 2.5			
	Mechanical valve in the atrial position	Initial dosing: 2.5–5 mg q24 h (see precautions) titrated to range INR 2.0–3.0; target of 2.5			
	Mechanical valve in the mitral position	Initial dosing: 2.5–5 mg q24 h (see precautions) titrated to range INR 2.5–3.5; target of 3.0			
	Mechanical valve in *both* the atrial and mitral position	Initial dosing: 2.5–5 mg q24 h (see precautions) titrated to target INR 2.5–3.5; target of 3.0			
	Bioprosthetic valve in the mitral position	Initial dosing: 2.5–5 mg q24 h (see precautions) titrated to target INR 2.0–3.0; target of 2.5 × 3 mo			

(continued)

TABLE 96-9 Continued

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions	Contraindications
				■ Congestive heart failure ■ Severe diabetes ■ Excessive dietary vitamin K ■ Elderly or debilitated patients (lower dosing may be required) ■ Hepatic impairment ■ Hyperthyroidism/ hypothyroidism ■ Epidural catheters ■ Infectious diseases or disturbances of intestinal flora, such as sprue or antibiotic therapy ■ Poor nutritional state ■ Protein C deficiency ■ Heparin-induced thrombocytopenia ■ Vitamin K deficiency	

[a] *Indicates off label use of medication*
VTE, venous thromboembolism; INR, international normalized ratio; MI, myocardial infarction; CBC, complete blood count; PT, prothrombin time

TABLE 96-10 Potential Drug and Dietary Supplements that Interact with Warfarin Resulting in Alteration of International Normalized Ratio (INR)

Agents known to interact with warfarin and increase INR	Agents known to interact with warfarin and decrease INR
Antimicrobial/antifungal	
Cephalopsorins Fluoroquinolones (levofloxacin, ciprofloxacin, moxifloxacin) Macrolides (azithromycin, erythromycin) Miconazole Neomycin (PO) Sulfonamides Tetracyclines	Nafcillin Rifampin
Cardiovascular	
Amiodarone Fluvastatin/lovastatin Quinidine derivatives Thiazide diuretics (HCTZ)	Alcohol (chronic) Atorvastatin Estrogen-containing oral contraceptives Spirinolactone
Central nervous system agents	
SSRIs (fluoxetine, sertraline) Tricyclic antidepressants	Barbiturates (phenobarbital, pentobarbital) Carbamazepine Trazadone
NSAIDs	
COX-2 inhibitors (celecoxib, rofecoxib) Ibuprofen, ketoprofen	
Steroids	
Anabolic steroids (testosterone)	Corticosteroids (methylprednisolone, hydrocortisone)
Miscellaneous	
Antihistamines Glucagon Influenza vaccine Tamoxifen Thyroid drugs (synthetic thyroid, levothyroxine)	Mercaptopurine Raloxifene Sucralfate Vitamin K
Herbal supplements	
Ginkgo biloba Ginseng	St. John's Wort

HCTZ, hydrochlorothiazide; SSRIs, selective serotonin reuptake inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs

TABLE 96-11 Fibrinolytics

Drug	Indications	Dosing, timing, duration	Monitoring	Precautions	Contraindications
Alteplase (Activase and Cathflo Activase)	Acute ST-elevation MI	>67 kg 15 mg IV bolus, followed by 50 mg infusion over 30 min, then 35 mg infusion over 60 min (total = 100 mg) ≤67 kg 15 mg IV bolus, followed by 0.75 mg/kg infusion over 30 min (max 50 mg), then 0.5 mg/kg over 60 min (max 35 mg)	■ Blood pressure ■ Signs and symptoms of bleeding ■ CBC Signs of orolingual angioedema ■ Cranial CT scan, improved neurologic recovery (acute ischemic stroke) ■ Cardiac enzymes, ECG, resolution of chest pain (acute myocardial infarction) ■ Aspiration of blood and catheter contents (catheter occlusion) ■ CBC, thrombin time (TT), activated partial thromboplastin time (aPTT), prothrombin time (PT); at baseline, 4 h after therapy initiation, and TT only within 3 to 4 h after therapy ■ ECG during and immediately following administration ■ Blood pressure, signs, and symptoms of serious bleeding	■ Recent major or minor surgery (within 10 d) ■ Cerebrovascular diseases ■ Recent gastrointestinal or genitourinary bleeding ■ Recent trauma ■ Hypertension: systolic BP ≥175–180 mm Hg and/or diastolic BP ≥110 mm Hg ■ High likelihood of left heart thrombus ■ Acute pericarditis ■ Subacute bacterial endocarditis ■ Hemostatic defects ■ Severe hepatic or renal dysfunction ■ Pregnancy ■ Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions ■ Septic thrombophlebitis or occluded AV cannula at a seriously infected site ■ Advanced age ■ Patients currently receiving oral anticoagulants ■ Known or suspected infection in the catheter during use for catheter clearance	■ Hypersensitivity to alteplase, reteplase, tenecteplase, streptokinase, urokinase, or formulation excipients ■ Active internal bleeding ■ Severe uncontrolled hypertension ■ Recent intracranial or intraspinal surgery or trauma (within 3 mo) ■ Intracranial neoplasm, arteriovenous (AV) malformation, or aneurysm ■ Known bleeding diathesis ■ History of cerebrovascular accident ■ Evidence, suspicion, or history of intracranial hemorrhage ■ Seizure at the onset of stroke (ischemic stroke) ■ Platelet count <100,000/mm^3 (ischemic stoke) ■ Administration of heparin with 48 h, preceding stroke onset and have an elevated activated partial thromboplastin time at presentation (ischemic stroke
	Lysis of massive and submassive PE	Routine administration for PE (***non-cardiac arrest***): 100 mg IV administered over 2 h During cardiopulmonary resuscitation: 50 mg IV single dose administered over 5 min			
	Acute ischemic stroke (within 3 h of symptom onset)	0.9 mg/kg IV (not to exceed 90 mg total dose) infused over 60 min with 10% of the total dose administered as an initial intravenous bolus over 1 min			
	Peripheral arterial or venous thrombosis	Catheter-directed administration: 1.5 mg/h by transcatheter intra-arterial infusion until lysis of thrombus			

	Clear occluded CVAD	Weight >30 kg 2 mg/2 mL Patient weight >10 kg but <30kg — 110% of the internal lumen volume, not to exceed 2 mg/2 mL	■ Severe neurologic deficit (NIHSS >22) (ischemic stroke) ■ Patients with major early infarct signs on computerized cranial tomography (ischemic stroke) ■ History of streptococcal infection (within 5 d to 12 mo) (Streptokinase) ■ Previous anistreplase or streptokinase administration (within 5 d to 12 mo)
Reteplase (Retavase)	Acute ST elevation MI	10 U IV bolus, two doses give 30min apart
	Clear occluded CVAD[a]	0.4 units/2 mL
Tenecteplase (TNKase)	Acute ST-elevation MI	<60 kg: 30 mg dose ≥60 to <70 kg: 35 mg ≥70 to <80 kg: 40 mg ≥80 to <90 kg: 45 mg ≥90kg: 50mg
Streptokinase (Streptase)	Acute ST-elevation MI	1.5 million units (IU) over 1 h
Urokinase (Abbokinase or Kinlytic)	Lysis of PE with or without hemodynamic instability	Loading dose: 4,400 international units/kg IV over 10 min Infusion of 4,400 IU/kg/h IV for 12 h
	Clear occluded CVAD[a]	5,000 IU /mL

[a] *Indicates off label use of medication*

MI, myocardial infarction; PE, pulmonary embolism; CVAD, central venous access devices; CT, computed tomography; CBC, complete blood count; ECG, electrocardiogram; BP, blood pressure; NIHSS, National Institute of Health Stroke Scale

III. FIBRINOLYTICS (Table 96-11)

- **A.** General principles
  - **1.** Methods of administration
    - **a.** Intravenous
    - **b.** Intravascular (i.e., catheter directed)
- **B.** Mechanism of action
  - **1.** Enhances the conversion of plasminogen to plasmin
  - **2.** Plasmin initiates fibrinolysis (i.e., degradation of fibrin clots, fibrinogen, and other plasma proteins) with limited systemic proteolysis
- **C.** Reversal of fibrinolytic effect
  - **1.** No specific reversal agent is available.
  - **2.** Hold agent, duration of effect is agent specific.
  - **3.** Elimination half life varies (alteplase 4 to 8 minutes; tenecteplase 20 to 24 minutes).

Suggested Reading

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A randomized, double-blind trial in patients with unprovoked venous thromboembolism showed conventional intensity warfarin therapy (target INR of 2.0 to 3.0) was more effective than low intensity therapy target (INR of 1.5 to 1.9) for the long-term prevention of recurrent venous thromboembolism.

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A weight-based heparin nomogram decreased time to achieve therapeutic activated partial thromboplastin time with no change in bleeding rates.

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Stone GW, McLaurin BT, Cox DA, et al. The ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;355(21):2203–2216.
Patients with moderate or high-risk acute coronary syndromes were randomized to unfractionated heparin or enoxaparin plus a glycoprotein IIb/IIIa inhibitor, bivalirudin plus a glycoprotein IIb/IIIa inhibitor, or bivalirudin alone. Bivalirudin was associated with similar event rates when compared with heparin but when used as monotherapy produced significantly lower rates of bleeding.

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Review of anticoagulation strategies to prevent and treat heparin induced thrombocytopenia.

97 THROMBOTIC DISORDERS IN THE INTENSIVE CARE UNIT

Ashkan Emadi and Michael B. Streiff

I. HEPARIN-INDUCED THROMBOCYTOPENIA/THROMBOSIS (HIT/T)

A. General principles

1. HIT (also see Chapter 95)
   - a. Immune-mediated prothrombotic disorder
   - b. Caused by heparin-dependent, platelet-activating immunoglobulin G (IgG) antibodies
     - i. Antibodies recognize complexes of the platelet α-granule protein, platelet factor 4 (PF4, a polycation) that is bound to heparin (a polyanion)
     - ii. IgA and IgM antibodies not thought to be pathogenic
2. HIT/T
   - a. Defined as HIT with concurrent thrombosis.
   - b. Arterial (cerebrovascular accident [CVA], myocardial infarction [MI], peripheral arterial) or venous (deep venous thrombosis [DVT], pulmonary embolism [PE], other) thromboses are possible.
   - c. Risk of thrombosis due to HIT persists for 30 days following detection of thrombocytopenia (see I. E in subsequent text).
   - d. Thrombosis can occur before recognition and/or confirmation of underlying HIT.
3. Incidence of HIT and HIT/T
   - a. HIT
     - i. Approximately 1% to 3% of all patients exposed to unfractionated heparin (UFH)
     - ii. Less than 1% of patients exposed to low molecular weight heparin (LMWH)
     - iii. Very rare with fondaparinux
   - b. HIT/T
     - i. Fifty percent of patients with HIT will develop thrombosis without optimal management including treatment with an alternative anticoagulant.
4. Clinical characteristics
   - a. HIT: see Chapter 95
   - b. HIT/T
     - i. Venous thromboses (e.g., DVT, PE, cerebral dural sinus thrombosis, adrenal hemorrhagic infarction)
     - ii. Arterial thromboses (e.g., aortic occlusion, acute thrombotic stroke, MI, cardiac intraventricular, upper limb, lower limb, mesenteric, renal, and spinal arteries)
     - iii. Digital/extremity gangrene is a classic finding

B. Pathophysiology of HIT/T

1. Activation of platelets:
   - a. Owing to binding of IgG anti-Hep-PF4 immune complexes to FcγRIIa (CD32) receptor on platelets
   - b. Owing to release of additional PF4 and procoagulant microparticles—activates additional platelets, promotes thrombin generation, and clot formation

TABLE 97-1 Determination of Pretest Probability of Heparin-Induced Thrombocytopenia

Scoring element	Category	Points
Degree of thrombocytopenia	>50% platelet decrease to nadir ≥20 × 10^9/L	2
	30%–50% platelet decrease *or* nadir 10–19 × 10^9/L	1
	<30% platelet decrease *or* nadir <10 × 10^9/L	0
Timing of onset of thrombocytopenia[a]	Onset of thrombocytopenia between 5–10 d of heparin therapy *or* ≥1 d if heparin exposure within 5–30 d	2
	Unclear *or* ≤1 d (heparin exposure within 31–100 d) *or* <10 d of exposure	1
	≤4 d *and* no antecedent heparin exposure	0
Thrombosis[b]	Proven thrombosis *or* skin necrosis *or* anaphylactic reaction after heparin bolus	2
	Progressive or recurrent or suspected thrombosis or erythematous skin reaction	1
	No thrombosis	0
Presence of the other potential etiologies of thrombocytopenia[c]	No other plausible explanation	2
	Other potential causes	1
	Other definite cause	0
Interpretation		
Pretest probability	High	6–8
	Intermediate	4–5
	Low	0–3

[a]From time of most proximate exposure to heparin.
[b]Venous (e.g., DVT, PE) or arterial (e.g., MI, CVA) thromboses, or characteristic skin lesions, are possible.
[c]Include sepsis; disseminated intravascular coagulaton; effect of other drugs (vancomycin, sulfa-based, etc.).
Adapted from Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4 Ts) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost* 2006;4:759–776.

2. Generation of platelet-leukocyte-endothelial aggregates ("white clot") leads to thrombosis.

C. Diagnosis of HIT
1. Assess pretest probability—"4 T Score" (Table 97-1)
2. Laboratory tests
   a. HIT (Heparin-PF4) antibody assay (enzyme linked immunosorbent assay [ELISA]):
      i. Unit: optical density (OD)
      ii. Sensitive (>90%) with low specificity (80%)
      iii. Specificity improved by assaying only for *IgG* antibodies
      iv. If OD ≥1.0 likelihood ratio (LR) of thrombosis = 5
      v. If OD ≥2.0 LR of thrombosis = 20
   b. Serotonin release assay (SRA):
      i. Unit: percentage release of ^{14}C-serotonin from platelets
      ii. High specificity (97%)
      iii. SRA = 80% release → LR = 10
   c. If there is a high clinical suspicion, treatment should be started regardless of the status of laboratory test results.

3. If high suspicion of HIT and no overt thrombosis, perform lower and upper extremity duplex ultrasound

D. Diagnosis of HIT/T
1. Requires a suspected or proven diagnosis of HIT (see preceding text) and demonstration of a concurrent thrombotic event
2. Imaging
   a. Should be performed based on anatomic location of suspected thrombosis
   b. May include Doppler ultrasonography (DVT), computed tomography (CT) (CVA and PE), angiography (peripheral arterial thrombosis)
3. Ancillary studies may include electrocardiogram (ECG) and cardiac enzymes (MI)

E. Treatment of HIT/T
1. Stop all heparin (including LMWH and heparin administered as "flushes," and remove heparin-coated catheters).
2. Start an *alternative anticoagulant such as a direct thrombin inhibitor* (DTI) (Table 97-2) as initial anticoagulation.
3. Avoid warfarin (or other vitamin K antagonists) as initial anticoagulation.
   a. If warfarin has already been started, it should be reversed with vitamin K.
4. Avoid platelet transfusions unless clinically significant bleeding is present.
5. Duration of anticoagulation
   a. HIT: generally for 30 days beyond detection of HIT (due to risk of thrombosis)
   b. HIT/T: as dictated by the thrombotic event (at least 3 months for DVT, 6 months for PE)
6. DTI (Table 97-2; also see Chapter 96)

F. Prognosis
1. Before DTI, HIT/T mortality was 18% and 37% suffered new thromboses or amputation.
2. Since DTI, HIT/T mortality is 11%, with 17% suffering new thromboembolism or amputation.

II. THROMBOHEMORRHAGIC EVENTS IN MYELOPROLIFERATIVE DISORDERS (POLYCYTHEMIA VERA AND ESSENTIAL THROMBOCYTHEMIA)

A. General principles
1. Philadelphia chromosome-negative chronic myeloproliferative disorders (MPD) include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).
   a. Overlapping clinical features
   b. Exhibit different natural histories and may have different therapeutic requirements
2. *JAK2*-V617F
   a. Somatic gain-of-function mutation
   b. Involves the *JAK2* tyrosine kinase gene
   c. Occurs with variable frequency in MPD (Table 97-3)
3. PV
   a. Annual incidence: 2 per 100,000 population with median age of 70 years
   b. At initial presentation, the incidence of thrombosis and bleeding are 12% to 39% and 2% to 20%, respectively

TABLE 97-2 Direct Thrombin Inhibitors as Initial Treatment of Heparin-Induced Thrombocytopenia/Thrombosis

	Argatroban	Lepirudin	Bivalirudin
Clearance	Hepatic	Renal	Enzymatic (80%), renal (20%)
Half-life	45 min (normal hepatic function)	80 min (normal renal function)	25 min (normal renal function)
Initial dosing	Normal liver function, non–ICU patient: 2 μg/kg/min Liver dysfunction (Total bilirubin ≥1.8 mg/dL or AST or ALT ≥150 U/L) and patients in the ICU: 0.25–0.5 μg/kg/min Severe liver dysfunction (total bilirubin >3.6 mg/dL or AST or ALT >600 U/L): avoid argatroban, consider lepirudin, bivalirudin	Est. CrCl >60 mL/min): 0.1 mg/kg/h Est. CrCl 45–60 mL/min: 0.05 mg/kg/h Est. CrCl 31–44 mL/min: 0.03 mg/kg/h Est. CrCl <30 mL/min: avoid, consider argatroban, bivalirudin	Est. CrCl. >60 mL/min) : 0.15 mg/kg/h Est. CrCl 45–60 mL/min: 0.1 mg/kg/h Est. CrCl 31–44 mL/min : 0.075 mg/kg/h Estimated CrCl <30 mL/min (no RRT): 0.05 mg/kg/h RRT or combined hepatic/renal failure: Consider argatroban for isolated renal failure or use 0.03 mg/kg/h
Monitoring	Measure aPTT 2 h after initiate therapy and after each dose adjustment[a] once stable, measure aPTT at least daily Therapeutic aPTT range: 1.5–3 × baseline value	Measure aPTT 6 h after initiation and after each dose adjustment[a] once stable, measure aPTT at least daily Therapeutic aPTT range: 1.5–2.0 × baseline value	Measure aPTT 2 h after initiation and after each dose adjustment[a] once stable, measure aPTT at least daily Therapeutic aPTT range: 1.5–2.5 × baseline value
Major bleeding	6%–7%	17%–18%	2%–3%
Comments	Start warfarin once platelet count normal; monitor PT/INR; when >4, stop argatroban and check aPTT, PT/INR after 6 h. If INR 2.5–3.5 and aPTT normal, do not restart argatroban; if INR <2.5, restart argatroban and increase warfarin dose; ensure argatroban bridge to warfarin monotherapy ≥5–7 d	No IV bolus due to higher bleeding risk Start warfarin once platelet count normal Check baseline PT/INR before transition to warfarin Antilepirudin antibodies develop in up to 44%, increasing the circulating half-life of the drug and bleeding risk	Consider use in combined renal/hepatic failure Start warfarin once platelet count normal Check baseline PT before transition to warfarin

[a] Dose adjustments should not exceed 20% dose for increases or 50% dose for decreases.
Est. CrCl, estimated creatinine clearance; RRT, renal replacement therapy; ICU, intensive care unit; AST, aspartate aminotransferase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio.

TABLE 97-3 Frequency of *JAK2*-V617F Mutation in Myeloproliferative Disorders

Disorder	Frequency of *JAK2* mutation (%)
Polycythemia vera	>90
Essential thrombocythemia	~50
Primary myelofibrosis	~50
Atypical myeloproliferative disorder	≤20
De novo myelodysplastic syndrome	3
Chronic myeloid leukemia	0

As assessed on peripheral blood. Expression of *JAK2*-V617F mutation establishes the presence of an MPD but does not inform the type (i.e., PV vs. ET). Absence of *JAK2*-V617F does not exclude MPD.

4. ET
   a. Annual incidence: 0.5 to 2.5 per 100,000 population with median age of 60 years.
   b. The overall risk of thrombosis and bleeding in ET has been reported 6.6% per patient-year and 0.33% per patient-year, respectively.

B. Clinical features
1. Thrombosis in PV and ET occurs in arterial, venous or microcirculation.
2. Large vessel arterial events: predominant cause of morbidity and mortality.
   a. CVAs (stroke and transient ischemic attacks)
   b. MI
   c. Peripheral arterial occlusion
3. Lower extremity DVT and PE account for most venous events.
4. Unusually high rate of intra-abdominal (portal and hepatic) vein thrombosis which together account for a substantial proportion of potentially catastrophic events.
   a. Particularly high frequency in young women with PV
   b. Underlying MPD in 31% and 53% of patients presenting with otherwise unexplained (i.e., without cirrhosis or hepatobiliary carcinoma) portal or hepatic vein thrombosis, respectively, in one study
5. Microcirculatory symptoms (headache, paraesthesias, erythromelalgia):
   a. More common in ET than PV
   b. Erythromelalgia
      i. Microvascular thrombotic syndrome
      ii. Presents with unilateral or bilateral asymmetric erythema, congestion, and burning pain of the hands and feet
      iii. Without treatment, may progress to acrocyanotic ischemia and, eventually, frank peripheral gangrene.
      iv. Typically symptoms promptly resolve with aspirin
6. Bleeding in ET and PV
   a. Involves primarily the skin and mucous membranes (suggests defective primary hemostasis)
   b. Ecchymosis, epistaxis, menorrhagia and gingival hemorrhage; gastrointestinal (GI) bleeding: less frequent
   c. Often associated with aspirin use
   d. Can be severe, requiring hospitalization and blood transfusion
7. Surgical procedures:
   a. Associated with an even higher morbidity and mortality than MPD at baseline, due to both thrombosis and hemorrhage

b. Risks particularly high when underlying disease is poorly controlled (erythrocytosis in PV or thrombocytosis in both PV and ET)

C. Pathophysiology
1. Different MPDs share the following common features:
a. Overproduction of one or more of the formed elements of the blood in the absence of a defined stimulus
b. Marrow hypercellularity
c. Abnormalities predominantly involving chromosomes 1, 8, 9, 13, and 20
d. Thrombotic and hemorrhagic diatheses
e. Spontaneous transformation to acute leukemia or the development of marrow fibrosis
2. Pathogenesis of thrombohemorrhagic events in PV and ET thought to be related to:
a. Erythrocytosis
b. Thrombocytosis
c. Functional and structural platelet abnormalities
d. Platelet membrane receptor abnormalities
e. Leukocyte activation
f. Acquired von Willebrand syndrome
3. Risk factors for development of thrombohemorrhagic events in PV and ET (Table 97-4).

D. Diagnosis
1. PV and ET: diagnostic criteria (Table 97-5)
2. MPD-related thrombosis
a. Brain magnetic resonance angiography (MRA) or magnetic resonance venography (MRV), CT-angiography, duplex ultrasound, and coronary angiography depending on suspected location of thrombosis.
b. Any persistent abdominal pain requires contrast CT scan of hepatic, portal, and mesenteric veins.

E. Treatment
1. Acute venous thrombosis
a. Initial management is heparin or LMWH followed by oral anticoagulant therapy.
b. Systemic anticoagulation alone may not be sufficient to prevent recurrent thrombosis; treatment of MPD usually also is required (see subsequent text).

TABLE 97-4 Risk Factors for Development of Thrombohemorrhagic Events in Polycythemia Vera (PV) and Essential Thrombocythemia (ET)

Age older than 65 yr
Previous history of thrombotic events
Poorly controlled erythrocytosis (PV)
Leukocytosis (PV and ET)
Thrombocytosis (PV and ET, bleeding but not thrombosis)
Cardiovascular risk factors
Hypertension
Smoking
Hypercholesterolemia
Diabetes mellitus
Concurrent thrombophilia (hereditary or acquired)
Monoclonal X-chromosome inactivation (ET)

TABLE 97-5 Requirements for Diagnosis of Polycythemia Vera and Essential Thrombocythemia

Polycythemia vera[a]	Essential thrombocythemia
Elevated red cell mass and normal or elevated plasma volume	Persistent thrombocytosis >400 × 10^9/L in the absence of a reactive cause
Normal arterial O_2 saturation	Absence of iron deficiency (normal serum ferritin for gender)
Splenomegaly	Hemoglobin <16 g/dL in a man or <14 g/dL in a woman in the absence of splenomegaly
If no splenomegaly, any two of the following:	Red cell mass and plasma volume normal (determinations are mandatory if a *JAK2*-V617F assay is positive)
Leukocytosis >12 × 10^9/L	Negative Bcr-Abl FISH (peripheral blood) if a *JAK2*-V617F assay is negative
Thrombocytosis >400 × 10^9/L	If there is anemia or macrocytosis or leukopenia, or evidence of extramedullary hematopoiesis (i.e., circulating nucleated erythrocytes, immature myelocytes, or splenomegaly), a bone marrow examination (including flow cytometry and cytogenetics) is mandatory regardless of *JAK2*-V617F expression status
Leukocyte alkaline phosphatase >100	
Serum B_{12} >900 pg/mL	
Unbound B_{12} binding capacity >2,200 pg/mL	

[a] Bone marrow examination or assays for erythropoietin and erythroid colony-forming cells are not part of the diagnostic criteria.

2. Acute arteriovascular events
   a. Initial management is per the usual manner.
   b. Treatment of MPD usually also is required (see subsequent text).
3. Treatment of MPD
   a. Does not cure the underlying disease or prevent clonal evolution in either PV or ET.
   b. For patients who have experienced thrombosis, goal is prevention of a recurrent thrombotic event.
4. PV
   a. Cytoreductive therapy (e.g., hydroxyurea) usually administered to patients who have experienced thrombosis
   b. Phlebotomy usually reserved for lower-risk (i.e., no prior thrombosis), younger patients with PV (goal: hematocrit <45% in males and <42% females)
5. ET
   a. Cytoreductive therapy (e.g., hydroxyurea) is usually administered to patients who have experienced thrombosis.
      i. Goal of therapy: platelet count of 400 × 10^9/L
      ii. Not recommended for low-risk (age younger than 65 and no previous thrombosis) patients
   b. Randomized clinical trial comparing aspirin plus either hydroxyurea (initial dose of 0.5 to 1 g/day) or anagrelide (initial dose of 0.5 mg bid) in at-risk ET patients showed:
      i. Transient ischemic attack frequency lower in hydroxyurea group
      ii. DVT frequency lower in anagrelide group
      iii. No difference in unstable angina, MI, stroke, arterial embolus of the lower or upper limbs, hepatic vein thrombosis or PE
      iv. Serious hemorrhage (GI bleeding) more frequent in anagrelide group

c. The risk (the potential leukemogenicity and myelotoxicity, especially in younger patients) and benefit ratio must be carefully reviewed with patients before the initiation of cytoreductive treatment.

6. Aspirin
   a. ET and PV: effectively controls microvascular symptoms.
   b. PV: low-dose aspirin (100 mg/day) reduces both arterial and venous thrombosis.
   c. ET patients with extreme thrombocytosis: monitor carefully (hemorrhagic effects of antiplatelet therapy and acquired von Willebrand disease, if present, may be additive).
7. Other antiplatelet agents: limited data on efficacy in MPDs

F. Prognosis
1. Natural history of ET: compatible with a normal life span
2. Natural history of PV
   a. Not completely defined.
   b. Neither staging criteria nor factors affecting prognosis have been established.
   c. Age and sex have an important influence.

III. PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

A. General principles
1. Definition
   a. Rare clonal hematopoietic stem cell disorder
   b. Causes episodic intravascular hemolytic anemia, abdominal pain, esophageal spasm, fatigue, thrombosis and bone marrow suppression
2. PNH may be isolated or occur in the setting of bone marrow failure (aplastic anemia or hypocellular MDS)
3. Thrombosis
   a. Occurs in approximately 40% of PNH patients and predominantly involves the venous system
   b. Large PNH clones (>50% of granulocytes affected) and classical symptoms (hemolytic anemia and hemoglobinuria) have a greater propensity for thrombosis

B. Pathophysiology
1. Mutation in X-linked *PIG-A* (phosphatidylinositol glycan class A) gene
   a. Present in the PNH stem cell and all of its progeny
   b. Critical for expression of cell surface glycosylphosphatidylinositol-anchored proteins (GPI-AP)
2. Leads to lack of membrane inhibitor of reactive lysis (CD59) and decay accelerating factor (CD55) on membranes of circulating blood cells
   a. Increased susceptibility of PNH erythrocytes to complement-mediated lysis
   b. Results in intravascular hemolysis and the release of large amounts of free hemoglobin into the plasma
   c. Free plasma hemoglobin acts as a *nitric oxide scavenger* resulting in abdominal pain, esophageal spasm, and erectile dysfunction
3. Pathogenesis of thrombosis in PNH
   a. Related to intravascular hemolysis
   b. Increased platelet aggregation and adhesion and accelerated fibrin clot formation due to nitric oxide depletion
   c. Increased thrombin generation resulting from platelet microvesicle formation and changes in platelet membrane, due to complement-mediated damage of platelet membrane
   d. Perturbed fibrinolysis from the loss of GPI-anchored urokinase receptor
   e. Decreased activity of tissue factor pathway inhibitor (TFPI)

C. Clinical presentation
1. Thrombosis may occur at any site.

2. Venous or arterial thrombosis is possible.
3. For unclear reasons, thrombosis at unusual locations (e.g., hepatic vein thrombosis/Budd-Chiari syndrome, sagittal vein thrombosis) occur with increased frequency in PNH.

D. Diagnosis
1. Flow cytometry
   a. Identifies blood cells (typically erythrocytes and leukocytes) that lack GPI-anchored proteins
   b. Diagnostic approaches
      i. Flow cytometry using antibodies against CD59 (a GPI-linked protein)
      ii. Flow cytometry using fluorescein-labeled proaerolysin variant (FLAER)—a bacterial protein that binds to GPI anchors (more sensitive that CD59 flow cytometry)
   c. PNH clone size best determined by assessment of granulocytes and monocytes, as recent hemolytic episodes/blood transfusion can affect the proportion of erythrocytes that express GPI-anchored proteins

E. Treatment
1. Allogeneic hematopoietic stem cell transplantation
   a. It is the only curative therapy for PNH.
   b. Best candidates are younger patients with severe pancytopenia or life-threatening thrombosis who have an human leukocyte antigen (HLA)-identical sibling.
2. Eculizumab
   a. First effective drug therapy for PNH (approved by U.S. Food and Drug Administration [FDA] in 2007)
   b. Humanized monoclonal antibody against C5 that inhibits terminal complement activation
      i. Leads to significant reduction in hemolysis and increased transfusion independence, lessened fatigue, mitigation of the smooth muscle dystonias, and improved overall health-related quality of life.
      ii. Leads to 85% absolute reduction in the risk for thrombosis while on eculizumab treatment (thromboembolism rate 1.07 events/100 patient-years compared to 7.37 events/100 patient-years post- and pre-eculizumab, respectively, in one study).
   c. May be associated with an increased risk for *Neisserial* infections
      i. Owing to pharmacologic blockade of terminal complement complex
      ii. Must vaccinate all patients treated with eculizumab against *Neisseria meningitides* before administering drug
3. Anticoagulation
   a. Appropriate for initial phase of treatment in individuals with PNH who experience thrombosis
   b. Chronic anticoagulation
      i. Significantly reduces thrombotic event rate in patients with large PNH clone size
      ii. Associated with an overall risk of 7.6 bleeding complications/100 patient-years with the risk increasing to 11.0 bleeding complications/100 patient-years during the first 90 days of treatment
      iii. Whether anticoagulants can be reduced or eliminated in patients with PNH receiving eculizumab is the subject of future investigation

F. Prognosis
1. Thrombosis is an ominous complication of PNH and the leading cause of death.
2. Independent factors are related to poor survival (Table 97-6).

TABLE 97-6 Factors Related to Poor Survival in Paroxysmal Nocturnal Hemoglobinuria

Diagnosis before 1996
Age 40 yr or older at diagnosis
Hemoglobin level ≤10 g/dL at diagnosis
Neutropenia
Absence of specific treatment (no use of immunosuppressive therapy (antithymocyte globulin [ATG] and/or cyclosporine [CsA]), no corticosteroids, no androgens or Danazol, and no warfarin therapy) during the first yr
Severe complications occurring during follow-up such as progression to bi- or pancytopenia
Development of thrombosis
Development of myelodysplastic syndrome or aplastic anemia

IV. CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME (APS)

A. General principles
  1. Antiphospholipid syndrome
    a. Autoimmune disorder
    b. Characterized by *both* production of antibodies directed against phospholipid binding proteins (APL) *and* arterial and/or venous thromboembolism or recurrent miscarriages
  2. Catastrophic antiphospholipid syndrome (CAPS)
    a. Rare, life-threatening manifestation of APS
    b. Occurs in <1% of patients with APS
    c. Characterized by acute-onset, multiorgan failure (kidneys, brain, liver, etc.)
    d. Almost always requires intensive care unit (ICU)-level care

B. Pathophysiology of CAPS
  1. Often triggered by infections, major surgery or discontinuation of immunosuppression or anticoagulation
  2. Diffuse microvascular thrombosis leads to tissue ischemia and organ failure (Table 97-7)
  3. Potential mechanisms
    a. Endothelial damage or activation by APL or APL-induced monocyte adhesion to endothelial cells
    b. Platelet activation by APL binding to platelet membrane phospholipid-bound annexins
    c. Increased monocyte and endothelial cell tissue factor (TF) activity
    d. Production of proinflammatory cytokines (interleukin [IL-1β] and tumor necrosis factor α [TNF-α])

C. Diagnosis
  1. On the basis of International Classification Criteria for CAPS (Table 97-8)
  2. Differential diagnosis includes severe sepsis, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), disseminated intravascular coagulation (DIC), infectious purpura fulminans (IPF), HIT/T

D. Treatment
  1. General: treatment of potential precipitating factors is extremely important.
    a. Broad spectrum antibiotics for infections
    b. Aggressive hemodynamic resuscitation in case of shock
    c. Debridement or amputation of necrotic tissues
    d. Mechanical ventilation

TABLE 97-7 Clinical Manifestations of the Catastrophic Antiphospholipid Antibody Syndrome

Anatomic site	Possible manifestation
Lung	Acute respiratory distress syndrome (ARDS): most common
	Pulmonary hypertension with normal cardiac output and pulmonary capillary wedge pressure
	Pulmonary hemorrhage
Kidney	50% increase in serum creatinine
	Severe systemic hypertension (>180/100 mm Hg), and/or{\par}proteinuria (>500 mg/24 h)
Brain	Stroke
	Encephalopathy
	Seizure
	Transient ischemic attack (TIA)
Heart	Valvular lesions: Libman-Sacks endocarditis
	MI
	Heart failure
Skin	Livedo reticularis
	Skin ulcers
	Digital ischemia
	Purpura
	Skin necrosis
Peripheral vasculature	DVT/PE
	Arterial thrombosis: most common = femoral artery
	Portal vein and inferior vena cava thrombosis
	Retinal artery and vein thrombosis
Blood	Coombs positive hemolytic anemia
	Thrombocytopenia
	DIC
	Bone marrow infarct

MI, myocardial infarction; DVT, deep venous thrombosis, PE, pulmonary embolism, DIC, disseminated intravascular coagulation.

- **e.** Renal replacement therapy
- **f.** Tight glycemic control
- **g.** Stomach acid suppression
- **h.** Control of malignant hypertension in case of renal artery or vein thrombosis
- **i.** Intravascular instrumentation, especially arterial, should be minimized because of the potential to trigger new clots

2. First-line therapies:

- **a.** Anticoagulation
  - **i.** Typically administered in conjunction with other treatments (see subsequent text).
  - **ii.** UFH infusion:
    - **(a)** 60 to 80 units/kg bolus, followed by 15 to 18 units/kg/hour to achieve therapeutic activated prothrombin time (aPTT).
    - **(b)** If patient previously had been anticoagulated with warfarin before detection of CAPS, it usually is held while therapeutic-dose heparin is administered.

TABLE 97-8 Diagnostic Criteria for the Catastrophic Antiphosholipid Antibody Syndrome

Criteria	
1. Evidence of involvement of three or more organ systems, and/or tissues **2.** Development of manifestations simultaneously or in <1 wk **3.** Confirmation by histopathology of small vessel occlusion in at least one organ/tissue **4.** Laboratory confirmation of the presence of APL (IgG / IgM anti-cardiolipin (>40 GPL or MPL units) or anti-β_2-glycoprotein I antibodies (>99th percentile) or positive lupus inhibitor on coagulation testing	
Interpretation	
Definite CAPS	All four criteria
Probable CAPS	All four criteria, except for involvement of only two organs, systems, and/or tissues *or* All four criteria, except for the absence of laboratory confirmation at least 12 wk apart attributable to the early death of a patient never tested for APL before the catastrophic APS *or* 1, 2, and 4 *or* 1, 3, and 4 and the development of a third event in more than 1 wk but less than 1 mo, despite anticoagulation treatment

APL, phospholipid binding proteins; Ig, immunoglobulin.

iii. Upon discharge from ICU, warfarin can be (re-)started; therapeutic anticoagulation with heparin should be continued until international normalized ratio (INR) is in desired range.

b. Corticosteroids

i. Mechanism of action: decreases nuclear factor (NF)-κB activation and decreases expression of inflammatory mediators

ii. Pulse methylprednisolone (1,000 mg/day) IV for 3 to 5 days followed 1 to 2 mg/kg/day

3. Second-line therapies: frequently necessary in the absence of a clinical response or ongoing thrombosis despite first-line treatment.

a. Intravenous immunoglobulins (IVIG)

i. Several potential mechanisms of action including interference with APL activity

ii. Total dose = 2 g/kg (400 mg/kg for 5 days or 1,000 mg/kg for 2 days)

iii. In case of renal insufficiency use non–sucrose containing products

iv. Contraindicated in patients with IgA deficiency (rare) due to risk of anaphylaxis

b. Plasmapheresis

i. Remove pathogenic antibodies and cytokines.

ii. Exchange one plasma volume for a minimum of 3 to 5 days.

iii. β2-GPI levels can be used as a marker of response to plasma exchange.

c. Unclear which treatment (plasma exchange or IVIG) is superior

4. Third-line treatments:

a. Fibrinolytics

i. Indications: life- or limb-threatening venous or arterial thrombosis

b. Cyclophosphamide: multiple protocols

- **c.** Prostacyclin: 5 ng/kg/minute for 7 days (per case reports)
- **d.** Defibrotide: 100 to 275 mg/kg/day for a minimum of 3 weeks
- **e.** Rituximab: 375 mg/m^2 weekly for 4 weeks

E. Prognosis

1. Mortality rate remains as high as 48% despite all therapies.
2. Clinical manifestations associated with a poor prognosis and higher mortality include:
   - **a.** Renal involvement
   - **b.** Splenic involvement
   - **c.** Pulmonary involvement
   - **d.** Adrenal involvement
   - **e.** Systemic lupus erethematosus (SLE) diagnosis
3. Recurrent CAPS is unusual; patients usually have a stable course with continued anticoagulation.
4. One fourth of the survivors will develop further APS-related events, but it is rare to develop recurrent CAPS.

V. DRUG-ASSOCIATED THROMBOSIS

A. Oral and transdermal contraceptives

1. Venous thromboembolism (VTE) risk increases within 3 to 4 months of the initiation and decreases to previous levels within 3 to 4 months of cessation.
2. Third-generation oral contraceptives: 2 to 3 fold higher VTE risk than with second generation.
3. Transdermal contraceptives: estimated one- to twofold increased VTE risk compared to oral contraceptives.
4. Progestin-only contraceptives: lower risk of VTE than estrogen-containing contraceptives.
5. Risk is further increased by the presence of thrombophilic conditions, obesity, age older than 35 years and smoking.

B. Hormone replacement therapy (HRT)

1. Two- to threefold increase in VTE risk.
2. VTE risk is greatest in the first year of treatment.
3. VTE risk is higher in older, obese women with hereditary thrombophilia or a past history of VTE.
4. VTE risk is lower with transdermal HRT compared with oral HRT.

C. Chemotherapy

1. Increases VTE risk 6.5-fold
2. Risk factors
   - **a.** Cancer site (pancreas and stomach: highest risk)
   - **b.** Baseline platelet count >350,000/μL
   - **c.** Baseline white blood count (WBC) count >11,000/μL
   - **d.** Baseline hemoglobin <10 g/dL or use of erythropoietic stimulatory agents
   - **e.** Body mass index (BMI) >35 kg/m^2
3. Efficacy of prophylactic anticoagulation remains to be demonstrated

D. Tamoxifen and raloxifene

1. Frequency of VTE varies with patient population exposed to tamoxifen
   - **a.** Premenopausal women with breast cancer: chemotherapy and tamoxifen (3% VTE frequency) versus chemotherapy alone (1%)
   - **b.** Postmenopausal women with breast cancer: tamoxifen and chemotherapy (8%) versus tamoxifen alone (2.3%) versus untreated patients (0.4%)

E. Thalidomide and lenalidomide

1. Risk of thrombosis with these agents alone (1% to 3%) increases when combined with dexamethasone and/or anthracyclines (10% to 20%).

2. Thromboprophylaxis:
   a. LMWH probably more effective than aspirin
   b. LMWH (enoxaparin 40 mg once daily or dalteparin 5,000 units once daily) or full-dose warfarin: appropriate for patients who receive high-dose dexamethasone or doxorubicin or multiagent chemotherapy, unless a contraindication
   c. Aspirin recommended only for low VTE risk patients at high risk for bleeding

F. Erythropoietin
1. Indicated for anemia associated with chemotherapy, myelodysplastic syndrome, and chronic renal failure
2. Rule out other causes of anemia before administration
3. Must not be administered with hemoglobin >12 g/dL
4. Has been associated with a 1.5-fold increased risk of VTE in cancer patients

G. Antipsychotics
1. Atypical antipsychotics (clozapine, quetiapine, olanzapine, resperidone) are associated with a twofold increased risk of VTE.
2. Low potency antipsychotics (e.g., chlorpromazine) are associated with a higher risk than high-potency antipsychotics (e.g., haloperidol).
3. Further increase in VTE risk:
   a. In the initial 3 months of treatment
   b. Use of >1 antipsychotic
   c. Supratherapeutic serum drug concentrations
4. Mechanism may involve drug-induced sedation, obesity, hyperleptinemia, antiphospholipid antibodies, or activation of platelets or coagulation proteins.
5. Weigh risks and benefits carefully in patients who have suffered VTE.

VI. MAJOR TRAUMA-ASSOCIATED THROMBOSIS

A. General principles
1. Very high risk for VTE in patients with major trauma with an ISS ≥9 in the absence of prophylaxis (venographic DVT 58%).
2. Patients receiving enoxaparin prophylaxis have an incidence of DVT as high as 31%.
3. Risk factors for VTE in the major trauma patient (Table 97-9).

B. Pathophysiology
1. Virchow's triad:
   a. Stasis (accumulation of activated coagulation factors, damage to endothelial cells due to decreased oxygen and nutrient delivery)
   b. Vessel wall damage/dysfunction (exposes subendothelial TF, collagen leading to activation of platelets and coagulation)

TABLE 97-9 Risk Factors for VTE in Patients with Major Trauma

Pelvic and or lower extremity fractures
Spinal cord injury
Injuries requiring surgical intervention
Femoral venous catheters
Major venous injuries
Age older than 40
Prolonged immobility
Delayed institution of thromboprophylaxis

   c. Hypercoagulability (increased coagulation factor levels, increased TNF, increased leukocyte production)
2. Shock/serious injury diminishes antithrombin-III (AT-III) levels in the trauma and patients in the ICU.
3. Elevated plasminogen activator inhibitor 1 (PAI-1) levels, which inhibits tissue plasminogen activator (tPA) and decreases the production of plasmin, suppresses fibrinolysis.
   a. Most frequent abnormality among major trauma and total hip arthroplasty patients who subsequently developed thrombosis

C. Diagnosis
1. Depends on anatomic site:
   a. Lower or upper extremities: duplex ultrasound
   b. Lung (pulmonary emboli): helical CT or V/Q scan
   c. Brain: MRV or CTV
   d. Venogram useful in all locations but rarely available and not infallible
2. The positive and negative predictive values of the above tests depend of the prevalence (pretest probability) of the disorder and sensitivity and specificity of the test.

D. Prophylaxis
1. Moderate risk trauma patients (i.e., no major VTE risk factors) without contraindications: *enoxaparin 30 mg subcutaneously every 12 hours*
   a. Significantly more effective than 5,000 units UFH subcutaneously two times per day
   b. Estimated decrease in risk of DVT from baseline, 47%, compared with UFH (only 30%)
   c. Note: major hemorrhage nonsignificantly increased with enoxaparin than low dose UFH (2.9% versus 0.6%, respectively)
2. High-risk trauma patients: enoxaparin at above dose plus mechanical prophylaxis (sequential compression devices and graduated compression stockings)
3. Patients with contraindications to pharmacologic VTE prophylaxis (intracranial bleeding, active bleeding, spinal hematoma)
   a. Mechanical prophylaxis until contraindication is no longer present
   b. Contraindications to sequential compression devices: acute DVT, arterial insufficiency, open extremity wounds
4. Vena cava filters or surveillance duplex ultrasonography: insufficient data to recommend use

E. Management
1. Objective documentation of VTE (e.g., duplex ultrasound, CT angiography, etc.) essential
2. Initial treatment: UFH or LMWH in therapeutic doses
   a. If high risk of bleeding, UFH without bolus is preferable to LMWH.
   b. If contraindication to anticoagulation, strongly consider a vena cava filter.
   c. Give UFH/LMWH for at least 5 to 7 days, continue until an INR of 2 or more is achieved with warfarin.
3. Long-term treatment
   a. Usually warfarin is used.
   b. Duration of therapy: 3 months (DVT) to 6 months (PE).
4. Vena cava filters
   a. Transient contraindication to anticoagulation: consider retrievable filter
   b. Long-term contraindications to anticoagulation: consider permanent vena cava filter

5. Thrombolysis
   a. Reserve for trauma patients without contraindications *and* life- or limb-threatening thrombosis

Suggested Reading

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ANEMIA IN THE CRITICAL CARE PATIENT

98

Thomas G. DeLoughery

I. EPIDEMIOLOGY OF ANEMIA IN CRITICALLY ILL PATIENTS

- **A.** Ninety-five percent of patients admitted to intensive care settings become anemic.
- **B.** Half of the patients in the intensive care unit (ICU) will receive red cell transfusion.
- **C.** Most common etiologies:
  - **1.** Inflammation (i.e., anemia of chronic disease)
  - **2.** Blood loss
  - **3.** Hemolysis

II. CLASSIFICATION OF ANEMIA

- **A.** Indices—classifies anemia by size of red cells (measured in femtoliters, fL)
  - **1.** Microcytic (typically <80 fL)—caused by anything that interferes with hemoglobin production
    - **a.** Iron deficiency
    - **b.** Anemia of chronic disease
      - **i.** Thirty percent of cases are microcytic.
      - **ii.** It results from inhibition of iron delivery to developing red cells.
    - **c.** Thalassemia
    - **d.** Sideroblastic anemia
  - **2.** Macrocytic
    - **a.** Two forms
      - **i.** Round macrocytes
      - **ii.** Oval macrocytes
    - **b.** Round macrocytes—caused by excess red blood cell (RBC) membrane
      - **i.** Liver disease
      - **ii.** Alcohol abuse
      - **iii.** Renal disease
    - **c.** Oval macrocytes—caused by interference with DNA synthesis
      - **i.** Megaloblastic anemia (e.g., B_{12} and folate deficiency)
      - **ii.** Myelodysplastic syndrome
      - **iii.** Chemotherapy agents
- **B.** Mechanism
  - **1.** Blood loss
  - **2.** Hemolysis
  - **3.** Production defects
    - **a.** Nutritional deficiencies
    - **b.** Anemia of chronic disease
    - **c.** Erythropoietin deficiency (e.g., in renal insufficiency)
    - **d.** Aplastic anemia/pure red cell aplasia
    - **e.** Myelodysplastic syndrome
    - **f.** Thalassemia

III. ANEMIA DUE TO BLOOD LOSS

- **A.** Overt blood loss (e.g., trauma, gastrointestinal bleeding)
- **B.** Subtle blood loss (e.g., through routine phlebotomy for laboratory testing)
  - **1.** Average ICU daily blood loss may approximate up to 240 mL/day in some patients.
  - **2.** Minimize laboratory draws and "batch" laboratory testing.

IV. HEMOLYTIC ANEMIA: BASIC PRINCIPLES

- **A.** Many processes lead to destruction of red cells (see individual disorders, in subsequent text).
- **B.** Laboratory diagnosis—can be difficult to assess hemolysis if it is subtle or patient has other abnormalities.
  - **1.** Indirect bilirubin—sensitive but not specific
    - **a.** Elevated in liver disease and Gilbert's syndrome.
  - **2.** Lactate dehydrogenase LDH—sensitive but not specific
    - **a.** Elevated in liver disease, myocardial infarctions, and rhabdomyolysis.
  - **3.** Haptoglobin—specific but not sensitive
    - **a.** Acute phase reactant
    - **b.** In 2% of the population haptoglobin is genetically absent
  - **4.** Coombs' test (i.e., direct antiglobulin test)—sensitive but not specific for autoimmune hemolytic anemia
    - **a.** False positives seen in renal disease, human immunodeficiency virus (HIV), liver disease, and in patients who have received intravenous (IV) immunoglobulin.

V. ACQUIRED HEMOLYTIC ANEMIAS

- **A.** Autoimmune
  - **1.** Warm antibody
    - **a.** Clinical presentation: acute onset of severe anemia, patient can complain of back pain and dark urine
    - **b.** Risk factors: Lupus, chronic lymphocytic leukemia, idiopathic
    - **c.** Diagnostic testing
      - **i.** Coomb's test: immunoglobulin G (IgG) positive ± C3d positive
    - **d.** Therapy:
      - **i.** Corticosteroids—prednisone 1 mg/kg daily or pulse dexamethasone 40 mg/day × 4 days
      - **ii.** Transfusions: can be difficult to cross-match; choose "least incompatible" units
      - **iii.** Refractory cases—rituximab, splenectomy
  - **2.** Cold agglutinin disease
    - **a.** Clinical presentation: anemia of variable severity, often worse in cold weather; acrocyanosis often present
    - **b.** Risk factors
      - **i.** Acute—sequelae of viral illness (e.g., mycoplasma)
      - **ii.** Chronic—lymphoproliferative disease
    - **c.** Diagnostic testing
      - **i.** Coombs' test: C3 d positive, IgG negative
    - **d.** Therapy
      - **i.** Corticosteroids, splenectomy typically ineffective
      - **ii.** Rituximab may be effective
      - **iii.** Plasma exchange for cases of severe anemia
      - **iv.** Avoidance of cold if anemia mild or moderate and compensated
  - **3.** Drug-induced
    - **a.** Clinical presentation: acute onset of anemia in the setting of exposure to one or more offending drugs

TABLE 98-1 Drug-Induced Hemolytic Anemia

Mechanism	Hapten	Ternary complex	Autoantibody	Unknown
Description	Drug directly binds to RBC membrane	Drug–antibody complex binds to RBC	Alters immune system function, production of autoantibodies	Unknown
Associated drugs	Penicillin Cephalosporin Tetracycline Tolbutamide Ampicillin Methicillin Carbenicillin	Amphotericin B Cefotaxine Ceftriaxone Cephalosporins Chlorpropamide Chlorpromazine Diclofenac Doxepin Hydrochlorothiazide Fenoprofen Isoniazid Melphalan Nomifensine Probenecid Quinidine Quinine Probenecid Rifampin Tetracycline Thiopental Tolmentin	Cephapirin Tolmentin Nomifensine Methyldopa Levodopa Mefenamic acid Teniposide Procainamide Diclofenac	Chlorpromazine Melphalan Isoniazid Acetaminophen Thiazides Ibuprofen Erythromycin Sulindac Omeprazole Sulfa drugs Rifampin Tricyclic antidepressants

RBC, red blood cell.

b. Risk factors: exposure to offending drugs (Table 98-1)
c. Diagnostic testing
i. Coombs' test: positive (usually IgG)
d. Therapy
i. Stop offending agent
ii. RBC transfusions
iii. Immunosuppression with corticosteroids rarely required

B. Microangiopathic (also see "Thrombocytopenia", Chapter 95)
1. Clinical presentation—hemolytic anemia of variable severity accompany by schistocytosis on blood smear, markedly elevated LDH
2. Thrombotic thrombocytopenic purpura
a. Clinical features: microangiopathic anemia, thrombocytopenia, end organ damage (e.g., renal, central nervous system [CNS], cardiac)
b. Risk factors: HIV, lupus
c. Diagnostic testing
i. Blood smear with corroborative clinical features
ii. Very low levels of ADAMTS13 specific, but often not immediately available
d. Therapy: plasma exchange ± corticosteroids

3. Hemolytic uremic syndrome
   a. Clinical features: microangiopathic anemia, thrombocytopenia, renal failure
   b. Risk factors: preceding *Escherichia coli* O157:H7 gastroenteritis
   c. Diagnostic testing
      i. Blood smear with corroborative clinical features
      ii. Levels of ADAMTS13 often normal
   d. Therapy
      i. Supportive care
      ii. Value of plasma exchange uncertain, but may be performed for severe cases
4. HELLP (*h*emolysis *e*levated *l*iver functions *l*ow *p*latelets) syndrome
   a. Clinical presentation: microangiopathic anemia in mid- or late pregnancy, accompanied by elevation of liver transaminases and thrombocytopenia
   b. Risk factors: previous pregnancy, advanced maternal age, and preeclampsia
   c. Diagnostic testing: nonspecific (i.e., clinical diagnosis)
   d. Therapy: prompt delivery and supportive care
5. Malignant hypertension
   a. Hematologic picture: microangiopathic anemia with mild to moderate thrombocytopenia, severe hypertension
   b. Risk factors: scleroderma
   c. Diagnostic testing: nonspecific (i.e., clinical diagnosis)
   d. Therapy: treat hypertension
6. Cardiac valvular disease
   a. Hematologic picture: microangiopathic anemia in patient with history of mitral repair
   b. Risk factors: recent valvular repair (in last 6 to 12 months)
   c. Diagnostic testing: demonstration of mitral regurgitant jet
   d. Therapy: valvular repair, afterload reduction

C. Paroxysmal nocturnal hemoglobinuria
1. Clinical features
   a. Acute episode(s) of (recurrent) hemolysis
   b. Markedly elevated LDH
   c. Thrombosis in unusual locations (e.g., portal or hepatic vein, cerebral venous circulation)
2. Risk factors: may have concurrent bone marrow failure of variable severity
3. Diagnostic test: flow cytometry demonstrates loss of glycosylphosphatidylinositol anchored proteins (such as CD59) on leukocytes and erythrocytes
4. Therapy
   a. Anticoagulation (due to high risk of recurrence)
   b. Complement C5 inhibitor eculizumab can suppress hemolysis

VI. INHERITED HEMOLYTIC ANEMIAS

A. Sickle cell disease
1. Clinical presentation: chronic hemolytic anemia, episodes of painful sickle crises, chronic and acute lung disease
2. Risk factors (for crises): infection, hypoxia
3. Diagnostic testing: blood smear showing sickle cells, hemoglobin electrophoresis showing presence of hemoglobin S
4. Therapy (for crises):
   a. Acute—pain control, oxygen, hydration, transfusion for severe anemia
   b. Chronic—hydroxyurea for patients with more than three painful crisis/year

5. Complications:
   a. Chest crisis—acute respiratory disease/failure with severe hypoxemia; therapy is red cell exchange.
   b. Aplastic crisis—acute infection with parvovirus B19 leads to suppressioncytopoiesis; therapy is transfusion.
   c. Megaloblastic crisis—due to folate deficiency; therapy is administration of folate.

B. G6PD deficiency
1. Clinical presentation: acute onset of severe anemia and abrupt hemolysis.
2. Risk factors: ingestion of oxidative drugs by patients with G6PD deficiencies. Patients of Mediterranean descent are more at risk of severe and prolonged hemolysis than are individuals of African descent.
3. Diagnostic testing: G6PD levels.
   a. Can be falsely normal during episodes of acute hemolysis
4. Therapy: supportive care, avoidance of suspect drugs (Table 98-2).

C. Membrane defects
1. Clinical presentation: variable and chronic hemolytic anemia (typically mild to moderate)
2. Risk factors (for acute episodes of hemolysis): hemolysis can acutely worsen with infections
3. Diagnostic testing: blood smear (Table 98-3)
4. Therapy: transfusion for acute severe anemia, splenectomy for chronic severe disease

VII. NUTRITIONAL DEFICIENCIES

A. Iron
1. Clinical presentation: microcytic anemia, concurrent thrombocytosis if severe
2. Risk factors: chronic bleeding, gastric surgery, heavy periods
3. Diagnostic testing
   a. Low serum iron, normal to high transferring, low ferritin
4. Therapy: oral or (refractory cases) IV iron

TABLE 98-2 Drugs That May Precipitate a Hemolytic Crisis in G6PD deficiency

Acetanilid
Furazolidone
Nalidixic acid
Naphthalene
Isobutyl nitrate
Sulfamethoxazole
Phenazopyridine
Nitrofurantoin
Sulfacetamide
Sulfanilamide
Methylene blue
Phenylhydrazine
Sulfapyridine
Primaquine
Pamaquine
Dapsone
Quinolones

TABLE 98-3 Findings on Peripheral Blood Smear and Associated Diseases

Finding	Associated disorder(s)
Microcytosis	Iron deficiency Thalassemia Anemia of inflammation (30% of cases)
Hypochromia	Same as microcytosis
Anisocytosis	Nonspecific finding
Poikilocytosis	Nonspecific finding
Spherocytes	Autoimmune hemolytic anemia Hereditary spherocytosis
Elliptocytosis	Iron deficiency, hereditary elliptocytosis
Target cells and concurrent microcytosis	Iron deficiency Thalassemia
Target cells and concurrent macrocytosis	Liver disease
Schistocytes	Microangiopathic hemolytic anemia
Ovalomacrocytosis	B_{12} or folate deficiency Myelodysplastic syndromes
Burr cells	Liver disease Kidney disease
Spur cells	Severe liver disease

B. Folate
  1. Clinical features: macrocytic anemia, hypersegmented neutrophils, pancytopenia if severe
  2. Risk factors: poor nutrition, alcohol use
  3. Diagnostic test: high homocystiene level
  4. Therapy: oral folate (1 mg/day)

C. Vitamin B_{12}
  1. Hematologic picture: macrocytic anemia, hypersegmented neutrophils, pancytopenia if severe
  2. Risk factors: pernicious anemia, gastric or bowel surgery (including gastric bypass)
  3. Diagnostic testing
    a. Low vitamin B_{12} level
    b. Elevated methylmalonic acid level
  4. Therapy
    a. Oral vitamin B_{12}: 1 to 2 mg/day, or
    b. Parenteral (intramuscular [IM]) B_{12}: 1 mg daily for 1 week, followed by weekly for 1 month, followed by monthly thereafter

D. Copper
  1. Features: anemia and severe neutropenia, thrombocytopenia very rare
  2. Risk factors: gastric surgery, malnutrition, tube feedings
  3. Diagnostic testing
    a. Low copper level
      i. Low ceruloplasmin level
  4. Therapy: copper orally, 2 mg/day

VIII. DISORDERS OF DECREASED RED CELL PRODUCTION

A. Anemia of inflammation (i.e., anemia of chronic disease)
  1. Hematologic features: mild to moderate anemia; microcytic in one third of cases

2. Risk factors: may be secondary to infections, cancer, autoimmune disease, trauma, other entities
3. Diagnostic testing
   a. Low serum iron, low transferrin, normal or elevated ferritin
   b. Inappropriately low erythropoietin for degree of anemia
4. Therapy: therapy of underlying disease, transfusions; erythropoietin (see subsequent text)

B. Anemia of renal insufficiency
1. Clinical presentation: anemia in the setting of renal disease
2. Risk factors: renal disease—can be subtle in older patients
3. Diagnostic testing: low erythropoietin, glomerular filtration rate (GFR) <60 mL/minute
4. Therapy: erythropoietin replacement

C. Aplastic anemia
1. Hematologic picture: anemia with very low reticulocyte count and pancytopenia
2. Risk factors: most often idiopathic
3. Diagnostic testing
   a. Low reticulocyte count (nonspecific)
   b. Bone marrow biopsy showing hypocellularity and reduced erythrocytic precursors
4. Therapy: immunosuppression or bone marrow transplantation

D. Pure red cell aplasia
1. Hematologic features: anemia with very low reticulocyte count, but other cell lines normal
2. Risk factors
   a. Immunosuppressed patient—parvovirus B19
   b. Drugs—phenytoin, azathioprine, isoniazid, valproic acid, and chlorpropamide
3. Diagnostic testing
   a. Bone marrow biopsy showing lack of red cell precursors
   b. Polymerase chain reaction (PCR) for parvovirus B19
4. Therapy
   a. Discontinue offending agent
   b. Immunoglobulin for parvovirus B19 infection
   c. Immunosuppression for idiopathic cases

E. α Thalassemia
1. Thalassemia minor (i.e., "thalassemia trait")
   a. Hematologic features: mild microcytic anemia
   b. Risk factors: African American or Asian
   c. Diagnostic testing
      i. Mild microcytic anemia with normal iron stores
      ii. Hemoglobin electrophoresis generally normal
      iii. Positive α thalassemia mutational analysis
   d. Therapy
      i. None required
      ii. Avoid inappropriate iron supplementation
2. Hemoglobin H disease
   a. Hematologic features: moderate hemolytic anemia
   b. Risk factors: Asian background
   c. Diagnostic testing
      i. Microcytosis
      ii. Erythrocytes with Heinz bodies
   d. Therapy: severe cases may require splenectomy

- **F.** β Thalassemia
  - **1.** Thalassemia minor (i.e., thalassemia trait)
    - **a.** Hematologic features: mild microcytic anemia
    - **b.** Risk factors: Mediterranean or Asian origin
    - **c.** Diagnostic testing
      - **i.** Hemoglobin electrophoresis showing increased Hgb A_2
    - **d.** Therapy: none required
  - **2.** Thalassemia major
    - **a.** Hematologic features: severe microcytic anemia
    - **b.** Risk factors: Mediterranean or Asian origin
    - **c.** Diagnostic testing
      - **i.** Hemoglobin electrophoresis showing increased Hgb A_2
    - **d.** Therapy: chronic transfusion, stem cell transplantation if human leukocyte antigen (HLA)-matched sibling donor available
- **G.** Hemoglobin E
  - **1.** Hematologic features: mild microcytic anemia
  - **2.** Risk factors: Asian origin
  - **3.** Diagnostic testing
    - **a.** Hemoglobin electrophoresis showing increased hemoglobin E
  - **4.** Therapy: none
- **H.** Myelodysplasia
  - **1.** Hematologic features: mild to severe macrocytic anemia, often other cytopenias (especially thrombocytopenia) present
  - **2.** Risk factors: older age, previous exposure to chemotherapy or radiation
  - **3.** Diagnostic testing
    - **a.** Bone marrow aspirate and biopsy demonstrating morphologic abnormalities of developing blood cells
    - **b.** Abnormal cytogenetics (in 40% to 70% of cases only)
  - **4.** Therapy
    - **a.** Must be individualized
    - **b.** May include RBC growth factors, transfusions, chemotherapy, and/or stem cell transplantation

IX. DIAGNOSTIC APPROACH TO ANEMIA

- **A.** Complete blood count (CBC)
  - **1.** Evaluate RBC indices
  - **2.** Presence of other cell line abnormalities
- **B.** Blood smear (Table 98-3)
- **C.** Reticulocyte count
  - **1.** Measurement of "new" red cells
    - **a.** Surrogate marker for marrow erythropoietic activity
    - **b.** Absolute reticulocyte count
      - **i.** Normal range is approximately 35 to 90,000/ul.
      - **ii.** Normal range assumes no anemia (i.e., represents physiologic erythropoiesis).
    - **c.** Corrected reticulocyte count
      - **i.** Percent reticulocyte count multiplied by patient's hematocrit, then divided by 45
  - **2.** Interpretation of reticulocyte count
    - **a.** Decreased (<0.01% or <5,000/ul): indicates marrow aplasia or myelodysplasia
    - **b.** "Normal" (1%, 35 to 90,000/ul): may still represent
      - **i.** Production defect, as values should increase above the normal range in response to anemia
    - **c.** Increased (>3%, or >100,000/ul): characteristic of hemolysis or blood loss

D. Additional testing as guided by items 1 to 3 above in conjunction with assessment of clinical factors

X. THERAPY

A. Specific therapy (e.g., iron for iron deficiency)
B. Transfusion—see Chapter 99
C. Erythropoietin
1. Clearest indications for use
a. Renal failure/insufficiency (e.g., dialysis dependent)
b. Use in other settings may be considered
i. For example, myelodysplasia with refractory anemia and baseline erythropoietin level <200 to 500 mIU/mL
c. Studies of erythropoietin use in patients in the ICU have not shown benefit in preventing transfusions when a restrictive transfusion protocol is followed.

Suggested Reading

Andrès E, Loukili NH, Noel E, et al. Vitamin B12 (cobalamin) deficiency in elderly patients. *CMAJ* 2004;171(3):251–259.
Good overview on current thoughts on B12 deficiency, especially its presentation in older patients.

Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. *Lancet* 2008;371(9606):64–74.
Recent review that covers both basic science and clinical aspect of this common hemolytic anemia.

Clark SF. Iron deficiency anemia. *Nutr Clin Pract* 2008;23(2):128–141.
Review article on the multiple manifestations of iron deficiency.

Ezzie ME, Aberegg SK, O'Brien JM, Jr. Laboratory testing in the intensive care unit. *Crit Care Clin* 2007;23(3):435–465.
Provocative article on the potential overuse of laboratory testing in the critical care setting.

Ganz T. Hepcidin and its role in regulating systemic iron metabolism [Review]. *Hematology Am Soc Hematol Educ Program* 2006;29–35:507.
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Hagar W, Vichinsky E. Advances in clinical research in sickle cell disease. *Br J Haematol* 2008;141(3):346–356.
A recent update by two leading experts in the field.

Zarychanski R, Turgeon AF McIntyre L, et al. Erythropoietin-receptor agonists in critically ill patients: a meta-analysis of randomized controlled trials. *CMAJ* 2007;177(7):725–734.
Review of all the erythropoietin critical care trials showing minimal benefit.

99 TRANSFUSION THERAPY: BLOOD COMPONENTS AND TRANSFUSION RISKS

Suchitra Pandey and Ashok Nambiar

I. RED BLOOD CELLS (RBCS)

- **A.** General principles
  - **1.** Manufacture and contents
    - **a.** Obtained by apheresis collection or prepared from anticoagulated (citrated) whole blood. Following centrifugation, plasma is removed and 100 mL additive solution is added.
    - **b.** Each unit: red cells: approximately 200 mL; plasma: <50 mL; hematocrit: 55% to 60%.
- **B.** Indications
  - **1.** Augment O_2 carrying capacity in anemic patients.
  - **2.** Hemoglobin (Hgb) threshold for transfusion is controversial.
    - **a.** General guideline: patients with Hgb level >10 g/dL rarely need transfusion; those with Hgb levels <6 g/dL benefit from transfusion. Decision to transfuse patients with Hgb between 6 and 10 g/dL depends upon cardiopulmonary risk factors, ongoing blood loss, and clinical judgment.
    - **b.** A recent trial in normovolemic critical care patients showed that a restrictive red cell transfusion strategy (keeping Hgb levels between 7 and 9 g/dL) was as effective as a more liberal strategy (keeping Hgb levels between 10 and 12 g/dL).
- **C.** Dose, administration
  - **1.** Each packed red blood cells (PRBC) unit typically raises Hgb by approximately 1 g/dL in a euvolemic adult patient.
- **D.** Special requests
  - **1.** Cytomegalovirus (CMV)-negative, leukoreduced, irradiated, washed, or volume reduced products (Table 99-1)

II. WHOLE BLOOD

- **A.** General principles
  - **1.** Manufacture and contents
    - **a.** Limited availability
    - **b.** Approximately 450 to 500 mL donor blood and anticoagulant solution
    - **c.** Platelets not functional in whole blood preparations
- **B.** Indications
  - **1.** Massive blood loss, such as trauma

III. PLATELETS

- **A.** General principles
  - **1.** Manufacture and contents
    - **a.** Platelet concentrates (PC)
      - **i.** Prepared from whole blood by centrifugation
      - **ii.** Contain 5.5×10^{10} platelets suspended in 50 mL plasma
      - **iii.** Five to six PCs pooled to obtain an adult dose

TABLE 99-1 Requests for Special Red Cell and Platelet Products

Request/ modification	Description	Indications
CMV-negative	Product is from a donor negative for CMV IgG antibodies	Immunosuppressed patients, transplant candidates/recipients, and pregnant women who are CMV negative Fetus/neonate
Leukocyte-reduced	Prestorage filtration removes 99.9% of WBCs (residual white cell count $<5 \times 10^6$ WBCs)[a] Bedside leukoreduction filters are less efficient[b]	Same as CMV-negative Frequently transfused patients (reduces HLA antigen alloimmunization) Patients with recurrent febrile reactions
Irradiation	Gamma irradiation (25 Gy) prevents proliferation of lymphocytes — prevents transfusion-associated graft-versus-host disease	Congenital/acquired immunodeficiency Stem cell transplant recipients HLA-matched products, transfusions from relatives, and granulocyte products Fetus/neonate
Washing[c]	Removes >98% of plasma proteins, electrolytes, and antibodies	Patients with recurrent or severe allergic/febrile reactions Patients with IgA or haptoglobin deficiency Patients at risk for hyperkalemia
Volume reduction[d]	Platelet unit centrifuged and most of plasma removed	Patients at risk for circulatory overload Patients with recurrent allergic reactions

[a] Many hospitals consider leukoreduced products as an equivalent to CMV-negative products; 1% to 2% breakthrough infections have been reported with use of either seronegative or leukoreduced products.
[b] Bedside leukoreduction may cause a hypotensive reaction in patients on angiotensin converting enzyme (ACE) inhibitor therapy
[c] Washing causes a 15% to 20% loss of red cells and up to 50% loss of platelets (remaining platelets may suffer functional damage).
[d] Platelet loss/dysfunction is less compared with washing.
CMV, cytomegalovirus; IgG, immunoglobulin G; HLA, human leukocyte antigen.

b. Apheresis platelets
  i. Collected from single donors by apheresis; many hospitals use only apheresis platelets
  ii. Contain 3×10^{11} platelets in 200 to 400 mL plasma; equivalent to "6-pack" PC

B. Indications
1. Active bleeding in thrombocytopenic patients or patients with acquired or inherited platelet dysfunction
2. Prophylactically
  a. Platelet counts <10,000/uL in patients with stable hematologic disease

b. Platelet counts <20,000/uL in febrile patients or those with mucositis
c. Platelet counts <50,000/uL in patients requiring invasive procedures
d. Platelet counts <100,000/uL in patients with intracranial bleeding or requiring neurosurgery

3. In the absence of severe bleeding, platelet transfusions are generally avoided in patients with thrombotic thrombocytopenic purpura (TTP), heparin-induced thrombocytopenia and idiopathic thrombocytopenic purpura (ITP)

C. Dose, administration

1. One apheresis platelet dose (or a 6-pack PC) typically raises platelet counts by 30,000 to 60,000/μl.
2. Suspect platelet refractoriness if posttransfusion (10 to 60 minutes) counts show poor increments.
   a. Clinical or 'nonimmune' causes include hypersplenism, fever, medications and disseminated intravascular coagulation (DIC).
   b. Immune-mediated refractoriness resulting from antibodies to human leukocyte antigen (HLA) and/or platelet-specific antigens requires transfusion of crossmatched or HLA-matched platelets.

IV. FRESH FROZEN PLASMA (FFP)/PLASMA FROZEN WITHIN 24 HOURS OF COLLECTION (FP24)

A. General principles

1. Manufacture and contents
   a. Obtained by apheresis or separation of plasma from centrifuged whole blood. Plasma is frozen within 6 to 8 hours of collection (FFP) or within 24 hours (FP24).
   b. One FFP/FP24 unit (200 to 250 mL) contains approximately 400 mg fibrinogen.
      i. FFP contains an average of 1 IU/mL of each coagulation factor.
      ii. FFP and FP24 are essentially equivalent. Slightly lower levels of factors V and VIII in FP24.
2. Indications
   a. Multiple coagulation factor deficiency
      i. Prothrombin time (PT) >1.5 × normal in bleeding patients or those requiring invasive procedures
   b. Dilutional coagulopathy (massive transfusion)
   c. Deficiency of single coagulation factors or other plasma proteins like protein C, protein S, C1 esterase inhibitor or antithrombin III, when specific concentrates are unavailable
   d. Rapid reversal of warfarin in actively bleeding patients or those requiring emergent procedures
   e. Therapeutic plasma exchange in patients with TTP
   f. FFP should not be used to 'correct' mild elevations in PT/international normalized ratio (INR)/partial thromboplastin time (PTT), reverse heparin effect or expand intravascular volume

B. Dose, administration

1. For coagulation factor replacement, a dose of 10 to 20 mL/kg increases coagulation factor activity by 20% to 30% soon after infusion, providing significant hemostatic improvement.

V. CRYOPRECIPITATE

A. General principles

1. Manufacture and contents
   a. Cold-insoluble precipitate (15 to 20 mL) recovered from slowly thawed FFP

b. Each unit contains 200 to 300 mg fibrinogen; approximately 80 IU each of factor VIII and von Willebrand factor (vWF) and 40 to 60 IU factor XIII

B. Indications
1. Replacement of fibrinogen in dilutional coagulopathy, DIC, or dysfibrinogenemia
2. Factor XIII deficiency
3. Bleeding uremic patients whose platelet dysfunction is uncorrected by dialysis and desmopressin acetate (DDAVP) therapy

C. Dose, administration
1. A dose (10 units) increases fibrinogen by approximately 50 mg/dL in adults without massive bleeding.
2. Units are usually pooled (5 to 10 units/pool) to facilitate transfusion.

VI. INTRAVENOUS IMMUNOGLOBULIN (IVIG)

A. General principles
1. Manufacture and content
a. Pools of plasma fractionated to create concentrated immunoglobulin product (mainly IgG)
2. Indications
a. Hematologic conditions: acquired hypogammaglobulinemia, acquired red cell aplasia, human immunodeficiency virus (HIV)-associated thrombocytopenia, ITP and posttransfusion purpura (PTP). May be used in life-threatening cases of acquired hemophilia, acquired von Willebrand disease, autoimmune hemolytic anemia, autoimmune neutropenia, hemolytic transfusion reaction, TTP and viral-associated hemophagocytic syndrome.
b. Neurologic conditions: acute disseminated encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, dermatomyositis, Guillain–Barré syndrome, Lambert–Eaton myasthenic syndrome and myasthenia gravis.

VII. TRANSFUSION RISKS

A. General principles
1. Transfusion-associated infections (Table 99-2)
2. Transfusion reactions
a. Acute hemolytic transfusion reaction (AHTR)
i. ABO-incompatible RBCs lysed by preexisting antibodies in recipient plasma or incompatible antibodies in transfused plasma products lyse recipient RBCs.
ii. Non–immune-mediated hemolysis may result from malfunctioning blood warmers or addition of medications or hypotonic solutions to RBC bags.
iii. Fever, rigors, flank or infusion site pain, vomiting, dyspnea, hypotension, hemoglobinuria, renal failure, and DIC may develop early in the infusion.
iv. Stop transfusion immediately. Check patient's identity with identifiers on blood bag. Send product and patient sample to blood bank for hemolysis workup (includes visual check for hemolysis, direct Coombs test and repeat of type and crossmatch).
v. Therapy: aggressive hydration; cardiopulmonary and renal support. Monitor for DIC.
b. Delayed hemolytic transfusion reaction
i. RBC lysis by newly formed antibody or rising levels of previously undetectable antibody
ii. Asymptomatic or fever, jaundice, drop in hematocrit, 3 to 14 days following transfusion

TABLE 99-2 Transfusion Transmitted Infectious Risks

Infectious agent	Risk per unit transfused	Screening in US donors
HIV-1/2	1 in 1.8 million	Anti-HIV 1/2, nucleic acid testing (NAT) for HIV-1
Hepatitis C	1 in 1.6 million	Anti-HCV, NAT
Hepatitis B	1 in 220,000	Surface antigen (HBsAg), anti-HBc
HTLV-I/II	1 in 3 million	Anti-HTLV I/II
CMV	Infrequent with leukoreduced or CMV-negative products	Anti-CMV
West Nile virus (WNV)	Rare	NAT for WNV began in 2003[a]
Chagas	Rare	*Trypanosoma cruzi* antibody[b]
Malaria, other parasites	Rare	Donors deferred for high risk travel
Parvovirus B19	1 in 3,000 to 40,000[c]	No routine screening
Bacterial sepsis	RBC: 1 in 30,000 Platelets: 1 in 75,000 to 200,000[d]	All platelets are screened for bacterial growth before release

[a] During 2002 epidemic before NAT, risk per unit transfused was 2 to 5/10,000. Since NAT, only rare cases of transfusion transmission reported.
[b] Although not required, many blood centers screen for antibodies to *T.cruzi*. Only seven cases of transfusion transmitted Chagas have been reported in the US and Canada in the past 20 years.
[c] Infected units rarely cause clinical sequelae.
[d] Reflects data of reported sepsis cases since implementation of bacterial screening.
HIV, human immunodeficiency virus; HCV, hepatitis C virus; CMV, cytomegalovirus; HTLV, human T-lymphotropic virus; RBC, red blood cell.

iii. Blood bank provides antigen-negative units for future RBC transfusions

c. Febrile non–hemolytic transfusion reaction
- **i.** Rise (>1° C) in temperature during or immediately after transfusion. Chills, rigors, and vomiting may accompany reaction.
- **ii.** Inflammatory cytokines in product or reactions between antibodies in the recipient and white blood cells (WBCs)/platelets in the transfused component have been implicated in the pathogenesis.
- **iii.** Stop transfusion. Rule out hemolytic transfusion reaction and bacterial contamination by appropriate testing (hemolytic reaction workup, Gram stain and culture of product).
- **iv.** Fever and rigors respond to antipyretics and Meperidine respectively.

d. Allergic transfusion reaction
- **i.** Usually due to recipient antibodies directed against proteins in donor plasma.
- **ii.** Mild reactions (hives, urticaria): stop transfusion; administer antihistamines. Resume transfusion only if symptoms are mild and abate with medications.
- **iii.** Severe/anaphylactic reactions: stop transfusion; administer antihistamines, steroids and vasopressors as needed. Premedicate with antihistamines and steroids for future transfusions. Washing or further reducing plasma from cellular products may minimize reactions.

iv. IgA-deficient patients with anti-IgA antibodies and patients with antihaptoglobin antibodies are at risk for anaphylactic reactions. All cellular products must be extensively washed.

e. Transfusion-related acute lung injury (TRALI)
   i. Severe hypoxemia (Pao_2: FIo_2 <300) and radiologic evidence of pulmonary edema occurring during or within 6 hours of transfusion in patients without evidence of left atrial hypertension.
   ii. HLA class I and II antibodies, antineutrophil antibodies and biologically active lipids have been implicated. Severe reactions are usually reported with plasma-containing components (FFP and platelets).
   iii. Rule out cardiogenic pulmonary edema and other causes of acute lung injury.
   iv. Therapy
      (a) Rapid and intensive respiratory support
      (b) TRALI usually resolves in 72 to 96 hours

f. Transfusion-associated circulatory overload
   i. Increased risk in elderly patients, patients with heart failure, and children
   ii. Signs/symptoms: dyspnea, pulmonary edema on chest x-ray, increased central venous or pulmonary arterial wedge pressures, elevated B-type natriuretic peptide (BNP) levels
   iii. Therapy
      (a) Stop transfusion.
      (b) Begin intravenous (IV) diuresis and reassess fluid balance. Transfuse units slowly.

g. Citrate toxicity
   i. Occurs in the setting of massive transfusion due to citrate anticoagulant in blood products
   ii. Signs/symptoms: hypocalcemia can lead to coagulopathy, tetany, and cardiac arrhythmia
   iii. Therapy: monitoring levels of ionized calcium and magnesium; replacement as needed

Suggested Reading

American Association of Blood Banks, America's Blood Centers, American Red Cross. *Circular of information on the use of human blood and blood components*. Bethesda: American Association of Blood Banks, 2002.
Provides general information on blood donor selection and testing, component preparation and contents, and adverse effects of transfusion.

American Society of Anesthesiologists Task Force on Blood Component Therapy. Practice guidelines for blood component therapy. *Anesthesiology* 1996;84:732–747.
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Anderson D, Ali K, Blanchette V, et al. Guidelines on the use of intravenous immune globulin for hematologic conditions. *Trans Med Rev* 2007;21:S9–S56.
Panel of experts convened to develop evidence-based practice guidelines on IVIG use.

Bowden RA, Slichter SJ, Sayers M, et al. Comparison of filtered leukocyte-reduced and cytomegalovirus seronegative blood products for the prevention of transplant-associated CMV infection after marrow transplant. *Blood* 1995;86:3598–3603.
Large trial demonstrated leukocyte reduced products were comparable to CMV sero-negative products in the prevention of transfusion transmitted CMV.

Delaflor-Weiss E, Mintz PD. The evaluation and management of platelet refractoriness and alloimmunization. *Trans Med Rev* 2000;14:180–196.
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Eder AF, Kennedy JM, Dy B, et al. Bacterial screening of apheresis platelets and the residual risk of septic transfusion reactions: the American Red Cross Experience (2004–2006). *Transfusion* 2007;47:1134–1142.
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Gajic O, Gropper MA, Hubmayr RD. Pulmonary edema after transfusion: how to differentiate transfusion-associated circulatory overload from transfusion-related acute lung injury. *Crit Care Med* 2006;34:S109–S113.
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Hebert PC, Wells G, Blajchman, et al. A multicenter randomized controlled clinical trial of transfusion requirements in critical care. *N Eng J Med* 1999;340:409–417.
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A review of red cell storage lesion, oxygen transport, transfusion triggers, and complications.

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Rebulla P, Finazzi G, Marangoni F, et al. The threshold for prophylactic platelet transfusions in adults with acute myeloid leukemia. *N Eng J Med* 1997;337:1870–1185.
Study compares bleeding risks in acute myeloid leukemia patients when the trigger for platelet transfusion is decreased to 10,000/uL from 20,000/uL.

Stainsby D, MacLennan S, Thomas D, et al. Guidelines on the management of massive blood loss. *Br J Haematol* 2006;135:635–641.
Provides current guidelines for clinical management of massive transfusion.

Stramer SL. Current risks of transfusion-transmitted agents. *Arch Pathol Lab Med* 2007;131:702–707.
Review of current risk estimates of transfusion transmitted infections.

Stroncek DF, Rebulla P. Platelet transfusions. *Lancet* 2007;370:427–438.
A review of platelet components, transfusion practices, and adverse consequences of platelet transfusions.

Wu WC, Rathore SS, Wang Y, et al. Blood transfusion in elderly patients with acute myocardial infarction. *N Eng J Med* 2001;345:1230–1236.
A study showing association of RBC transfusion with lower short-term mortality rate among elderly patients with acute myocardial infarction if the hematocrit on admission $\leq$30%.

THE LEUKEMIAS

Karen K. Ballen

100

I. GENERAL PRINCIPLES

- **A.** Leukemias are curable with chemotherapy
- **B.** Approximately 30% of adults with acute leukemia can be cured of disease.
- **C.** High-dose chemotherapy followed by allogeneic stem cell transplantation is now used as a curative therapy for high-risk patients with acute and chronic leukemia.
- **D.** Four types of leukemia
  - **1.** Acute lymphoblastic leukemia (ALL)
  - **2.** Acute myelogeneous leukemia (AML)
  - **3.** Chronic lymphocytic leukemia (CLL)
  - **4.** Chronic myelogeneous leukemia (CML)

II. ETIOLOGY

- **A.** Most cases idiopathic
- **B.** Not usually familial in origin, no lifestyle risk factors known
- **C.** Acute myelogeneous leukemia may arise as a result of prior chemotherapy or radiation therapy
  - **1.** Therapy-related AML poor prognosis
  - **2.** Associated with abnormalities of chromosome 5, 7, and 11
- **D.** AML may arise from a prior myelodysplastic syndrome
  - **1.** Secondary AML more common in older patients

III. PATHOPHYSIOLOGY

- **A.** ALL more common in children, but can occur in adults
  - **1.** Can present with mediastinal mass.
  - **2.** Can present with central nervous system (CNS) and testicular involvement.
- **B.** AML more common in adults
  - **1.** Monocytic variants can have skin, gum, and CNS involvement.
- **C.** Acute promyelocytic leukemia (APML)
  - **1.** Associated with bleeding and disseminated intravascular coagulation (DIC)
- **D.** Chronic lymphocytic leukemia
  - **1.** Often indolent disease of elderly
- **E.** Chronic myelogeneous leukemia
  - **1.** Can progress to acute leukemia
    - **a.** Myeloid blast crisis (70% of cases)
    - **b.** Lymphoid blast crisis (30% of cases)

IV. DIAGNOSIS

- **A.** History
  - **1.** Nonspecific symptoms of fatigue, shortness of breath, infection, bleeding
- **B.** Examination
  - **1.** Pallor, petechiae, sometimes splenomegaly, flow murmur
- **C.** Laboratory studies
  - **1.** Complete blood count
    - **a.** Anemia or thrombocytopenia
    - **b.** White blood cell (WBC) count may be normal, high, or low

D. Peripheral blood smear
   1. Increased immature cells
E. Bone marrow aspirate and biopsy
   1. Flow cytometry, cytogenetics, molecular studies
   2. Acute leukemia defined as >20% blasts
F. Molecular diagnostic studies
   1. BCR-ABL mutation diagnostic of CML
   2. PML-RAR α diagnostic of APML
   3. FLT3 mutation negative prognostic feature in AML

V. TREATMENT

A. Acute lymphoblastic leukemia

1. Induction chemotherapy with four to five chemotherapy drugs
   a. Asparaginase, prednisone, vincristine, doxorubicin (Adriamycin), cyclophosphamide
   b. CNS prophylaxis with intrathecal chemotherapy
   c. Intensification and maintenance chemotherapy over 18 to 24 months (outpatient)
   d. Philadelphia chromosome positive patients also receive imatinib (Gleevec)
   e. Allogeneic transplantation in first remission for high risk or young patients

B. Acute myelogeneous leukemia

1. Elderly patients have poor prognosis—consider supportive care with hydroxyurea, transfusions, and antibiotics
2. Induction chemotherapy with idarubicin and cytosine arabinoside
3. Consolidation chemotherapy with high dose cytosine arabinoside
4. Allogeneic stem cell transplantation for patients at high risk of relapse, often based on cytogenetics

C. Acute promyelocytic leukemia

1. Cure rate of 70% to 80%
2. Five percent of patients die of bleeding before diagnosis can be made
3. Prompt diagnosis and treatment essential
4. All *trans* retinoic acid (ATRA) plus chemotherapy
5. Consolidation with ATRA, daunorubicin, and arsenic

D. Chronic lymphocytic leukemia

1. Observation until disease progression, often many years
2. Fludarabine-based therapy
   a. Fludarabine/cyclophosphamide
   b. Fludabine/rituximab
   c. Fludarabine/rituximab/cyclophosphamide

E. Refractory patients
   1. Alemtuzumab (Campath)
   2. Allogeneic stem cell transplantation

F. Chronic myelogeneous leukemia

1. Oral tyrosine kinase inhibitor imatinib (Gleevec)

G. If Gleevec refractory, alternative tyrosine kinase inhibitors
   1. Dasatinib
   2. Nilotinib
   3. Allogeneic stem cell transplantation for refractory patients

VI. COMPLICATIONS

A. Leukostasis
   1. Most likely when the blast count >50,000/mm^3
   2. Can occur even with lower WBC
   3. Most common in AML because blasts large

4. Hypoxia, pulmonary infiltrates, visual changes, mental status changes, CNS bleeding
5. Treatment for leukostasis
   a. Intravenous fluids
   b. Prompt initiation of chemotherapy
   c. Hydroxyurea 1 to 2 g PO twice daily to lower WBC
   d. Leukopheresis
   e. Avoid red blood cell (RBC) transfusions which increase viscosity

B. Bleeding
1. Thrombocytopenia
   a. Increased risk CNS bleed when platelet count $<10{,}000/mm^3$
   b. Platelet transfusion when platelet count $<10{,}000/mm^3$ or bleeding
   c. Irradiated, filtered blood products only
   d. Human leukocyte antigen (HLA) matched platelets if alloimmunized
   e. No family member donations if patient a transplant candidate
2. Disseminated intravascular coagulation
   a. Common with APML, but can also be seen in AML/ALL
   b. Life threatening bleeding, stroke, CNS bleed
   c. Treat with fresh frozen plasma, platelets, and cryoprecipitate for fibrinogen <100
   d. If APML or suspected APML, start ATRA promptly

C. Infection
1. General principles
   a. WBC may be high but abnormal WBC function—patient functionally neutropenic
   b. Chemotherapy suppresses immune system
   c. Imaging procedures such as computed tomographic (CT) scans may help guide coverage
2. Bacterial infections
   a. Gram-positive infections related to indwelling catheters
   b. Gram-negative infections related to damaged intestinal tract
3. Fungal infections
   a. Increased with neutropenia, antibiotics, indwelling catheters, parenteral nutrition, steroids
   b. *Candida* (skin, liver, esophagus)
   c. *Aspergillus* (lung, sinuses)
4. Viral infections
   a. Herpes simplex virus, herpes zoster
   b. Influenzae, respiratory syncytial virus serious infections in leukemia patients
5. Other infections
   a. Pneumocystis pneumonia (PCP) seen in ALL patients receiving steroids
6. Treatment of infections
   a. Treat fever immediately as presumptive infection
   b. Coverage for gram-negative infections including pseudomonas
   c. Persistent fever, coverage for gram-positive infections and fungus
   d. Preventative regimens include gram-negative coverage (quinolone) antifungal coverage (fluconazole), and PCP coverage (in ALL patients)
7. Tumor lysis syndrome
   a. Rapid destruction of tumor cells
   b. High uric acid, low calcium, high potassium
   c. Can progress to acute renal failure
   d. Treatment of tumor lysis syndrome
      i. Hydration before chemotherapy
      ii. Alkalinization of urine

TABLE 100-1 Side Effects of Common Chemotherapy Drugs

Drug	Alopecia	Nausea/ vomiting	Bone marrow suppression	Other
Cytosine arabinoside (ARA-C)	+	+	++	Fever, renal failure, cerebellar toxicity
Idarubicin, daunorubicin	++	++	++	Cardiac, mucositis, vesicant
Etoposide	+	+	+	Hypotension
All *trans* retinoic acid (ATRA)	–	–	–	Increased white blood cells
	–	–	–	Lung infiltrates
Cyclophosphamide (Cytoxan)	+	++	++	Hemorrhagic cystitis
Prednisone	–	–	–	Muscle weakness, edema, glucose intolerance
Vincristine	–	+	–	Neuropathy
Asparginase	–	–	–	Pancreatitis, coagulopathy
Imatinib (Gleevec)	–	–	+	Elevated liver tests, rash
Fludarabine	–	+	–	Increased risk late infection

+, Mild toxicity; ++, moderate to severe toxicity; –, atra toxicity.

   iii. Allopurinol or (high risk patients) intravenous uricolytics (Rasburicase)
   iv. Follow renal function, electrolytes carefully
8. Chemotherapy toxicity (Table 100-1)

Suggested Reading

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101 ONCOLOGIC EMERGENCIES

Diane M.F. Savarese

I. SUPERIOR VENA CAVA (SVC) SYNDROME

- **A.** General principles
  - **1.** SVC syndrome results from
    - **a.** Obstruction of blood flow due to invasion of tumor into SVC or
    - **b.** External compression of the SVC
- **B.** Etiology
  - **1.** Sixty-five percent to 80% of cases due to malignancy
    - **a.** Predominantly lung cancer and lymphoma
  - **2.** Other causes
    - **a.** Thrombosis (usually in the setting of an indwelling intravascular device)
    - **b.** Mediastinal or radiation fibrosis
- **C.** Diagnosis
  - **1.** Symptoms and signs of SVC syndrome (Table 101-1) are related to:
    - **a.** Poor venous return
    - **b.** Increased intravenous (IV) pressure
    - **c.** Collateral vessel engorgement
  - **2.** Radiographic studies are usually diagnostic
    - **a.** Chest radiograph (CXR) is abnormal in >80%; findings include mediastinal widening and pleural effusion
    - **b.** Contrast chest computed tomography (CT)
      - **i.** Preferred diagnostic study
      - **ii.** Identifies venous obstruction
      - **iii.** Suggests etiology
      - **iv.** Identifies impending complications (e.g., vertebral spread)
    - **c.** Upper extremity venography
      - **i.** Gold standard for defining the level and extent of SVC obstruction
      - **ii.** Cannot identify the etiology of SVC obstruction unless thrombosis is the sole cause
    - **d.** Magnetic resonance venography
      - **i.** May be useful if venous access cannot be obtained for contrast-enhanced CT.
  - **3.** Tissue diagnosis
    - **a.** Less invasive options
      - **i.** Sputum or pleural fluid cytology
      - **ii.** Biopsy of enlarged peripheral lymph nodes
      - **iii.** Percutaneous transthoracic CT-guided biopsy
      - **iv.** Bronchoscopy
    - **b.** More invasive procedures: should be pursued if a definitive diagnosis cannot otherwise be established
      - **i.** Mediastinoscopy
      - **ii.** Video-assisted thoracoscopy
      - **iii.** Thoracotomy
    - **c.** Routine diagnostic procedures carry little excess risk in patients with elevated venous pressures

TABLE 101-1 Common Symptoms and Signs of Superior Vena Cava Syndrome

Symptom or sign	Incidence (%)
Facial swelling	43
Trunk and/or extremity swelling	40
Dyspnea	20
Chest pain	20
Cough	20
Dysphagia	20
Dizziness	10
Syncope	10
Visual disturbance	10
Thoracic vein distention	67
Neck vein distention	59
Facial edema	56
Tachypnea	40
Plethora of face	19
Cyanosis	15
Upper extremity edema	9
Paralyzed true vocal cord	3
Horner's syndrome	2

d. Emergent treatment before pursuing a histologic diagnosis required if:
- **i.** Stridor due to tracheal compression or laryngeal edema
- **ii.** Depressed central nervous system function due to cerebral edema

D. Treatment
1. Aims: alleviation of symptoms and treatment of underlying cause
2. Historical approach
   - **a.** Immediate radiation therapy (RT) due to perception of SVC syndrome as a medical emergency
3. Current approach
   - **a.** Endovascular stenting for rapid relief of symptoms, and
   - **b.** Establishment of histologic diagnosis to select appropriate therapy for malignancy-associated SVC syndrome
4. Definitive therapy depends upon the specific underlying etiology
   - **a.** Cases due to malignancy
     - **i.** Histology and tumor stage dictate initial antitumor treatment
     - **ii.** Initial chemotherapy
       - **(a)** Preferred for chemosensitive tumors
       - **(b)** Lymphomas, mediastinal germ cell tumors, limited-stage small cell lung cancer
     - **iii.** Intraluminal metal stent
       - **(a)** Useful in cases of extrinsic tumor compression.
       - **(b)** Provides more rapid relief of symptoms in a higher proportion of patients than RT.
       - **(c)** Does not compromise the ability to establish a histologic diagnosis.
     - **iv.** RT
       - **(a)** Commonly administered
       - **(b)** May be lifesaving in the setting of tracheal compression

b. Cases due to nonmalignant causes
   i. Intravascular device-associated
      (a) Remove device, if possible
      (b) Consider thrombolysis if the thrombus is ≤5 days old
   ii. Mediastinal fibrosis
      (a) Benefits of stenting are generally short-lived.
      (b) Surgical bypass may be required.

5. Supportive care
   a. Bed rest with head elevated to reduce central venous pressures
   b. Diuretics (avoiding depletion of intravascular volume)
   c. Decreased salt intake
   d. Oxygen
6. Glucocorticoids
   a. Commonly prescribed.
   b. Most useful in lymphoma and thymoma (cytolytic effect).
   c. Short course of high-dose corticosteroids may be recommended for patients undergoing emergent RT for impending airway obstruction.
      i. Minimizes edema, and risk of central airway obstruction.

II. TUMOR LYSIS SYNDROME (TLS)

A. General principles
1. Caused by massive cytolysis of malignant cells.
2. Leads to release of large amounts of potassium, phosphate, and uric acid into the systemic circulation with secondary hypocalcemia.
3. Acute renal failure can result from precipitation of uric acid and/or calcium phosphate in the renal tubules.

B. Etiology
1. Most commonly encountered after initial chemotherapy for:
   a. High-grade lymphomas (particularly the Burkitt and lymphoblastic subtypes)
   b. Acute lymphoblastic leukemia (ALL)
2. May also occur spontaneously in high-grade lymphoma or ALL.
3. May occur in other tumor types with a high proliferative rate, large tumor burden, or high sensitivity to cytotoxic therapy.

C. Diagnosis
1. Cairo–Bishop definition (Table 101-2)

TABLE 101-2 Cairo–Bishop Definition of Tumor Lysis Syndrome

Laboratory tumor lysis syndrome

Abnormalities in two or more of the following serum values, present within 3 days before, or 7 days after instituting chemotherapy:

- Uric acid ≥8 mg/dL (476 μmol/L) or 25% increase from baseline
- Potassium ≥6.0 mmol/L or 25% increase from baseline,
- Phosphate ≥ 6.5 mg/dL (2.1 mmol/L) in children, or ≥4.5 mg/dL (1.45 mmol/L) in adults, or 25% increase from baseline
- Calcium ≤7 mg/dL (1.75 mmol/L) or 25% decrease from baseline

Clinical tumor lysis syndrome

Laboratory tumor lysis syndrome plus one or more of the following:

- Increased serum creatinine concentration (≥1.5 times the upper limit of normal [ULN])
- Cardiac arrhythmia/sudden death
- Seizure

D. Treatment
  1. Best management is prevention.
  2. Key components of both prevention and treatment.
    a. Aggressive IV hydration (2 to 3 L/m^2/day)
    b. Diuresis
    c. Administration of hypouricemic agent(s)
      i. Allopurinol
      ii. Rasburicase (recombinant urate oxidase)
        (a) Prophylactic rasburicase is indicated in high-risk patients who are undergoing initial chemotherapy (all patients with Burkitt or lymphoblastic lymphoma, Burkitt–ALL, or other ALL with a white blood cell (WBC) $\geq 100 \times 10^9$/L), and if initial uric acid ≥ 8 mg/dL
  3. Urinary alkalinization
    a. Generally not recommended.
    b. Benefit in increasing uric acid excretion is unproven.
    c. Potential harms, particularly in the setting of hyperphosphatemia.
  4. Indications for dialysis
    a. Oliguria
    b. Persistent hyperuricemia
    c. Hyperphosphatemia
    d. Hypocalcemia

III. EPIDURAL SPINAL CORD COMPRESSION (ESCC)

A. General principles
  1. Results when there is neoplastic mass (typically in the epidural space) that extrinsically compresses the spinal cord.

B. Pathophysiology
  1. Increasing intradural pressure or direct invasion from
    a. Enlarging vertebral body metastases
    b. Retroperitoneal lymphadenopathy extending through the paravertebral neural foramina
    c. Pathologic vertebral collapse
    d. Intradural metastases
  2. Vascular compromise leads to spinal cord infarction and rapid, irreversible loss of function.

C. Etiology
  1. Most common tumor types
    a. Lung
    b. Breast
    c. Prostate
    d. Kidney cancer
    e. Lymphoma
    f. Myeloma

D. Clinical presentation
  1. Back pain
    a. Initial symptom in >90% of patients.
    b. Consider ESCC in any patient with a known diagnosis of cancer (or whose symptoms suggest the presence of undiagnosed malignant disease) presenting with unexplained back pain.
  2. Symmetric lower extremity weakness and hyperreflexia below the level of compression
    a. If the lesion is below the conus medullaris (cauda equina lesion), the weakness is associated with depressed deep tendon reflexes in the legs.
    b. Motor weakness occasionally progresses to paraplegia within hours.

- **c.** Sensory deficits are rare initially, but usually develop at some point.
  - **i.** The spinal sensory level, if present, is typically one to five levels below the level of compression.
  - **ii.** Saddle sensory loss is common with cauda equina lesions, while higher lesions usually spare the sacral dermatomes.
- **3.** Loss of bowel or bladder control is a late and poor prognostic sign.

E. Diagnosis depends on (or requires) demonstration of a neoplastic mass that extrinsically compresses the thecal sac

- **1.** Early diagnosis essential
  - **a.** Patients who begin treatment when paraplegic almost never regain ambulation
- **2.** Thorough neurologic examination
- **3.** Plain spine radiographs
  - **a.** Pedicle loss
  - **b.** Vertebral compression fractures
  - **c.** Osteoblastic bone lesions
  - **d.** Osteolytic bone lesions
  - **e.** The finding of major vertebral body collapse or pedicle erosion on plain radiographs with a matching radiculopathy predicts a 75% to 83% chance of ESCC
- **4.** If either physical examination or radiographic study is abnormal, further spine imaging with magnetic resonance imaging (MRI) or myelography is necessary to exclude ESCC
  - **a.** Contrast-enhanced MRI of the entire spine
    - **i.** Preferred for diagnosing the location and extent of ESCC
  - **b.** CT myelography
    - **i.** Consider if timely MRI is unavailable or contraindicated because of a pacemaker or mechanical valve, or if the patient cannot lie still
    - **ii.** Protocol
      - **(a)** Contrast medium introduced through lumbar puncture until obstruction is encountered
      - **(b)** Anatomy above the obstruction defined by a cisterna magna or cervical spinal tap
      - **(c)** Rare complication of CT myelography: cerebrospinal fluid (CSF) pressure below a complete block is reduced by the lumbar puncture, leading to further neurologic deterioration

F. Treatment

- **1.** Corticosteroids
  - **a.** Suggested regimen: dexamethasone 10 to 24 mg IV bolus followed by 16 to 24 mg orally daily in divided doses
  - **b.** Higher initial doses (e.g., dexamethasone 100 mg)
    - **i.** May enhance analgesia.
    - **ii.** Do not improve neurologic outcome.
- **2.** Initial aggressive radical resection
  - **a.** Previously considered only for patients with symptomatic progression during or after RT, rapidly progressing neurologic deficits, or the need for spinal stabilization.
  - **b.** However, outcomes are better with aggressive anterior decompression followed by RT rather than RT alone in patients who are candidates for surgical intervention.
    - **i.** Landmark study: randomly assigned 101 patients with ESCC (excluding those with lymphoma) to radical resection followed by RT or RT alone.

(a) Radical resection followed by RT: threefold increase in achievement and maintenance of ambulation for the duration of remaining life span.
(b) RT alone: two third remained nonambulatory.
c. May not be appropriate for intraspinal tumors and chemosensitive malignancies such as lymphoma.
3. RT
a. Required following laminectomy
b. Treatment of choice if aggressive radical resection not feasible
4. Chemotherapy
a. Administer in chemoresponsive malignancies
b. Examples: small cell lung cancer, lymphoma

IV. HYPERCALCEMIA OF MALIGNANCY

A. General principles
1. Major metabolic abnormality in patients with cancer
a. Occurs in 10% of patients
2. Most common in breast, lung cancer; multiple myeloma
B. Etiology and pathophysiology
1. Develops through three mechanisms, all of which lead to increased osteoclast activation.
a. Osteolytic metastases
b. Ectopic tumor production of parathyroid hormone-related protein (PTHrP).
i. Lung (squamous cell)
ii. Kidney
iii. Pancreas cancer
c. Direct bone invasion, or local production of humoral factors (e.g., osteoclast activating factor)
i. Typical of hypercalcemia associated with hematologic malignancies (e.g., multiple myeloma)
C. Clinical manifestations
1. Dependent on the degree of elevation and the rate of rise of ionized serum calcium
2. Symptoms and signs most apparent when the rate of rise is rapid
3. Change in mental status
a. Can be subtle (e.g., lethargy or depression).
b. In the extreme, may include psychotic behavior, obtundation, and coma.
4. Cardiac arrhythmias
a. Electrocardiographic (ECG) changes: prolonged PR interval (may produce high-grade AV block), shortened QT interval
b. Digitalis-toxic arrhythmias may develop more easily in hypercalcemic patients
5. Renal consequences
a. Decrease in concentrating ability with polyuria
b. Dehydration and prerenal azotemia follow
c. Tubular damage from nephrocalcinosis can result in acidosis, glycosuria, hypomagnesemia, and aminoaciduria
6. Gastrointestinal symptoms
a. anorexia
b. nausea
c. vomiting

- **d.** constipation
- **e.** abdominal pain

D. Laboratory characteristics of hypercalcemia
- **1.** "Total serum calcium" not equivalent to "ionized calcium"
  - **a.** Approximately 40% of total serum calcium bound to protein (primarily albumin)
    - **i.** 1 g of albumin binds 0.8 mg of calcium
    - **ii.** Calculation of corrected serum calcium value: add 0.8 mg/dL to the measured total serum calcium for each 1 g/dL decrease in serum albumin below 4.0 g/dL
  - **b.** "Ionized calcium" represents biologically active calcium
  - **c.** In multiple myeloma, total serum calcium may be spuriously elevated because hyperglobulinemia leads to increased binding of calcium; in such cases, ionized calcium should be measured.
- **2.** Severity of hypercalcemia is based on corrected total serum calcium level
  - **a.** Mild = 11 to 12 mg/dL (2.8 to 3 mmol/L)
  - **b.** Moderate = 12 to 14 mg/dL (3 to 3.5 mmol/L)
  - **c.** Severe = >14 mg/dL (>3.5 mmol/L)

E. Diagnosis
- **1.** Laboratory confirmation of hypercalcemia (see preceding text)
- **2.** Once the presence of hypercalcemia is established, many potential causes can be eliminated by the patient's history (Table 101-3)

F. Treatment
- **1.** Best treatment: specific treatment of the underlying malignancy
- **2.** Avoid thiazide diuretics, which promote renal tubular resorption of calcium
- **3.** Fluid replacement with normal saline
  - **a.** Most hypercalcemia patients are volume-depleted
  - **b.** Initial rate of infusion: 150 to 300 mL per hour
  - **c.** Benefit from saline infusion usually temporary and insufficient to normalize the calcium level in most patients

TABLE 101-3 Differential Diagnosis of Hypercalcemia

Cancer
With bone metastasis (solid tumor)
Without bone metastasis (solid tumor)
Hematologic (e.g., multiple myeloma, leukemia, lymphoma with bone involvement)
Primary toxic hyperparathyroidism
Thiazides
Milk-alkali syndrome
Vitamin D or A toxicity
Endocrine
Thyrotoxicosis
Adrenal insufficiency
Pheochromocytoma (usually in association with primary hyperparathyroidism)
Granulomatous disease
Tuberculosis
Sarcoidosis immobilization (especially with underlying bone disease)
Artifactual
Hyperalbuminemia or hypergammaglobulinemia
Venous stasis (prolonged tourniquet application)

4. For euvolemic patients
   a. Avoid further volume depletion
   b. Furosemide: may help maintain urine output and enhance calciuresis
   c. Closely monitor total intake and output, weight, serum electrolytes, urine electrolytes (at least within the first 12 hours)
5. Parenteral zoledronic acid
   a. Treatment of choice
   b. Dose = 4 mg over 15 minutes
   c. Onset of action is within 24 hours
6. Calcitonin
   a. Consider in cases of urgent requirement for decrease in serum calcium (e.g., obtunded patient or ECG changes)
   b. Relatively weak effect; lowers serum calcium by a maximum of 1 to 2 mg/dL (0.3 to 0.5 mmol/L)
   c. Dose is 4 IU/kg IV; onset of action is 4 to 6 hours nasal calcitonin ineffective
      i. If a *hypo*calcemic response is seen in several hours, frequency of dosing can be lengthened to every 6 to 12 hours.
   d. Tachyphylaxis limits efficacy to the first 48 hours, even with repeated doses
      i. Concurrent steroids can delay development of tachyphylaxis, but do not enhance the hypocalcemic effect.
7. Corticosteroids may be useful for patients with hematologic malignancies or breast cancer.
8. Gallium nitrate (200 mg/m^2 IV daily for 5 days) may be considered for refractory patients.
9. Hemodialysis
   a. Treatment of last resort for severe hypercalcemia (serum calcium 18 to 20 mg/dL [4.5 to 5 mmol/L])
   b. May be required in patients with renal failure
10. In the absence of effective antineoplastic treatment, hypercalcemia typically recurs, and retreatment is required every 3 to 4 weeks.

V. CARDIAC TAMPONADE

A. Etiology and pathogenesis
   1. Accumulation of pericardial fluid under pressure
      a. Once the elastic limit of the pericardium is reached, the heart must compete with the intrapericardial fluid for the fixed intrapericardial volume.
      b. As cardiac filling is increasingly constrained, chamber volume becomes smaller, diastolic compliance is reduced, and systemic venous return is progressively shifted from diastole to systole.
      c. Eventually, total venous return falls, and cardiac output and blood pressure fall.
   2. The hemodynamics of the left and right heart chambers are directly influenced by each other to a greater degree than normal
      a. A clinical consequence is pulsus paradoxus, a large decrease in systolic blood pressure (> 10 mm Hg) on inspiration, that results from limitation on outward expansion of the right ventricle as blood flows in during inspiration.
      b. Subsequent bulging of the interventricular septum into the left ventricle leads to a decrease in stroke volume.
   3. Tamponade may be acute or subacute
      a. Acute bleeding into a relatively stiff pericardium can rapidly lead to tamponade with <500 mL of fluid in the pericardial space.

- **b.** With chronic accumulation of effusion (e.g., caused by tumor cells that interfere with subepicardial lymphatic drainage), pericardial compliance increases gradually and intrapericardial pressures increase more slowly.
  - **i.** In this setting, tamponade may not occur until 2 L or more have accumulated.

B. Clinical manifestations
1. Depend on whether acute or subacute
   - **a.** Most patients with malignancy-associated tamponade have a subacute presentation
     - **i.** Dyspnea
     - **ii.** Ill-defined chest discomfort or fullness
     - **iii.** Cough
     - **iv.** Peripheral edema
     - **v.** Orthopnea
     - **vi.** Facial swelling, and
     - **vii.** Fatiguability
   - **b.** Acute cardiac tamponade is sudden in onset
     - **i.** Chest pain
     - **ii.** Tachypnea
     - **iii.** Dyspnea
2. Physical examination
   - **a.** Tachycardia
   - **b.** Jugular venous distension
   - **c.** Pulsus paradoxus
   - **d.** Distant heart sounds
   - **e.** Narrowed pulse pressure
   - **f.** Pericardial friction rub
   - **g.** Peripheral edema
   - **h.** Signs of low cardiac output (venous hypotension, diaphoresis, cool extremities)
   - **i.** Cardiogenic shock in extreme cases

C. Diagnosis
1. Doppler echocardiography
   - **a.** Procedure of choice for diagnosis of pericardial effusion
   - **b.** Should be performed emergently in the setting of hemodynamic compromise
2. ECG abnormalities
   - **a.** Electrical alternans (rare)
   - **b.** Sinus tachycardia, diffuse S-T wave abnormalities, loss of voltage, T-wave inversions, or atrial arrhythmias (more common)
   - **c.** Pulseless electrical activity with a rapid, narrow-complex rhythm: consider tamponade
3. CXR often shows enlargement of the cardiac silhouette
4. Chest CT
   - **a.** May show pericardial thickening.
   - **b.** May reveal tumor extent and location.

D. Treatment
1. Volume expansion with blood, plasma, dextran, or saline.
   - **a.** Temporizing measure only
2. Medications that lower blood pressure, reduce preload, or decrease heart rate (e.g., diuretics or β-blockers).
   - **a.** May be deleterious due to decreasd diastolic filling
   - **b.** Should be avoided or used with extreme caution

3. Urgent removal of fluid
   a. Produces a rapid and dramatic improvement in symptoms and cardiac and systemic hemodynamics.
      i. Removal of as little as 50 mL may be sufficient to improve hemodynamics.
   b. Performed through pericardiocentesis under echocardiographic guidance
      i. A 16- to 22-gauge needle is attached to a syringe and inserted roughly at a 45-degree angle below the xiphoid process cephalad toward the tip of the scapula.
      ii. Advancement into the myocardium usually reveals an injury pattern on the ECG.
      iii. Most common complications are right ventricular puncture, hemopericardium, and ventricular ectopy.
   c. After pericardiocentesis, fluid reaccumulates in as many as 60% of cases.
      i. Measures to prevent **reaccumulation** include prolonged drainage through intrapericardial catheter with or without intrapericardial instillation of sclerosing agents (e.g., bleomycin 30 to 60 U).
      ii. Surgical decompression of the pericardium
         (a) Subxiphoid pericardial window placement
         (b) Limited thoracotomy with pleuropericardial window placement
         (c) Open thoracotomy with pericardiectomy
      iii. Balloon pericardiotomy
         (a) Deflated balloon catheter introduced into the pericardial space using a subxiphoid approach under ultrasonographic guidance
         (b) Balloon inflated then pulled out of pericardium to create a "window"
         (c) Allows drainage of fluid into the pleural or peritoneal space

E. Prognosis
1. Usually poor
2. Systemic antitumor treatment can be considered for chemotherapy-responsive cancers (e.g., breast, lymphoma)
3. Radiation therapy may be useful in selected cases

Suggested Reading

Ahman FR. A reassessment of the clinical implications of the superior vena cava syndrome. *J Clin Oncol* 1984;2:961.
This classic series reviews 1,986 cases of superior vena cava syndrome, with particular emphasis on the safety of diagnostic procedures and the benefit of proceeding with a diagnostic study before embarking on treatment.

Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol* 2004;127:3.
The authors delineate a system for classifying and grading the severity of clinical and laboratory tumor lysis syndrome.

Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol* 2008;26:2767.
Evidence-based guidelines for prevention and treatment of tumor lysis syndrome, stratified according to risk and expected response to treatment.

Cole JS, Patchell RA. Metastatic epidural spinal cord compression. *Lancet Neurol* 2008;7:459.
This is an excellent recent summary of pathophysiology, presentation, diagnostic approach to and treatment of epidural spinal cord compression.

Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001;19:558.

In a randomized study directly comparing pamidronate and zoledronic acid for the treatment of hypercalcemia of malignancy, a single dose of zolendronate (4 mg) normalized the corrected serum calcium level in 87% to 88% of patients, compared with only 70% of those receiving pamidronate (90 mg). Moreover, the median duration of calcium control was longer for those receiving zolendronate (32 to 43 days versus 18 days).

Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet* 2005;366:643.

This randomized trial demonstrated the superiority of initial aggressive surgical resection and postoperative radiation therapy compared to radiation therapy and salvage surgery, in patients initially presenting with epidural spinal cord compression that was not due to lymphoma or an intraspinal tumor.

Rodichok LD, Harper GR, Ruckdeschel JC, et al. Early diagnosis of spinal epidural metastases. *Am J Med* 1981;70:1181.

This is a classic article describing a study of 87 patients with back pain and a diagnosis of cancer. The use of the neurologic examination and plain radiographs of the spine to predict the risk for epidural cord compression is described.

Spodick DH. Acute cardiac tamponade. *N Engl J Med* 2003;349:684.

A contemporary review of the pathophysiology underlying cardiac tamponade, and management of this condition.

Wilkes JD, Fidias P, Baikus L, et al. Malignancy-related pericardial effusion. *Cancer* 1995;76:1377.

This article reviews 127 cases of malignant pericardial effusion from the Roswell Park Cancer Institute, demonstrating that subxyphoid pericardiotomy is a safe intervention that effectively relieves pericardial effusion in 99% of cases with <10% recurrence and reoperation rates. An excellent review of surgical approaches to the management of pericardial effusion is provided

Wilson LD, Detterbeck FC, Yahalom J. Clinical practice. Superior vena cava syndrome with malignant causes. *N Engl J Med* 2007;356:1862.

The authors provide a succinct review of management strategy for patients with malignancy-associated SVC syndrome.

Pharmacology, Overdoses, and Poisonings

IX

TOXICOLOGY

102

Luke Yip

This section focuses on the aspects of acute poisoning that are potentially life-threatening or may lead to permanent organ damage and hence require immediate, usually intensive, medical care. This has been organized into a Table format to facilitate rapid access to concise toxicology information guiding management of acutely poisoned patients. The Table is divided into four columns. The first column is alphabetically organized into either a specific agent (e.g., acetaminophen) or a class of agent (e.g., alcohol) with specific references (e.g., ethylene glycol, isopropanol, and methanol); individual agents appear alphabetically in the Index. This is followed by a list of organ system targeted by the agent or its systemic effect. The second column focuses on action alert, critical laboratory values, guidelines for clinical intervention, and dosing of therapeutic drug, antidote, and antivenom. The third column brings attention to adjunct therapy and extracorporeal support. The fourth column highlights caveats and potential complications. The content of this section is not a substitute for consultation with a medical toxicologist, reference textbooks in medical toxicology (e.g., Goldfrank's Toxicologic Emergencies and Medical Toxicology) and does not address envenomations outside the United States. A bibliography primarily of chapters in textbooks and review articles was chosen for their comprehensive review and references to journal articles on a given subject.

TABLE 102-1

Agent Target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
Acetaminophen (APAP) Acute: GI ■ Hepatotoxicity. ■ FHF. Neurologic ■ Encephalopathy. ■ Coma and metabolic acidosis with serum APAP >800 μg/mL (5,292 μmol/L) 4–12 h postingestion. GU ■ Oliguric renal failure 24–48 h with proteinuria, microscopic hematuria and back pain; usually preceeded by hepatotoxicity; nonoliguric renal failure is rare.	Serum APAP concentration above "treatment" line on acetaminophen toxicity (Rumack-Matthew) nomogram (Figure 102-1): NAC ■ Oral: 140 mg/kg followed by 70 mg/kg every 4 h (dilute 3:1 with carbonated/fruit beverage for palatability); administer IV antiemetic (e.g., ondansetron 8 mg; Peds: 0.2 mg/kg, max 8 mg) and repeat the same oral dose if vomiting occurs within 1 h. *or* ■ IV: 150 mg/kg in 200 mL D5W over 1 h followed by 50 mg/kg in 500 mL D5W over 4 h followed by 100 mg/kg in 1 L D5W over 16 h (6.25 mg/kg/h). NAC therapy may be terminated if patient remains asymptomatic, serum APAP concentration below "treatment" line *and* AST/ALT remains in laboratory reference range at 20–24 h; continue NAC therapy (oral: every 4 h; IV 6.25 mg/kg/h) if patient's clinical condition deteriorates *or* AST/ALT becomes abnormal.	Oral activated charcoal: 1–2 g/kg may be considered in a cooperative patient who presents within 4 h of overdose. Hemodialysis consideration: Patient presenting soon after an acute overdose, NAC not available, no other options and hemodialysis can be expeditiously initiated; coma and metabolic acidosis with serum APAP >800 μg/mL (5,292 μmol/L); terminate when serum APAP <30 μg/mL (198 μmol/L) and correction of acid–base disturbances.	Acetaminophen toxicity nomogram valid following an acute single overdose of nonmodified release APAP occurring between 4–24 h; plots above "probable" and "high-risk" lines indicate 60% and 90% hepatotoxicity risk, respectively. NAC therapy: Anaphylactoid reaction; infusion volume in pediatrics.

	APAP/NAC induced emesis: IV ondansetron 8 mg (Peds: 0.2 mg/kg, max 8 mg); metoclopramide 1–2 mg/kg. Encephalopathy or FHF: IV NAC with the final infusion rate (6.25 mg/kg/h) until recovery or death. Transfer to liver ICU consideration: PT (measured in seconds) exceeds the time in hours after overdose, or INR >5.0 at any time, or metabolic acidosis, hypoglycaemia, or renal failure. OLT consideration: ■ Consider listing for transplantation Arterial lactate >3.5 mmol/L after fluid resuscitation. ■ List for transplantation Arterial pH <7.30 and lactate >3.0 mmol/L after fluid resuscitation. *or* PT/INR >100 sec/>6.5, Cr >3.3 mg/dL (300 μmol/L) *and* encephalopathy grade ≥III within a 24-h period and normal arterial pH. Unreliable time of ingestion ■ Patient with signs and symptoms consistent with hepatotoxicity: NAC treatment same as above; continue NAC treatment (oral: every 4 h; IV 6.25 mg/kg/h) until clear clinical and laboratory evidence of improvement in		

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
	patient's condition. If deterioration in clinical and laboratory status consider parameters for referral to liver ICU or OLT. ■ Asymptomatic patient with serum APAP concentration <10 mg/L (66 μmol/L) *and* AST/ALT within laboratory reference range: Repeat serum APAP level and AST/ALT in 6–8 h. If *both* normal, no further treatment for APAP overdose is needed. If *either* elevated, treat with NAC (same as above); NAC treatment may be terminated if patient remains asymptomatic, serum APAP concentration below "treatment" line *and* AST/ALT remains within or falls to near upper limit of laboratory reference range at 20–24 h otherwise continue NAC (oral: every 4 h; IV 6.25 mg/kg/h) until clear clinical and laboratory evidence of improvement or if deterioration in clinical and laboratory status consider parameters for referral to liver ICU or OLT.		
Nonacute/repeated supratherapeutic ingestion: Same as "Acute."	Signs and symptoms consistent with hepatotoxicity: NAC treatment same as "Acute;" continue NAC until clear clinical and		Same as "Acute" except acetaminophen toxicity nomogram *not* valid at any time.

	laboratory evidence of improvement; if deterioration in clinical and laboratory status consider referral to liver transplant center (see Acute Ingestion section). Asymptomatic patient with *either* serum APAP concentration >10 mg/L (66 μmol/L) *or* serum AST/ALT ≥50 IU/L: NAC treatment same as "Acute;" recheck laboratory tests for APAP, AST/ALT at end of 12 h of NAC treatment; if serum APAP <10 mg/L (66 μmol/L) *and* serum AST/ALT <50 IU/L, terminate NAC treatment; otherwise continue NAC treatment until serum APAP <10 mg/L (66 μmol/L) *and* serum AST/ALT < 50 IU/L. Asymptomatic patient with serum APAP concentration <10 mg/L (66 μmol/L) *and* AST/ALT<50 IU/L: No further treatment for APAP overdose is needed.		
Alcohol Ethylene glycol (EG) ■ Neurologic: CNS dysfunction/depression, coma; multiple cranial nerve deficits. ■ Metabolic: Anion gap metabolic acidosis. ■ CV: Cardiopulmonary failure.	Serum bicarbonate <20 mmol/L or arterial pH <7.30: IV sodium bicarbonate 1–2 mmol/kg boluses, target blood pH 7.40 and urine pH 7.0–8.0. Known or high index of suspicion of ingestion, clinical poisoning, or serum EG level ≥20 mg/dL (3.2 mmol/L): ■ IV 4MP 15 mg/kg followed by 10 mg/kg every 12 h × 4 doses, then 15 mg/kg	Maximize GFR: IV NS target urine output 2–4 mL/kg/h. IV pyridoxine 3–5 mg/kg/d *or* 50 mg every 6 h until toxic alcohol is undetectable and acidemia resolved. IV thiamine 100 mg/d *or* every 6 h until toxic alcohol is undetectable and acidemia resolved.	Clinical-biochemical manifestation: Latent onset 8–12 h; variable with coingestion of ethanol. Osmol and anion gap: An inverse relationship occurs with time; not sensitive surrogate marker for toxic alcohol exposure.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
■ GU: Renal failure.	every 12 h thereafter until toxic alcohol is undetectable and clear clinical-biochemical recovery; all infusions over 30 min. *or* ■ IV ethanol (10% solution in D5W) 10 mL/kg over 1 h followed by 1.5 mL/kg/h, target serum ethanol 100 mg/dL until toxic alcohol is undetectable and clear clinical-biochemical recovery.	Hemodialysis consideration: Serum EG ≥25 mg/dL (4.0 mmol/L) and acidemia or renal insufficiency. ■ 4MP dosing: Administer next scheduled dose if ≥6 h since last dose; during hemodialysis dosing is every 4 h; end of dialysis and time of last dose 1 to 3 h administer half of next scheduled dose, >3 h administer next scheduled dose. ■ Ethanol therapy: Increase to 3.0 mL/kg/h at the time of hemodialysis and decrease to 1.5 mL/kg/h after hemodialysis; closely monitor serum ethanol and glucose level; adverse events include hypoglycemia, fluid overload, inebriation. ■ Continue 4MP/ethanol treatment until undetectable serum EG level (significant EG may rebound following hemodialysis).	Sodium bicarbonate: Large doses may be needed to treat metabolic acidosis; hypocalcemia. 4MP and ethanol only *inhibits* metabolism of toxic alcohols.

Isopropanol ■ Neurologic: CNS dysfunction/depression, coma. ■ Metabolic: Acetonemia, acetonuria; anion gap metabolic acidosis (mild). ■ CV: Hypotension; myocardial depression.	Supportive care.	Maximize GFR: See Ethylene glycol. Hemodialysis consideration: Hypotension (systolic <100 mm Hg), coma or serum isopropanol ≥400 mg/dL (66.7 mmol/L).	Isopropanol is metabolized to acetone and high serum acetone concentration can give falsely high serum Cr concentration with Jaffe-alkaline-picrate-colorimetric method used on automated chemistry instruments.
Methanol (MeOH) ■ Neurologic: CNS dysfunction/depression, coma. ■ Metabolic: Anion gap metabolic acidosis. ■ Ophthalmologic: Blindness.	Serum bicarbonate <20 mmol/L or arterial pH <7.30: See Ethylene glycol. Known or high index of suspicion of ingestion, clinical poisoning, or serum MeOH level exceeding 20 mg/dL (6.3 mmol/L): IV 4MP *or* ethanol; See Ethylene glycol.	Maximize GFR: See Ethylene glycol. IV leucovorin 2 mg/kg every 4 to 6 h until toxic alcohol is undetectable, clear clinical-biochemical recovery; if leucovorin not available IV folic acid 50–70 mg every 4 h; leucovorin preferred over folic acid, infusion rate <160 mg/min. Hemodialysis consideration: CNS, visual or funduscopic abnormality, serum MeOH ≥25 mg/dL (7.8 mmol/L), acidemia or renal insufficiency. ■ Leucovorin: Administer additional dose at end of hemodialysis. ■ Continue 4MP/ethanol treatment until undetectable serum MeOH level (significant MeOH may rebound following hemodialysis).	Clinical-biochemical manifestation, osmol and anion gap, sodium bicarbonate, 4MP/ethanol: See Ethylene glycol. Hemodialysis is superior to CVVH in clearing methanol; CVVH may have limited application in less severely poisoned patients if hemodialysis is not available and may be the only option in hypotensive patients until hemodialysis can be tolerated.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
Anticholinergics (e.g., antihistamines [H_1-blockers], cyclic antidepressants, antispasmodics, antipsychotics, antiparkinsonian drugs, mydriatics, chlorpheniramine, cyclizine, cyproheptadine, diphenhydramine, hydroxyzine, meclizine, promethazine, tripelennamine, scopolamine, ipatropium, cyclobenzaprine, plants: *Myristica fragrans* [nutmeg], *Brugmansia*, *Datura*, *Hyoscyamus niger*, *Solanum*, *Amanita muscaria*) ■ Ophthalmologic: Mydriasis (variable). ■ CV: Hypertension, tachycardia. ■ Skin: Warm, dry, flushed; dry mucous membranes. ■ GI: Decreased bowel sounds; ileus.	Hallucinations, agitated delirium: See Withdrawal syndromes, sedative hypnotics; IV diazepam or lorazepam, propofol or pentobarbital. Physostigmine diagnostic aid: Selective use in anticholinergic agitation and delirium resulting from unknown ingestion; a positive response (e.g., patient awakens, provides history consistent with anticholinergic toxicity) obviates additional testing (e.g., cranial computed tomography and lumbar puncture); IV physostigmine 0.5-2 mg at ≤0.5 mg/min (Peds: 0.02 mg/kg at 0.5 mg/min), if no positive response within 10–20 min administer an additional 1–2 mg. Hyperthermia: Rapid cooling measures. Urinary retention: Insert Foley catheter.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (see Box I.) in acutely sick patients followed by activated charcoal 1–2 g/kg.	Physostigmine: Contraindications include bronchospasm, mechanical intestinal or urogenital tract obstruction, early (<6 h) cyclic antidepressant overdose, overdose with cardiac conduction delay, cyclic antidepressant poisoning with high-dose/drug-level phenomena (e.g., hypotension, coma, seizures, cardiac conduction delays, and dysrhythmias). Complications include dehydration, rhabdomyolysis.

■ GU: Urinary retention. ■ Neurologic: Loss of short-term memory; confusion, disorientation; visual/auditory hallucinations; ataxia/incoordination; picking/grasping movements; extrapyramidal reactions; psychosis; coma; agitated delirium; respiratory failure; hyperthermia; seizures.			
Anticonvulsants Carbamazepine (CBZ) ■ Neurologic: Slurred speech; nystagmus; lethargy; ataxia; ophthalmoplegia, diplopia; depressed sensorium, coma; absent doll's eye/caloric reflexes; respiratory depression; cyclic coma; seizures; SIADH. ■ CV: Atrial and ventricular dysrhythmias; intraventricular conduction defects (e.g., prolonged QRS/QTc); heart blocks.		GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (see Box I.) in acutely sick patients; activated charcoal 1–2 g/kg followed by activated charcoal hourly, every 2 h, *or* every 4 h at a dose equivalent to 12.5 g/h (Peds: 10–25 g) for 12–24 h, not in patients with decreased bowel sounds/ileus; WBI (see Box II.) for large ingestion of modified release formulation; procedural removal of bezoar/concretion.	Pharmacobezoar: Serum CBZ concentration continues to significantly rise or not significantly decreasing over time, delayed symptoms, relapse or deteriorate after appropriate GI decontamination as late as 48 h after overdose; imaging studies with contrast to confirm diagnosis. Risk stratification based on *peak* serum CBZ concentration: ■ Delayed peak concentration following modified released formulation may be >96 h.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
■ Anticholinergic syndrome: Hyperthermia, sinus tachycardia, hypertension, urinary retention, mydriasis, ileus. ■ Adventitious movements: Oculogyric crisis, dystonia, opisthontonus, choreoathetosis, ballismus.		Extracoporeal enhanced elimination (i.e., hemodialysis, hemoperfusion, CVVH) consideration: Persistently high serum CBZ concentrations and coma.	■ >40 mg/L (170 μmol/L) increased risk for coma, seizures, respiratory failure, cardiac conduction defects.
Phenytoin ■ Neurologic: Nystagmus; blurred vision, diplopia; slurred speech; dizziness, ataxia; tremor; lethargy, confusion; hallucinations; psychosis; seizures; progressive CNS depression, coma; respiratory depression. ■ CV: Dysrhythmias; hypotension; heart failure; respiratory arrest; asystole		Activated charcoal 1–2 g/kg and in patients with serum phenytoin concentration >40 μg/mL, moderate neurologic toxicity, or rising serum phenytoin levels following initial activated charcoal dose administer additional activated charcoal hourly, every 2 h, *or* every 4 h at a dose equivalent to 12.5 g/h (Peds: 10–25 g) for 12–24 h; not in patients with decreased bowel sounds/ileus; discontinue before drug levels reach therapeutic	

from *propylene glycol* toxicity during rapid IV phenytoin administration (e.g., >50 mg/min).		range in patients on phenytoin therapy.	
Valproic acid (VPA) ■ Neurologic: Drowziness, lethargy; confusion, disorientation; seizures; encephalopathy; cerebral edema; obtundation, coma; respiratory failure. ■ CV: Tachycardia; hypotension. ■ GI: Pancreatitis; hepatotoxicity. ■ Metabolic: Anion gap metabolic acidosis; hyperammonemia; hypernatremia; hypocalcemia. ■ Hematologic: Thrombocytopenia; leukopenia.	Coma, symptomatic hyperammonemia, symptomatic hepatotoxicity, or rising serum ammonia levels: IV L-carnitine 100 mg/kg (max 6 g) over 30 min followed by 15 mg/kg every 4 h over 10–30 min until clinical improvement; consider treatment for patients with serum VPA >450 μg/mL. Acute VPA overdose without hepatic enzyme abnormalities or hyperammonemia: Consider oral L-carnitine 100 mg/kg/d (max 3 g) divided every 6 h.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (see Box I.) in acutely sick patients; activated charcoal 1–2 g/kg followed by activated charcoal hourly, every 2 h, *or* every 4 h at a dose equivalent to 12.5 g/h (Peds: 10–25 g) for 12–24 h, not in patients with decreased bowel sounds/ileus; WBI (see Box II.) for large ingestion of modified release formulation; procedural removal of bezoar/concretion. Hemodialysis consideration: Coma, hemodynamic instability, rapid deterioration, hepatic dysfunction, metabolic acidosis unresponsive to fluids, serum VPA >1,000 μg/mL; terminate when serum VPA is in the therapeutic range.	Risk stratification based on *peak* serum VPA concentration: ■ Delayed peak concentration may be > 10 h post ingestion. ■ >450 μg/mL moderate to major outcome. ■ >850 μg/mL hypotension, coma, respiratory depression, aspiration, metabolic acidosis. Hemodialysis and CAVH/CVVH are not equivalent, and they are not mutually exclusive; CAVH/CVVT may be the only option in hypotensive patients until hemodialysis can be tolerated.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
Antidepressant Cyclic antidepressant ■ Neurologic: CNS depression; seizures; coma. ■ CV: Tachycardia; hypotension; ventricular dysrhythmias.	ECG (maximal limb-lead) QRS ≥120 msec or RaVR ≥3 mm or R/SaVR ≥0.7: IV sodium bicarbonate 1–2 mmol/kg bolus × 2; repeat ECG every 3–5 min; IV sodium bicarbonate 1–2 mmol/kg bolus until QRS duration stablized. Seizures and dysrhythmias: Current ACLS toxicology guidelines and avoid class IA/IC antidysrhythmics; class IB may be useful.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (see Box I.) in acutely sick patients; followed by activated charcoal 1–2 g/kg; WBI (see Box II.) for large ingestion of modified release formulation; procedural removal of bezoar/concretion.	Bupropion seizures: Therapeutic or overdose; brief; latent onset 10–24 h (sustained-release preparations). Amoxapine seizures: Recurrent and prolonged.
Monoamine oxidase inhibitors (MAOI) ■ Latent onset toxicity (6–24 h); sympathetic hyperactivity with CNS excitation and peripheral sympathetic stimulation (e.g., hypertension, tachycardia, tachypnea, pyrexia, agitation, confusion, tremor, hyperreflexia); may progress to CNS depression and cardiovascular collapse.	Sympathetic hyperactivity: IV BZD; neuromuscular paralysis and intubation; cooling measures. Severe hypertension and tachycardia: IV nitroprusside and esmolol. Hypotension: IV norepinephrine or epinephrine (avoid dopamine).	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): See Cyclic antidepressant. Maximize GFR: IV NS target urine output 2–4 mL/kg/h.	MAOI: Combined with serotoninergic drugs a significant risk for severe serotonin syndrome/death; interaction with sympathomimetics (e.g., amphetamines, ephedrine, phenylephrine) and tyramine in food (e.g., aged cheese, smoked/pickled meats, red wine, pasteurized light, pale beers) precipitate "hypertensive crisis" (i.e., agitation, tachycardia, hyperthermia, seizures) and ICH.

(Selective) serotonin reuptake inhibitor (SSRI) ■ Neuroexcitation: Neuromuscular hyperactivity (e.g., tremor, clonus, myoclonus, hyperreflexia, hypertonia/pyramidal rigidity); altered mental status (e.g., agitation, excitement, confusion); autonomic hyperactivity (e.g., diaphoresis, fever, mydriasis, tachycardia, tachypnea). ■ Serotonin syndrome (toxicity): Spontaneous clonus; inducible clonus *and* agitation or diaphoresis; ocular clonus *and* agitation or diaphoresis; tremor *and* hyperreflexia; hypertonic *and* temperature >38°C *and* ocular or inducible clonus.	Neuroexcitation/serotoinin syndrome: IV BZD; IV chlorpromazine 50 mg, repeat in 2–3 h as needed or oral (gastric tube) cyproheptadine 4–8 mg (max 24 mg/d), repeat every 2 h if no improvement or recurrent signs; neuromuscular paralysis and intubation; cooling measures.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): See Cyclic antidepressant. Maximize GFR: See MAOI.	Serotonin syndrome (toxicity): Can be caused by all antidepressants, alone or in combination, in therapeutic or overdoses, in combination with other serotonergic agents; escalating dose or additional serotonergic agent during chronic therapy; a spectrum of serotonin-related adverse events progressing to toxicity; complications include rhabdomyolysis, dysrhythmias. Venlafaxine: Seizures; prolonged QRS/QTc; ventricular dysrhythmias. Citalopram/escitalopram: Seizures; prolonged QTc; wide-complex tachycardia. Cyproheptadine: Urinary retention.
Antimalarial Choroquine ■ CV: Hypotension; intraventricular conduction defects (e.g., prolonged QRS/QTc); heart block; ventricular dysrhythmias. ■ Neurologic: CNS depression; dizziness, headache, seizures.	Symptomatic/severe poisoning or known/suspected chloroquine ingestion >5 g: ■ Rapid orotracheal intubation and *avoid* thiopental induction *and* ■ IV epinephrine 0.25 μg/kg/min of followed by increments of	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (see Box I.) in acutely sick patients followed by activated charcoal 1–2 g/kg.	Acute chloroquine poisoning results in hypokalemia (intracellular shifts, not total body depletion) that reflects severity of toxicity; serum potassium concentrations should be carefully monitored, particularly among patients who also receive catecholamine infusions and

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
■ Metabolic: Hypokalemia. ■ Respiratory: Respiratory depression; pulmonary edema.	0.25 μg/kg/min until systolic arterial pressure ≥100 mm Hg) *and* ■ IV diazepam 2 mg/kg over 30 min followed by 1–2 mg/kg/d × 2–4 d. ■ Transient CV compromise requires additional epinephrine and other catecholamines. Heart block or ECG (maximal limb-lead) QRS ≥120 msec: IV sodium bicarbonate 1–2 mmol/kg bolus × 2; repeat ECG every 3–5 min; IV sodium bicarbonate 1–2 mmol/kg bolus until QRS duration stablized. Seizures and dysrhythmias: Current ACLS toxicology guidelines and avoid class IA/IC/III antidysrhythmics; class IB may be useful.		overzealous potassium replacement invokes risk of subsequent hyperkalemia.
Quinine ■ Ophthalmologic: Blurred vision; visual field constriction, scotomata; diplopia; altered color	Heart block or ECG (maximal limb-lead) QRS ≥120 msec: See Chloroquine. Seizures and dysrhythmias: See Chloroquine.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (see Box I.) in acutely sick patients;	Complete blindness reported only after oral quinine ingestion and expected (can be lower) when serum quinine >20 mg/mL in the first 10 h following

perception; complete blindness (sudden visual loss can occur ≥14 h after overdose); pupils dilated and unreactive in proportion to degree of visual impairment. ■ CV: Hypotension; intraventricular conduction defects (e.g., prolonged QRS); complete heart block; dysrhythmias (e.g., *torsades de pointes*, ventricular tachycardia, ventricular fibrillation). ■ Neurologic: Delirium; coma; seizures; tinnitus; deafness. ■ Metabolic: Hypoglycemia rare except during high-dose IV quinine and concomitant metabolic stresses (e.g., malaria, malnutrition, alcoholism). ■ Respiratory: ARDS.	Hypoglycemia: IV dextrose (monitor serum potassium and QTc) *or* IV octreotide 50 μg/h *or* IM octreotide 100 μg.	activated charcoal 1–2 g/kg followed by hourly, every 2 h, *or* every 4 h at a dose equivalent to 12.5 g/h (Peds: 10–25 g) for 12–24 h; not in patients with decreased bowel sounds/ileus.	ingestion; residual impairment (e.g., peripheral field defects, scotomata, impaired color vision, complete blindness) in severe cases. Patients on therapeutic doses of quinine may experience nausea, vomiting, decreased hearing acuity, tinnitus, headache, and tachycardia ("cinchonism").
Beta-adrenergic blocker (BB) ■ CV: Hypotension and bradycardia (pindolol-tachycardia and	Bradycardia: ■ IV atropine (max 3 mg). ■ IV glucagon 50–150 mg/kg and start infusion dose to give effective bolus dose each h (e.g., heart rate increased after	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (see Box I.)in acutely sick patients followed	Bradycardia/hypotension seldom responds to atropine and fluid bolus. Glucagon most effective in increasing heart rate.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
hypertension); heart failure, pulmonary edema; intraventricular conduction delay (e.g., acebutolol, betoxalol, carvedilol, metoprolol, oxprenolol, and propranolol); heart block; ventricular dysrhythmias; asystole. ■ Neurologic: Depressed consciousness; confusion; lethargy; coma; seizures (especially BB with high lipid solubility-propranolol, penbutolol, metoprolol). ■ Respiratory: Bronchospasm. ■ Metabolic: Hypoglycemia/ hyperglycemia (rare).	2 successive 5 mg boluses, then administer 10 mg/h). ■ Cardiac pacing: Optimal pacing rate 50–60 beats per minute. Hypotension: IV NS bolus, catecholamine(s). QRS >120 msec: IV sodium bicarbonate 1–2 mmol/kg bolus; repeat for recurrent QRS widening. Hypodynamic myocardium Euglycemic clamp: IV regular insulin 1 IU/kg bolus followed by infusion 0.5 IU/kg/h titrated every 30 min to desired effect on contractility or blood pressure (echocardiography for measuring myocardial response); euglycemia = serum glucose 100–250 mg/dL (5.5–14 mmol/L) is maintained by IV dextrose 25 g bolus with initial insulin bolus [unless serum glucose	by activated charcoal 1–2 g/kg; WBI (see Box II.) for large ingestion of modified release formulation; procedural removal of bezoar/ concretion. Hemodialysis considerations: BB with significant renal clearance (e.g., acetbutolol, atenolol, bisoprolol, carteolol, pindolol, sotalol, nadolol). Extraordinary measures: Extracorporeal circulatory support, intraaortic balloon pump counterpulsation, prolonged CPR (e.g., 2.5–4 h).	Cardiac pacing: Often fails to capture; blood pressure not always restored. Catecholamine use/dosing base on cardiodynamic and hemodynamic monitoring (e.g., norepinephrine for hypotension due to low SVR); no one catecholamine superior for cardiovascular drug toxicity and may require large doses of multiple adrenergic agents. Euglycemic clamping: Response not immediate; increase chance of benefit with early detection of hypodynamic myocardium and early initiation of therapy; numerical hypoglycemia, hypokalemia, hypophosphatemia, hypmagnesemia.

	>400 mg/dL (22 mmol/L)] followed by dextrose infusion 0.5 g/kg/h titrated based on bedside glucose monitoring every 20–30 min until serum glucose is stable and then every 1–2 h; replace potassium if <2.5 mmol/L *and* a source of potassium loss.		
Body packer ■ Asymptomatic: Presents in custody of law enforcement officer(s) requesting medical evaluation or retreival of contraband from GI tract; *medico legal* issues may be involved. ■ Symptomatic: Exhibiting typical signs/symptoms of the drug (e.g., cocaine, heroin) being concealed. ■ May present with or develop signs/symptoms of intestinal obstruction, intestinal perforation, peritonitis.	Asymptomatic: Administer an oral dose of water soluble contrast (e.g., Gastrografin) 1 mL/kg, perform abdominal radiographs (supine and upright) at least 5 h after contrast administration, perform daily abdominal radiographs if radiographs are positive and after a spontaneous bowel movement, check all bowel movements for drug packets, continue until after passage of two packet-free bowel movements and negative abdominal radiographs; oral intake ad lib. Symptomatic heroin body packer: IV naloxone infusion (see Opioid); activated charcoal 1–2 g/kg and WBI (see Box II) after patient stablized, patient is able to tolerate charcoal/WBI and precautionary measures to minimize aspiration.		Usual precautions prior to acquiring imaging studies.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
	Surgical intervention: Symptomatic cocaine body packer; failed medical management in symtomatic heroin body packer; intestinal obstruction/perforation; packets fail to progress through GI tract after conservative management. Endoscopic retrieval of retained packets in stomach may be considered by experienced endoscopist.		
Calcium channel antagonist (CCA) ■ CV: See Beta-adrenergic blocker; bepridil-prolonged QTc and *torsade de pointes*. ■ Neurologic: See BB. ■ Metabolic: Hyperglycemia; lactic acidosis. ■ Respiratory: Noncardiogenic pulmonary edema. ■ Abdomen: Ileus; mesenteric ischemia/infarction.	Bradycardia: See BB. QRS >120 msec: See BB. Hypodynamic myocardium ■ See BB. ■ IV calcium gluconate (10%) 0.6 mL/kg bolus (0.2 mL/kg 10% calcium chloride) over 5–10 min followed by continuous calcium gluconate infusion at 0.6–1.5 mL/kg/h (0.2–0.5 mL/kg/h 10% calcium chloride), titrate infusion to affect improved blood pressure/contractility, follow ionized calcium levels every 30 min	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): See BB. Extraordinary measures: See BB.	See BB. Acidemia worsens myocardial dysfunction. Calcium treatment: Mixed clinical experience (disappointing at times), primarily inotropic effect; gluconate safest.

	initially and then every 2 h maintaining ionized calcium twice normal.		
Cardioactive steroid (e.g., digoxin, digitoxin, oleander, and bufo toxin) Digoxin ■ General: Nausea, vomiting; fatigue. ■ CV: Variety of dysrhythmias; atrial tachycardia with variable AV block (paroxysmal atrial tachycardia 2:1 block), accelerated junctional rhythm (regularized atrial fibrillation), and fascicular tachycardia highly suggestive and bidirectional ventricular tachycardia (i.e., narrow-complex tachycardia with right bundle branch morphology) highly specific for digitalis toxicity. ■ CNS: Headache; weakness; dizziness; confusion; syncope; coma.	Symptomatic patients, cardiac dysrhythmias that threaten or result in hemodynamic compromise, serum potassium >5.0 mmol/L, serum digoxin concentration >10.0 ng/mL (12.8 nmol/L) 6 h after overdose or >15 ng/mL (19.2 nmol/L) at any time: IV digoxin-specific antibody fragments (DigFab). DigFab dosing: ■ From dose ingested: One vial of DigFab (40 mg) binds 0.6 mg of digoxin; Example: Ingestion of 3 mg of digoxin (bioavailability 80% [0.8]) requires 4 vials. ■ From serum digoxin concentration: See Box III. ■ By titration: Administer 4–6 vials of DigFab and repeat depending on clinical effect. If *DigFab unavailable*, temporary transvenous cardiac pacing; IV magnesium sulfate 2.5 g (10 mmol) over 5 min for ventricular tachyarrhythmias, repeat as needed. Acute allergic reaction to DigFab: Stop infusion; treat according to current guidelines.	GI decontamination considerations (after patient stabilized and precautionary measures to minimize aspiration): Activated charcoal 1–2 g/kg followed by hourly, every 2 h, or every 4 h at a dose equivalent to 12.5 g/h (Peds: 10–25 g) for 12–24 h; not in patients with decreased bowel sounds/ileus.	Chronic digoxin toxicity: Similar to acute toxicity and hallucinations, visual disturbances such as cloudy or blurred vision, loss of vision, and yellow-green halos or everything appearing washed in yellow (xanthopsia); normo- or hypokalaemia is more common in patients with heart disease. Predisposition to toxicity: Hypokalemia, hypomagnesemia, and hypercalcemia, renal dysfunction. Serum digoxin levels most reliably correlate with toxicity when obtained ≥6 h after digoxin administration. Naturally occurring cardioactive steroids from plants and animals can cross-react with the digoxin assay; degree of cross-reactivity is unknown and no good correlation between serum levels and toxicity.

(continued)

TABLE 102-1 **Continued**

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
			A false positive digoxin assay (<3 ng/mL) may occur in patients (e.g., neonates, patients with renal insufficiency, liver disease, and pregnancy) not receiving digoxin therapy. Dysrhythmias: IV magnesium worsen atrioventricular block in bradydysrhythmias; avoid class 1A antidysrhythmics drugs. DigFab (1,200 mg) are safe and effective treatment for yellow oleander induced cardiac dysrhythmias (e.g., bradycardia <40/min), sinus arrest or block, atrial tachydysrhythmias, second or third degree atrioventricular block.
Envenomation Elapidae (coral snakes) ■ Local effects: Little or no pain or swelling at bite site;	Impending respiratory failure (e.g., any sign of cranial nerve palsy/paralysis, trismus,		Envenomation is a *dynamic* process.

paresthesias radiating proximally; muscle fasciculations. ■ Systemic effects: Latent onset (hours); drowsiness or euphoria; nausea, vomiting; increased salivation; bulbar-type paralysis and progresses to peripheral paralysis; extraocular muscle paresis, ptosis, pinpoint pupils; dysphagia, dysphonia, slurred speech; laryngeal spasm; respiratory failure; cardiovascular collapse.	laryngeal/pharyngeal spasm, cyanosis): Prophylactic endotracheal intubation and mechanical ventilation. Clinical envenoming or strong clinical suspicion for or proven coral snake bite: IV coral snake antivenom 4–6 vials (adults and pediatrics) with each vial diluted in 50 to 100 mL of normal saline and administered over 1 h; if signs/symptoms appear or progress, administer 4–6 more vials of antivenom. Acute allergic reaction to antivenom: Stop infusion; treat according to current guidelines. Bite site: Local wound care; antibiotics for infected wounds; tetanus prophylaxis.		Snake venoms do not appear to cross blood–brain barrier and CNS findings rare unless secondary to hypotension, hypoxia, or intracranial bleeding. Precaution: Be prepared to manage acute allergic reactions. Antivenom: Equine origin; may be effective in late presenters. Serum sickness: May occur 7–21 d following antivenom therapy; treat with oral steroids, antihistamines, and NSAIDs.
Viperidae (subfamily Crotalinae: pitvipers, e.g., rattle snake) ■ Local effects: Swelling, tenderness, tenseness, hypesthesia, pain; muscle necrosis; compartment syndrome; ecchymosis; bloody effluent from wound; lymphangitis; regional adenopathy; hemorrhagic bullae or serum-filled vesicles at bite	*Progression* of venom effects (i.e., worsening of local injury [e.g., pain, swelling, and ecchymosis], coagulopathy, *or* systemic effects (e.g., hypotension and altered mental status)]: ■ IV CroFab (Protherics, Inc., London): Administer 4–6 vials (adults or pediatrics); carefully monitor for further progression of local effects and systemic symptoms, and laboratory studies (i.e., CBC, PT/INR, fibrin, fibrin degradation products) are repeated one		Envenomation is a *dynamic* process. Snake venoms do not appear to cross blood-brain barrier and CNS findings rare unless secondary to hypotension, hypoxia, or intracranial bleeding. Precaution: Be prepared to manage acute allergic reactions. Antivenom: Ovine origin; most effective within first 24 h following envenomation, may be

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
site and along bitten extremity; petechiae or purpura. ■ Systemic effects: Nausea, vomiting; weakness; diaphoresis; fever, chills; dizziness; syncope; minty, rubbery, or metallic taste in mouth; muscle fasciculations; paresthesias of scalp, face, digits; systemic bleeding at any anatomic site; hypotension; noncardiogenic pulmonary edema; renal failure; neuromuscular respiratory failure may occur following severe Mojave envenomation. ■ Hematologic effects: Systemic coagulopathy.	hour after completing antivenom infusion; administer additional rounds of antivenom (4–6 vials) if initial control (i.e., reversal or marked attenuation of all venom effects) has not been achieved; continue this pattern until control is evident then administer two vials of CroFab every 6 h for three additional doses; most cases 8–12 vials to establish initial control. ■ Reconstituted each CroFab vial with normal saline 10 mL and roll vials between hands; dilute total dose to be administered in normal saline 250 mL and infused over 1 h. Acute allergic reaction to antivenom: See Elapidae. Suspected compartment syndrome: Measure intracompartmental pressures using any standard device; if pressures		beneficial in late presenters with severe findings (e.g., coagulopathy); limited efficacy in preventing wound necrosis or reversing cellular damage; thrombocytopenia may be resistant to antivenom therapy. Serum sickness: See Elapidae.

	>30–40 mm Hg, elevate limb and administer additional 4–6 vials of antivenom over 1 h; if this fails to reduce compartment pressure within 4 h and evidence of circulatory compromise, fasciotomy may be required. Bite site: See Elapidae. Hemorrhagic blebs: Unroof after the first few days, further debridement if significant necrosis (after coagulopathy has resolved).		
Brown spider (*Loxosceles* sp, e.g., brown recluse). ■ Local effects: Dermonecrosis. ■ Systemic (viscerocutaneous) effects: Uncommon; latent onset 24–72 h after the bite and occasionally occur before cutaneous findings become impressive; flulike symptoms with fever, chills, headache, malaise, weakness, nausea, vomiting, myalgias, and arthralgias; hemolytic anemia with hemoglobinemia; hemoglobinuria; jaundice; thrombocytopenia; disseminated intravascular	Supportive care.		No proven therapeutic treatment for local or systemic effects.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
coagulation; shock; seizures; coma; secondary acute renal failure; not necessarily correlate with cutaneous severity; rapidly progressive and particularly severe in children.			
Widow spider (*Latrodectus* sp., e.g., black widow) ■ Local effects: Bite site may be visible, area slightly warm, diaphoresis, and blanched with a surrounding erythematous, indurated zone; minimal swelling. ■ Systemic effects: Gradual progression; fever, headache, diaphoresis, nausea, vomiting, restlessness, anxiety; tachycardia and hypertension; pain, dull ache spreading to local muscle groups and then to regional muscle groups, muscles spasm with resultant rigidity.	Symptomatic treatment: IV BZD and opioid. Sever clinical envenoming, inadequate response to BZD and opioid, CV comorbidities, pregnant patient or patient in labor: IV antivenom (preferable) 1 reconstituted vial further diluted in 50–100 mL of normal saline over 30 min or IM 1 reconstituted vial in the anterolateral thigh; signs/symptoms should completely resolve within a few hours; a second vial can be administered if necessary. Acute allergic reaction to antivenom: See Elapidae.		Envenomation is a *dynamic* process. Venom does not appear to cross blood-brain barrier and CNS findings rare unless secondary to hypotension, hypoxia, *or* intracranial bleeding. Antivenom: Equine origin; most effective in the acute setting, may be beneficial in late presenters (e.g., 96 h) with prolonged symptoms. Precaution: See Elapidae. Serum sickness: See Elapidae.

Scorpion (*Centruroides* sp) ■ Local effects: Intense pain exacerbated by light palpation or tapping over the site. ■ Systemic effects: Restlessness, anxiety; hypersalivation; dysphagia; difficulty focusing or temporary blindness, roving eye movements; tachypnea, respiratory distress, wheezing, stridor; hypertension, tachycardia; incontinent of stool/urine; muscle fasciculations/spasm, alternating opisthotonus and emprosthotonus; paralysis; extreme neuromuscular hyperactivity.	Symptomatic treatment: IV BZD and judicious opioid use; consider beta-adrenergic blocker for hemodynamically significant tachycardia.		In the United States scorpion antivenom is unavailable for clinical use.
Herbicide Chlorate salts ■ GI: Vomiting, diarrhea; abdominal pain. ■ Hemotolgoic: Methemoglobinemia (cyanosis); hemolytic anemia (hyperkalemia); Heinz bodies; ghost cells. ■ GU: Hemoglobinuria (black-brown urine); acute renal failure.	Symptomatic methemoglobinemia or methemoglobin >20%: ■ Ventilate and oxygenate with 100% oxygen. ■ IV methylene blue 1–2 mg/kg over 5 min, repeat doses may be needed; onset of action ≤3 min; efficacy may be limited (chlorate inactivates glucose-6-phosphate dehydrogenase) and may need to proceed with hemodialysis.	Prolonged action of chlorate on red blood cells suggests early hemodialysis should be considered.	Repetitive or continuous methylene blue dosing and GI decontamination may be needed when there is continued absorption or slow elimination of an agent producing methemoglobinemia: IV methylene blue 0.05% (in normal saline) 0.1 mg/kg/h *or* 3–7 mg/h has been suggested.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
Chlorophenoxy herbicides (e.g., 2,4-dichlorophenoxyacetic acid [2,4-D], 2,4,5-trichlorophenoxyacetic acid [2,4,5-T], and 2-methyl-4-chloro-phenoxypropionic acid [MCPP]) ■ GI: Oral burning; vomiting; abdominal pain; diarrhea; GI hemorrhage. ■ CV: Hypotension; intraventricular conduction defects; supraventricular and ventricular dysrhythmias; bradycardia. ■ Respiratory: Tachypnea; respiratory insufficiency; pulmonary edema; hemoptysis. ■ Neurologic: Pyrexia; miosis, nystagmus; twitching or fasciculations, weakness, myotonia (may progress to rhabdomyolysis); hypertonia, hyperreflexia, or clonus; ataxia; agitation; confusion; hallucinations; CNS depression; seizures; coma.	Symptomatic patients: Urine alkalinization with IV sodium bicarbonate 2 mmol/kg bolus followed by continuous infusion of sodium bicarbonate 150 mmol mixed in 1,000 mL D5W starting at 1.5 to 2.0 times maintenance rate, adjusted to maintain urinary pH 8.0 and arterial pH <7.55; reassess clinical status/laboratory parameters (e.g., electrolytes, acid-base, urine pH) hourly; terminate when clear clinical-biochemical recovery.	Maximize GFR: IV NS target urine output 2–4 mL/kg/h. (GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Activated charcoal 1–2 g/kg. Hemodialysis consideration: Severe poisoning; produces good herbicide clearance without need for urine pH manipulation and administration of substantial IV fluids.	No published reports of acute chlorophenoxy herbicide poisoning following dermal or inhalational exposure in at least the last 20 yr, and no reported fatalities from such exposures in the history of chlorophenoxy herbicide use.

■ GU: Renal failure. ■ Metabolic: Metabolic acidosis; hypocalcemia; hypokalemia.			
Diquat ■ Local caustic effects; similar to paraquat. ■ Respiratory: Bronchopneumonia; ARDS/acute lung injury; respiratory failure. ■ CV: Hypovolemia, shock; ventricular dysrhythmias, subendocardial hemorrhages, cardiac arrest. ■ GI: Nausea, vomiting, diarrhea, abdominal pains; ileus, abdominal distention and rapid fluid sequestation in GI tract; liver injury. ■ GU: Proteinuria; renal failure. ■ CNS: Seizures; pontine hemorrhages/infarction; brain stem infarction; coma. ■ Hematologic: Pancytopenia.	Management of diquat exposure similar to paraquat, and does not include investigational management strategy.		Toxicity usually associated with ingestion and total amount of diquat cation ingested more important than its concentration in solution; systemic effects may be delayed up to 48 h following ingestion; mortality within hours to days following massive ingestion. Diquat may interfere with the Jaffé reaction for creatinine measurement. Poor prognosis: Rapid onset of acute renal failure, intestinal ileus and subsequent fluid sequestration, ventricular dysrhythmias, pulmonary complications requiring ventilation, and coma. Pulmonary fibrosis not been reported following diquat poisoning.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
Paraquat ■ Local caustic effects. ■ GI: Painful ulceration of the lips, tongue, pharynx, and larynx (caustic injury) leading to dysphagia, cough, dysphonia, dysphagia, inability to clear secretions, esophageal perforation; vomiting; abdominal pain; hematemesis; diarrhea; pancreatitis; centrilobular hepatic necrosis; cholestasis. ■ CV: Hypovolemia; shock; dysrhythmias. ■ Respiratory: Cough; prominent pharyngeal membranes (pseudodiphtheria); mediastinitis; pneumothorax; hemoptysis; (hemorrhagic) pulmonary edema; progressive pulmonary fibrosis. ■ GU: Acute renal failure. ■ Neurologic: Coma; seizures; cerebral edema.	Optimal fluid resuscitation should be guided by central venous or pulmonary capillary wedge pressures. Caustic injury to oral/GI tract: Current guidelines. Investigational management strategy: Patients presenting within 24 h of paraquat ingestion and has an expected mortality 50%–90% on nomogram (Figure 102-2): IV cyclophosphamide 15 mg/kg in 200 mL of 5% glucose saline infused over 2 h × 2 d *and* IV methylprednisolone 1 g in 200 mL of 5% glucose saline infused over 2 h × 3 d, IV dexamethasone 5 mg every 6 h until $Pao_2 \geq 80$ mm Hg (11.5 kPa); if $Pao_2 < 60$ mm Hg (8.64 kPa) administer IV methylprednisolone 1 g in 200 mL of 5% glucose saline over 2 h × 3 d; if white blood cell counts $<3{,}000/m^3$ and initial cyclophosphamide therapy >2 wk administer IV cyclophosphamide 15 mg/kg/d over 2 h × 1 d (IV dexamethasone 5 mg every 6 h is	Supplemental oxygen is withheld until the arterial oxygen tension <50 mm Hg and/or patient expresses respiratory distress. GI decontamination consideration (after patient stabilized, assessing GI tract integrity, and precautionary measures to minimize aspiration): Activated charcoal 1–2 g/kg or Fuller's earth (15% (w/L) aqueous suspension) 1–2 g/kg or bentonite (7% (w/v) aqueous slurry) 1–2 g/kg with a cathartic (e.g., magnesium salt or sorbitol 70%); IV antiemetic (e.g., ondansetron 8 mg; Peds: 0.2 mg/kg, max 8 mg) may be needed. Charcoal hemoperfusion: Initiate within 4 h of ingestion and continued for 6–8 h; CAVH reduces rebound in serum paraquat concentrations after hemoperfusion; hemodialysis ≥ renal paraquat clearance,	Spontaneous vomiting is a near certainty following significant paraquat ingestions (e.g., irritant effects and emetic added to many formulations). Serum and urine specimens should be placed in plastic containers and send for qualitative and quantitative paraquat concentration determination; treatment of patient should continue until results are available. Serum paraquat concentrations measured within 28 h after ingestion has some prognostic value based on an empirically derived nomogram from clinical (*not* statistical) data (Figure 102-2): Mortality 100% when initial serum paraquat >3 mg/L, cardiogenic shock and death with in 24 h of ingestion when serum paraquat >10 μg/mL.

■ Dermalologic: Caustic injury to skin, nails, cornea, conjunctiva, nasal mucosa. ■ Endocrine: Adrenal insufficiency.	continued until Pao_2 ≥80 mm Hg (11.5 kPa), then gradually reduce dose, or died).	should be performed for usual indications in acute renal failure and when hemoperfusion not available.	Paraquat may interfere with the Jaffé reaction for creatinine measurement.
Hydrofluoric acid (HF) ■ Dermal exposure: At risk for systemic fluoride toxicity (See Oral exposure) >5% body surface area (BSA) or >1% BSA exposure to ≥50% HF products.	Rapid irrigation with water ≥15 min, apply a 2.3%–2.5% calcium gluconate preparation in a water-soluble gel to exposed area(s) ≥30 min or until symptoms resolve. Pain unrelieved by gel therapy ■ Regional intra-arterial: Place catheter in direction of blood flow by Seldinger technique, continuously monitor arterial waveform (arteriography if any concern as to adequate placement), infuse 50 mL of 2.5% calcium gluconate in normal saline over 4 h; repeated doses may be required over 12–24 h. *or* ■ Administer 40 mL of a 2.5% calcium gluconate solution by Beir block technique (i.e., catherize a distal vein and exsangunate extremity by elevation and compression with an esmarch bandage, inflate blood pressure cuff to 100 mm Hg above systolic pressure and maintain for 15–20 min following calcium administration, gradually deflate cuff over 5 min).	Wound management for acid burns.	
■ Inhalation exposure: Airway and pulmonary injury; respiratory failure; at risk for systemic fluoride toxicity	Respiratory support; intubate/ventilate; nebulized 25% calcium gluconate may improve symptoms following mild exposure.		

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
(See Oral exposure); progression of minimal symptoms over time.			
■ Oral exposure: Risk of systemic fluoride toxicity in deliberate or accidental ingestion of products >7% HF; minimally symptomatic patients may rapidly progress to cardiovascular collapse.	Oral calcium or magnesium containing antacids 30–60 mL. History suggestive of a substantive exposure that may lead to systemic toxicity: IV calcium chloride 1 g over 30 min; patients with normal vital signs and remain stable should be monitored with serum calcium levels every 30 min for the first 2–3 h; IV calcium chloride 1 g boluses to maintain serum calcium concentration in the high normal laboratory reference range, repeat as needed; a fall in serum calcium concentration below the normal range, dysrhythmias or a fall in blood pressure is treated with IV calcium chloride 2–3 g boluses every 15 min *or* IV magnesium sulfate 2–6 g over 30 min follow by an infusion 1–4 g/h; additional magnesium boluses as indicated by careful clinical assessments and laboratory investigations.		Resuscitation from cardiac arrest following systemic fluoride toxicity is rare; focus on *early* intervention to prevent cardiac dysrhythmias and arrest. All patients should be admitted to an ICU following a deliberate HF ingestion.

Isoniazid (INH) ■ Dizziness; slurred speech; blurred vision; visual hallucinations (e.g., bright colors, spots, strange designs); stupor and coma can rapidly develop, followed by intractable tonic-clonic generalized or localized seizures, hyperreflexia or areflexia; cardiovascular and respiratory collapse. ■ Metabolic: Severe metabolic acidosis; hyperglycemia; ketonuria; hyperkalemia. ■ Triad: Metabolic acidosis refractory to sodium bicarbonate therapy, seizures refractory to anticonvulsants and coma.	First sign of neurotoxicity: IV diazepam or equivalent *and* pyridoxine in milligram doses equal to the amount of INH ingested or 5 g in cases of unknown amount of ingestion administered over 30–60 min. Seizing patients: IV diazepam or equivalent *and* pyridoxine (milligram doses equal to the amount of INH ingested or 5 g in cases of unknown amount of ingestion) at 500 mg/min until seizures terminate and remainder of dose infused over next few hours; repeat pyridoxine dose if seizures persist or recur. Seizures refractory to diazepam and pyridoxine: Induce thiopental coma.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (see Box I.) for acutely ill patients followed by activated charcoal (1–2 g/kg); activated charcoal for asymptomatic patients.	
Local anesthetic Bupivacaine ■ CV: Reductions in cardiac output while blood pressure is maintained; bradycardia, atrio- and intraventricular blocks, ventricular dysrhythmias; cardiovascular collapse often refractory to treatment.	Clinical bupivacaine toxicity: ■ Current ACLS guidelines. *and* ■ IV lipid emulsion (e.g., Intralipid, Liposyn III 20%) 1 mL/kg over 1 min; repeat twice more at 3–5 min intervals; then (or sooner if stability is restored) convert to an infusion at a rate of 0.25 mL/kg/min until hemodynamic recovery (>8 mL/kg is unlikely to be useful).		Laboratory data and accumulating clinical experience with lipid emulsion therapy in bupivacaine, levobupivacaine, mepivacaine, prilocaine, and ropivacaine toxicity suggests early lipid therapy to attenuate progression of local anesthetic toxic syndrome. Bupivacaine: More cardiotoxic than most other local anesthetics in

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
	or ■ IV lipid emulsion (e.g., Intralipid 20%) 100 mL followed by an infusion 0.5 mL/kg/min. Refractory cardiac arrest: Cardiopulmonary bypass.		clinical use (e.g., lidocaine, ropivacaine, levobupivacaine); earliest signs of cardiac toxicity are prolonged QRS/QTc.
Lidocaine ■ Neurologic: Numbness of the tongue, light headedness, visual/auditory disturbances, muscular twitching, unconsciousness, seizures, coma, respiratory depression/apnea. ■ CV: Hypertension and tachycardia (mild intoxication) progressing to bradycardia, hypotension, sinus arrest, heart blocks, intraventricular conduction defects (e.g., prolonged QRS), ventricular dysrhythmias (e.g., ventricular fibrillation), circulatory collapse, asystole.	Clinical local anesthetic toxicity: Current ACLS guideline and consider IV lipid emulsion therapy (See Bupivacaine) and cardiopulmonary bypass for refractory cardiac arrest.		Lidocaine toxicity: Dose related; neurotoxic manifestations before potentially cardiotoxic levels are reached. Amide local anesthetics may act as oxidizing agents and lead to methemoglobinemia in toxic doses.

Metals Arsenic (As) ■ Respiratory: Pulmonary edema. ■ CV: Prolonged QTc and polymorphic ventricular tachycardias (e.g., *torsades de pointes*). ■ GI: Abdominal pain; profuse watery stools; hemorrhagic gastroenteritis (hypovolemia shock). ■ Neurologic: Confusion, delirium, convulsions, encephalopathy, and coma; polyneuropathy (e.g., severe painful burning sensation in soles of feet, ascending weakness; paralysis with neuromuscular respiratory failure). ■ Hematologic: Reversible bone marrow depression with pancytopenia (particularly leukopenia), nadir at 1–2 wk with recovery 2–3 wk after the nadir.	Dysrhythmias: Current ACLS guidelines and avoid class IA/IC antidysrhythmics; limited success with lidocaine, magnesium, and isoproterenol in management of arsenic-induced *torsades de pointes*; transvenous pacemaker for overdrive pacing. Suspected acute symptomatic As poisoning: IM BAL 3–5 mg/kg every 4 h, gradually tapering to every 12 h over several days; switch to DMSA 10 mg/kg every 8 h for 5 d, reduced to every 12 h for another 2 wk; additional course of treatment may be considered based on post-treatment results: 24-h urinary As excretion is followed before, during, and after chelation with continued chelation therapy until the urinary As excretion <25 μg/24 h or during the recovery period when urinary inorganic As concentration <100 μg/24 h or total blood As <200 μg/L.	Maximize GFR: IV NS target urine output 2–4 mL/kg/h. GI decontamination consideration (after patient stabilized, assessing GI tract integrity, and precautionary measures to minimize aspiration): Gastric lavage (see Box I.) in acutely sick patients followed by activated charcoal 1–2 g/kg; WBI (see Box II.) when evidence of a heavy metal burden on abdominal imaging (absence of radiopacities on imaging study is nondiagnostic), monitor effectiveness by serial abdominal imaging studies.	BAL is most effective within hours of ingestion. Monitor respiratory function carefully in patients with progressive sensorimotor dysfunction (e.g., ascending weakness) for impending neuromuscular respiratory failure. Arsenic trioxide: Induction therapy in APL patients receiving daily median arsenic trioxide 0.15 mg/kg (range, 0.06 to 0.2 mg/kg) infusions over 1–2 h until bone marrow remission or for a maximum of 60 d has been associated with QTc prolongation, *torsades de pointes*, and sudden death. Laboratory diagnosis: Quantitative 24-h urine collection most reliable (spot urine sample in an emergency); normal *total* urinary As values <50 μg/L or <25 μg/24 h; first 2–3 d following acute symptomatic intoxications total 24-h urinary As excretion in excess of several thousand micrograms (spot urine concentration >1,000 μg/L); recent seafood ingestion may markedly elevate urinary As values for 48 h.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
Arsine gas ■ Latent onset toxicity (2–24 h). ■ General: Dizziness, malaise, weakness; dyspnea; vomiting, diarrhea; headache; abdominal pain. ■ Hemotologic: Coombs' negative hemolytic anemia. ■ GU: Dark-red urine; hemoglobinuria and/or hematuria; renal failure. ■ Dermatologic: Reddish staining of the conjunctiva; duskily bronzed skin.	Acute and severe arsine poisoning: Exchange transfusion; exchange transfusion *and* hemodialysis in patients with renal insufficiency/failure.	Maximize GFR: See Arsenic.	BAL treatment has been disappointing, does not appear to afford protection against arsine-induced hemolysis.
Iron (Fe) ■ Stage 1 (GI toxicity): Abdominal pain, vomiting, diarrhea, hematemesis, and hematochezia; variable severity; latent toxicity with enteric-coated tablets. ■ Stage 2 (relative stability): Apparent improvement in clinical status but not	Symptomatic patient (e.g., recurrent vomiting or diarrhea, acidosis, shock and decreased level of consciousness or coma) regardless of serum Fe concentration or asymptomatic patient with serum Fe concentration $\geq$500 μg/dL (90 μmol/L): IV deferoxamine initiated slowly and gradually increased to 15 mg/kg/h over 20–30 min and continued for 24 h; continuous IV	Maximize GFR with IV NS and target urine output 2–4 mL/kg/h. GI decontamination consideration (after patient stabilized, assessing GI tract integrity, and precautionary measures to minimize aspiration): ■ Gastric lavage (see Box I.) in acutely sick patients; WBI (see Box II.) when evidence of a heavy metal burden on abdominal	Serum Fe concentration: ■ Validates the ingestion, guides management, and provides prognostic information. ■ Blood sampling to determine peak serum concentration should be 4–6 h after an overdose of conventional tablets and several hours later

completely asymptomatic; careful assessment and repeated monitoring will document some degree of hypovolemia, circulatory shock, acidosis. ■ Stage 3 (circulatory shock): Hypovolemic, distributive, or cardiogenic; metabolic acidosis usually precedes circulatory shock. ■ Stage 4 (hepatotoxicity): Liver failure. ■ Stage 5 (GI scaring): Most common area is gastric outlet; obstruction.	deferoxamine therapy >24 h (rarley needed) is interrupted for 12 of every 24 h; endpoints in treatment include resolution of systemic signs/symptoms, correction of acidosis, and return of urine color to normal (if patient developed vin rosé colored urine during therapy).	imaging (absence of radiopacities on imaging study is nondiagnostic) or history of elemental iron ingestion >1.5 g (Peds: >60 mg/kg), monitor effectiveness by serial abdominal imaging studies. ■ Bezoar/concretion: Procedural removal if WBI ineffective.	for modified release formulations; serial serum Fe concentration determinations every 2 h until a definite downward trend is established. ■ Peak <500 μg/dL (90 μmol/L) usually associated with negligible to mild systemic toxicity; there may be significant GI symptoms. ■ Peak 500–1,000 μg/dL (90–180 μmol/L) associated with moderate systemic toxicity. ■ Peak >1,000 μg/dL (180 μmol/L) associated with severe toxicity (e.g., profound acidosis, shock, hepatotoxicity, and coma); mortality approaches 100% when >10,000 μg/dL (1,800 μmol/L). Acidosis is the first objective indicator of systemic toxicity, pH <7.30 indicative of significant toxicity. The total iron binding capacity (TIBC) is falsely elevated in the presence of high

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
			serum Fe concentrations and is unreliable during hyperferremic states; a serum Fe concentration < TIBC does *not* rule out acute iron poisoning. Pregnant patients: Consequences of Fe toxicity same as in other patients; fetus is relatively protected and its health depends on maternal health; treatment same as that given a nonpregnant patient. Adverse drug events from deferoxamine therapy: include tachycardia, hypotension, shock, a generalized beet red flushing of the skin, blotchy erythema, urticaria; acute renal failure when deferoxamine is administered to hypovolemic patients; pulmonary toxicity (e.g., ARDS) associated with continuous IV deferoxamine over several days; patients receiving deferoxamine at risk for *Yersinia* infections.

Lead (Pb) ■ Constitutional symptoms: Fatigue, arthralgias, decreased libido, irritability, impotence, depression, anorexia, malaise, myalgias, weight loss, insomnia. ■ GI: Constipation or diarrhea; intestinal spasm with severe, excruciating, paroxysmal, abdominal pain (i.e., "lead colic"). ■ Neurologic: Impaired concentration, visual-motor coordination, headache; encephalopathy characterized by vomiting, tremors, hyperirritability, ataxia, confusion, delirium, lethargy, obtundation, seizures, coma; children may exhibit SIADH; peripheral motor neuropathy predominantly affecting upper extremities (e.g., "wrist drop"). ■ Hematologic: Normochromic or microcytic anemia, may be accompanied by basophilic stippling of erythrocytes.	Seizures: IV BZD or phenobarbital. Symptomatic Pb encephalopathy: IM BAL is 75 mg/m^2 (3 to 5 mg/kg) every 4 h. After 4 h have elapsed since the priming dose of BAL start IV CaEDTA 1,500 mg/m^2/d (30 mg/kg/d). In cases of cerebral edema and or increased intracranial pressure associated with encephalopathy, administer CaEDTA (same dosage) by deep IM injection (extremely painful) along with procaine 0.5% in two to three divided doses every 8–12 h. Continue BAL and CaEDTA 5 d. Cessation of chelation is often followed by a rebound in blood Pb concentration, a second chelation course may be considered based on whole blood Pb concentration after 2 days' interruption of BAL and CaEDTA treatment, and the persistence or recurrence of symptoms. A third course may be required if the whole blood concentration rebounds ≥50 μg/dL within 48 h after second chelation treatment. If chelation is required for the third time, it should begin a week after the last dose of BAL and CaEDTA. Symptomatic patients who are not overtly encephalopathic: IM BAL is 50 mg/m^2 (2 to 3 mg/kg) every 4 h. After 4 h have elapsed since the priming dose of BAL, start IV CaEDTA 1,000 mg/m^2/d (20 to	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): See Arsenic, omit activated charcoal. Surgically remove lead-containing foreign body in or adjacent to synovial space if possible. Child with encephalopathy: Establishing adequate urine output by IV infusion 10–20 mL/kg of 10% dextrose in water over 1–2 h. If this fails to produce an urine output, infusion 1–2 g/kg of a 20% mannitol solution 1 mL/min. Once urine output has been established, IV fluids should be restricted to the calculated basal water and electrolyte requirements plus a careful assessment of continuing losses; indwelling Foley catheter to monitor rate of urine formation; adjusted IV fluids hourly to maintain urine flow within basal metabolic limits (i.e., 0.35–0.50 mL of urine secreted per calorie metabolized per 24 h or 350–500 mL/m^2/24 h).	CT head-scan in patients with encephalopathy to rule out cerebral edema.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
	30 mg/kg/d) or in 2–3 divided doses every 8–12 h. BAL and CaEDTA should be continued for 5 d with daily monitoring of whole blood Pb concentrations. BAL may be discontinued any time during these 5 d if the whole blood Pb level <50 μg/dL but CaEDTA treatment should continue for 5 d. A second or third course of chelation may be considered based on the same guidelines as in the previous paragraph. Asymptomatic patients with whole blood Pb levels ≥70 μg/dL: BAL and CaEDTA in the same doses and with the same guidelines as for treatment of symptomatic Pb poisoning without encephalopathy. A second course of CaEDTA chelation alone may be necessary if whole blood Pb concentration rebounds ≥50 μg/dL within 5–7 d after chelation has ceased. Alternative: Oral DMSA 10 mg/kg ($350\ mg/m^2$) every 8 h for 5 d then every 12 h for 2 wk. Additional course of treatment may be considered based on posttreatment whole blood Pb concentrations, and the		

	persistence or recurrence of symptoms. An interval ≥2 wk may be indicated to assess the extent of posttreatment rebound in whole blood Pb concentration. Cerebral edema: Current guidelines.		
Lithium (Li) Acute effects ■ Mild intoxication: Lethargy, fatigue, memory impairment, fine tremor. ■ Moderate intoxication: Confusion, agitation, delirium, coarse tremor, hyperreflexia, hypertension, tachycardia, dysarthria, nystagmus, ataxia, muscle fasciculations, extrapyramidal syndromes, choreoathetoid movements. ■ Severe toxicity: Bradycardia, coma, seizures, hyperthermia, hypotension. Permanent sequelae include choreoathetosis, nystagmus, ataxia. ■ CV: Bradycardia; sinoatrial block; intraventricular conduction defects (e.g., prolonged QRS/QTc in severe toxicity); ECG changes similar to hypokalemia.	Asymptomatic or mild/moderate toxicity: Maximize GFR with IV NS and target urine output 2-4 mL/kg/h if renal Li clearance [urine Li (mmol/L)/serum Li (mmol/L) × urine flow rate (mL/min] <15-30 mL/min furosemide and forced diuresis are of unproven efficacy.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (see Box I.) in acutely sick patients; WBI (see Box II.) for large ingestion of modified release formulation; procedural removal of bezoar/ concretion. Hemodialysis consideration: ■ Severe clinical toxicity (e.g., neurologic dysfunction). ■ Renal dysfunction. ■ Patient becomes clinically unstable or not improving. ■ Satisfactory Li clearance (≥15–30mL/min) cannot be achieved. ■ Patient unlikely to tolerate a target urine output 2–4 mL/kg/h (e.g., marginal cardiopulmonary reserve).	Acute overdose: Minor neurologic manifestations despite high serum Li concentration (e.g., 9.0 mmol/L) during initial 12 or more hours; toxicity may develop over subsequent 24–48 h even as serum concentration falls; serum Li concentration cannot predict toxicity or guide therapy; no clinical variable accurately predicts which patients will deteriorate; a reduced or absent anion gap may occur with severe Li carbonate toxicity. Chronic toxicity ■ CNS: Mild effects associated with serum Li concentrations <1.5 mmol/L, mild/moderate effects 1.5–3.0 mmol/L, severe/death >3–4 mmol/L. NDI does not respond to vasopressin, but may improve with amiloride, hydrochlorothiazide,

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
■ Metabolic: Hypercalcemia; hypermagnesemia; nonketotic hyperglycemia; transient diabetic ketoacidosis; goiter; hypothyroidism rare. ■ GU: Nephrogenic diabetes insipidus (NDI); sodium-losing nephritis.		■ Probability patient will become toxic or develop permanent neurologic deficits (e.g., progressive/worsening peripheral neurologic dysfunction such as tremors, fasciculations, and clonus). ■ Acute asymptomatic poisoning and serum Li >9 mmol/L. ■ Symptomatic patients with chronic serum Li >2.5 mmol/L. Hemodialysis should be repeated until serum Li concentration drawn 6–8 h after last dialysis is ≤1 mmol/L; CAVH/CVVH may be useful in attenuating rebound effect after hemodialysis or in asymptomatic patients with high/raising serum Li levels.	carbamazepine, or indomethacin; indomethacin may be more effective in the acute setting. Hemodialysis and CAVH/CVVH are not equivalent, and they are not mutually exclusive; CAVH/CVVT may be the only option in hypotensive patients until hemodialysis can be tolerated.

Mercury (Hg) Elemental Hg vapor ■ Systemic effects: Fever, chills, headache, dyspnea, gingivostomatitis, vomiting, paroxysmal cough, tachypnea, chest tightness, diarrhea, abdominal cramps. ■ Respiratory: Interstitial pneumonitis, pulmonary infiltrates, noncardiogenic pulmonary edema, interstitial pulmonary fibrosis; complications include subcutaneous emphysema, pneumomediastinum, pneumothorax.	Supportive care. Chelation therapy: ■ No proven effect on improving clinical outcome. ■ Oral DMSA (10 mg/kg every 8 h, tapering to every 12 h over the next several days and continued until urinary Hg concentration approaches background) may enhance urinary Hg excretion and reduce nephrotoxicity after GI absorption of elemental Hg. ■ BAL may redistribute Hg to the brain.		Neurologic: Toxicity typically result of *chronic* exposure. Confirming elemental Hg exposure: 24-h urinary Hg excretion <50 μg/24 h most useful tool in diagnosing acute exposure; normal whole blood mercury concentration <2 μg/dL and "spot" urine mercury Hg concentration <10 μg/L.
Inorganic Hg (e.g., mercuric chloride) ■ GI: Corrosive stomatitis; abdominal pain; hemorrhagic gastroenteritis; necrotizing esophagitis; gastritis; ulcerative colitis. ■ GU: Acute renal failure.	Suspected acute inorganic Hg poisoning: BAL and DMSA; See Arsenic.	Maximize GFR: See Arsenic. GI decontamination consideration (after patient stabilized, assessing GI tract integrity, and precautionary measures to minimize aspiration): See arsenic. Endoscopy if corrosive injury (e.g., stridor, drooling, dysphagia, abdominal pain) is suspected.	BAL is most effective within 4 h of ingestion. Confirming Hg exposure: See Elemental Hg; whole blood Hg concentrations >50 μg/dL in acute poisoning associated with gastroenteritis and acute renal tubular necrosis.

(continued)

TABLE 102-1 **Continued**

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
Organic Hg (e.g., methylmercury) ■ Latent onset (weeks to months); paresthesias, hearing impairment, progressive incoordination, loss of voluntary movement, mental retardation. ■ Classic triad of methylmercury poisoning: Dysarthria, ataxia, and constricted visual fields.	Supportive care. Chelation therapy: ■ No proven effect on improving clinical outcome. ■ DMSA appears promising in animal studies; See Elemental Hg.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (see Box I.); oral (repeated doses) polythiol resin.	Confirmatory Hg exposure: Whole blood Hg concentrations >20 μg/dL associated with symptoms; urinary Hg concentration not useful.
Methylxanthine Caffeine ■ GI: Nausea, vomiting; hematemesis. ■ Neurologic: Anxiety, agitation; seizures. ■ Metabolic: Hypokalemia, hyperglycemia; metabolic acidosis. ■ CV: Dysrhythmias; myocardial infarction.	Management of caffeine toxicity similar to theophylline toxicity.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): See Theophylline. Hemodialysis consideration: Seizures, cardiac dysrythmias, or serum caffeine concentrations >100 μg/mL.	Life-threatening events associated with serum concentrations >100 μg/mL, seizures have occurred at 50 μg/mL, death has been reported at 80 μg/mL; 385 μg/mL have been associated with survival. Hemodialysis and CAVH/CVVH: See Theophylline.

■ Musculoskeletal: Rhabdomyolysis.			
Theophylline ■ CV: Sinus tachycardia; ventricular irritability/dysrhythmias; hypotension with widened pulse pressure and increased cardiac index (i.e., marked fall in systemic vascular resistance). ■ Neurologic: Hyperventilation; agitation and anxiety; vomiting; seizures. ■ GI: Vomiting; diarrhea; hematemesis. ■ Musculoskeletal: Tremors, myoclonic jerks. ■ Metabolic: Metabolic acidosis; hypokalemia, hyperglycemia, hypophosphatemia, hypomagnesemia, hypercalcemia.	Vomiting: IV ondansetron 8 mg (Peds: 0.2 mg/kg, max 8 mg) *or* IV metoclopramide 1 mg/kg (Peds: 0.1 mg/kg, max 1 mg/kg). Sinus tachycardia, supraventricular tachyarrhythmias, ventricular irritability: IV propranolol 1–3 mg then 1 mg every 5–10 min (Peds: 0.02 mg/kg, not to exceed adult dose) until dysrhythmias corrected; *or* IV esmolol 500 μg/kg over 1 min followed by 25–200 μg/kg/min infusion. Ventricular irritability with hemodynamic compromise: IV lidocaine *or* amiodarone. Hypotension with a wide pulse pressure: IV crystalloid bolus, propranolol, vasopressor (e.g., phenylephrine, norepinephrine).	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): ■ WBI (see Box II.) for large ingestion of modified release formulation. ■ Procedural removal of bezoar/concretion. ■ Activated charcoal 1–2 g/kg followed by hourly, every 2 h, *or* every 4 h at a dose equivalent to 12.5 g/h (Peds: 10–25 g) until serum theophylline <15 μg/mL; alternatively, 0.25–0.5 g/kg/h through continuous nasogastric infusion; not in patients with decreased bowel sounds/ileus. Hemodialysis consideration: ■ Best before onset of life-threatening events, hemodynamic instability or repeated seizures. ■ Acute intoxication and serum theophylline >80 μg/mL. ■ Patients <6 mo or >60 yr with chronic overmedication	Alteration in theophylline clearance: CYP1A2 and CYP 3A4 inhibitors (e.g., erythromycin, clarithromycin, ciprofloxacin, cimetidine), heart failure, liver disease decreases clearance; barbiturates, carbamazepine polyaromatic hydrocarbons of cigarette smoke, hyperthyroidism, cystic fibrosis increases clearance. Risk stratification ■ Acute toxicity: Serum theophylline 20–40 μg/mL—nausea, vomiting, tachycardia; 40–70 μg/mL—premature ventricular contractions, agitation, tremors; >80 μg/mL—cardiac dysrhythmias, intractable seizures. ■ Chronic overmedication: Neonates or elderly patients (e.g., >75 yr) with underlying cardiac disease and/or take medications that inhibit

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
	Seizures: IV BZD, progress to thiopental or pentobarbital, and neuromuscular blockade and general anesthesia.	and serum theophylline >30 μg/mL. ■ Patient with moderate toxicity and unable to tolerate activated charcoal therapy. Exchange transfusion used successfully in neonates with severe toxicity.	theophylline metabolism; no correlation between serum theophylline concentration and appearance of life-threatening events (e.g., severe intoxication at steady-state serum theophylline concentrations as low as 20–30 μg/mL and seizures as low as 17 μg/mL). ■ Acute-on-therapeutic theophylline toxicity: Serum theophylline >60 μg/mL — life threatening events. Hypokalemia predominantly results as intracellular potassium shift with minimal total body potassium loss. Hemodialysis and CAVH/CVVH are not equivalent, and they are not mutually exclusive; CAVH/CVVT may be the only option in hypotensive patients until hemodialysis can be tolerated.

NSAID Acetylsalicyclic acid (ASA, Aspirin) ■ Metabolic: Respiratory alkalosis (hyperpnea/ tachynea), respiratory alkalosis/metabolic acidosis/aciduria, metabolic acidosis/respiratory acidosis/aciduria; anion gap metabolic acidosis; hypokalemia; hyperthermia. ■ Respiratory: Respiratory insufficiency/failure; acute lung injury/noncardiogenic pulmonary edema. ■ Neurologic: Agitation; slurred speech; altered mental status; hallucinations; encephalopathy; seizures; coma.	Signs and symptoms consistent with salicylate toxicity, serum ASA >30 mg/dL (2.17 mmol/L) after acute overdose: ■ Fluid resuscitation. *and* ■ Urine alkalinization: IV sodium bicarbonate 2 mmol/kg bolus followed by continuous infusion of sodium bicarbonate 150 mmol mixed in 1,000 mL D5W starting at 1.5 to 2.0 times maintenance rate, adjusted to maintain urinary pH 8.0 and arterial pH <7.55; assess clinical status/laboratory parameters (e.g., electrolytes, acid-base, urine pH) hourly; terminate when clear clinical-biochemical recovery and serial decline in serum ASA concentration toward therapeutic range. *and* ■ Potassium replacement/supplement. Respiratory insufficiency/failure: Adjust ventilator minute volume to maintain $Pco_2 \leq$ patient's preintubation Pco_2 and arrange for urgent hemodialysis. Pulmonary edema: Management same as acute lung injury/ARDS and arrange for urgent hemodialysis. Hyperthermia: External cooling.	Maximize GFR: IV NS target urine output 2–4 mL/kg/h; IV fluids should contain at least 50 g/L (5%) glucose, minimum 100 g/L (10%) glucose when hypoglycemia/CNS symptoms are evident. GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (see Box I.) followed by oral activated charcoal (1–2 g/kg) following serious overdose, otherwise oral activated charcoal; WBI (see Box II.) for large ingestion of modified release formulation; procedural removal of bezoar/concretion. Hemodialysis consideration: Salicylate >90 mg/dL (6.52 mmol/L), salicylism requiring ventilatory support, seizures, altered mental status, chronic salicylism, respiratory acidosis, severe acid-base disturbance, persistent acidemia or inability to establish an alkaline urine, renal/hepatic dysfunction, pulmonary edema, clinical deterioration or failure of improvement despite intensive supportive care, extremes of age especially with comorbidities.	ASA: Done nomogram not useful; carbonic anhydrase inhibitors (e.g., acetazolamide) contraindicated; delayed onset and progression of toxicity with enteric-coated/sustained-release tablets; nonacute/chronic intoxication masquerade as SIRS, acute abdomen, ACS/AMI, encephalopathy/encephalitis, alcohol intoxication/withdrawal, organic psychosis, sepsis, dementia or delirium, DKA. Urine alkalinization: Not a substitute for hemodialysis; success in patients treated early in the course of poisoning and not severely toxic/acidotic; contra-indication: severe ASA toxicity, renal/heart failure, cerebral/ pulmonary edema, arterial pH> 7.55; complication: hypokalemia, hypocalcemia, fluid/sodium overload, pulmonary edema, tetany. Hemodialysis and CAVH/CVVH are not equivalent, and they are not mutually exclusive; CAVH/CVVT may be the only option in hypotensive patients until hemodialysis can be tolerated.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
Other NSAID Ibuprofen ■ Metabolic acidosis, ARDS, renal failure, coma, seizures, GI bleeding, cholestasis, hepatotoxicity, thrombocytopenia, hypothermia, shock; meningoencephalitis (aseptic meningitis) with therapeutic dosing.	Supportive care.		
Mefenamic acid ■ Muscle twitching, tonic-clonic seizures, apnea, coma, cardiac arrest.	Supportive care.		
Phenylbutazone ■ GI: *Predominately* latent hepatotoxicity (12–24 h), and may be only manifestation of severe toxicity. ■ GU: Red urine (pyrazolone metabolite: rubazonic acid) may be observed.	Supportive care.	Adjunct hemoperfusion with uncoated amberlite XAD-4 resin in cases with a poor prognosis.	Phenylbutazone was withdrawn from United States market 1970s, still available from veterinary sources and other countries.

■ CNS: Progressive impairment of consciousness with coma and seizures. ■ Sudden respiratory arrest followed by cardiac arrest.			
Opioid General: Coma, miosis, respiratory depression, decreased GI motility. Dextromethorphan: Serotonin syndrome from MAOI interaction; long term use may result in bromide toxicity. Diphenoxylate: Recurrent respiratory/CNS depression. Fentanyl: Rapid IV administration may result in acute myoclonic truncal/chest wall rigidity impairing respiration. Heroin: Noncardiogenic pulmonary edema, cardiac conduction abnormalities/dysrhythmias; inhalation of heated heroin vapors (i.e., "chasing the dragon") associated with progressive spongiform leukoencephalopathy.	Respiratory depression/failure: IV naloxone 0.04–0.1 mg if opioid dependent, otherwise 2 mg; 10–20 mg may be required for high potency opioids (e.g., methadone, pentazocine, propoxyphene, diphenoxylate); repeat IV naloxone boluses may be required every 20–60 min. Therapeutic IV naloxone infusion: Multiply the effective naloxone bolus dose by 6.6, adding that quantity to 1,000 mL normal saline, infuse solution at 100 mL/h, titrated to maintain adequate spontaneous ventilation without precipitating opioid withdrawal, empirically continued for 12–24 h; carefully observed for 2–4 h for recurrent respiratory depression after discontinuing naloxone infusion; allow naloxone to abate in acute iatrogenic opioid withdrawal. Spongiform leukoencephalopathy: Supportive; coenzyme Q 30 mg 4x/d, vitamin E 2,000 mg every day, and vitamin C 2,000 mg every day has been advocated.		Naloxone: Goal is to reestablish adequate spontaneous ventilation; intralingual/endotracheal/intraosseous administration acceptable if no immediate IV access; IM/SC less desirable in urgent situation. Diphenoxylate: Formulated with atropine (Lomotil); decreased GI motility and difenoxine (metabolite) accumulation, a potent opioid with a long half-life. Heroin may be "cut" with amphetamine, cocaine ("speed ball") or scopolamine and naloxone therapy may "unmask" sympathomimetic or anticholinergic toxicity. Propoxyphene: Available alone or in combination with acetaminophen or aspirin. Complications include rhabdomyolysis, hyperkalemia, myoglobinuria, renal failure.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
Meperidine: Seizures from normeperidine (metabolite) accumulation (e.g., renal impairment); acute parkinsonism following contaminated analog MPPP use; fatal interaction with MAOI (serotonin syndrome). Methadone: Exceptionally prolonged duration of action (average half-life 25 h, may be 52 h during long-term therapy); association between high daily methadone dose (mean 397 ± 283 mg) and *torsades de pointes* (mean QTc 615 ± 77 msec). Propoxyphene: Rapidly progressive cardiac dysrhythmias, circulatory collapse, seizures, respiratory arrest. Tramadol: Seizures; serotonin syndrome.	Seizures: Current guidelines; adjunct naloxone therapy may be effective in propoxyphene, but not meperidine or tramadol seizures; reported immediately following naloxone administration for tramadol overdose. Serotonin syndrome: See Antidepressants.		

Pesticide Aluminum phosphide ■ GI: Retrosternal burning, epigastric discomfort; recurrent profuse vomiting; watery diarrhea; GI bleed; jaundice with abnormal liver function tests. ■ CV: Hypotension with clear mental status; shock (heart rate inappropriately slow for degree shock); myocardial injury; dysrhythmias; intraventricular conduction disturbances; global left ventriclar and interventricular septum hypokinesia with decreased ejection fraction; pericarditis (rare). ■ Respiratory: Tachypnea; ARDS. ■ Metabolic: Metabolic acidosis; hypomagnesemia; hyperkalemia.	Supportive care. IV hydrocortisone 400 mg every 4–6 h or IV dexamethasone 4 mg every 4 h, IV H_2 receptor antagonist (e.g., ranitidine), IV proton pump inhibitor (e.g., omeprazole) have been adovacated. Cardiac dysrhythmias or hypomagnesemia: IV magnesium 1–6 g over 30 min followed by infusion 0.5–2 g/h has been advocated.	Prevent secondary contamination and poisoning with appropriate precautionary measures. GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (see Box I.) with a solution of 1:5,000 potassium permanganate (remove and oxidize unabsorbed aluminum phosphide); nasal gastric 2% bicarbonate solution (minimize phosphine release).	A strong suspicion of aluminum phosphide poisoning when vomitus has typical rotten fish odor. Insufficient clinical evidence to mandate steroid and magnesium therapy. Toxicity can occur as a result of inhalation of phosphine gas released when phosphide contacts water.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
Anticoagulant (e.g., warfarin, superwarfarin) ■ Cutaneous bleeding, soft tissue ecchymosis; gingival bleeding; epistaxis; hematuria; menorrhagia; hemoptysis; GI, peritoneal, alveolar, intracranial hemorrhage.	Patients with or suspected major anticoagulant-related hemorrhage or INR >20 ■ IV prothrombin complex concentrate (PCC) 50 U/kg *or* IV fresh frozen plasma (FFP) 10–20 mL/kg or IV recombinant activated factor VII (rFVIIa) 15–90 μg/kg. *and* ■ IV vitamin K_1 10 mg (diluted with 5% dextrose, 0.9% sodium chloride, or 5% dextrose in 0.9% sodium chloride; administered at ≤1 mg/min; be prepare to treat anaphylaxis) *or* oral/nasogastric vitamin K_1 7 mg/kg/d divided every 6 h. Endpoint of vitamin K_1 therapy: Discontinue therapy at an arbitrary time and obtain serial INR/PT, restart vitamin K1 when INR/PT is elevated *or* monitor serum factor VII concentration when vitamin K_1 therapy is withheld, restart vitamin K_1 when a progressive decrease in factor VII levels to 30% of normal *or* serum brodifacoum concentration <10 ng/mL, *or* when serum vitamin K 2,3-epoxide concentration begins to fall.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Activated charcoal 1–2 g/kg.	PCC: Disseminated intravascular coagulation and uncompensated liver disease are contraindications to PCC; adverse drug events include thrombosis, disseminated intravascular coagulation, blood-borne pathogens transmission, allergic reactions. rFVIIa: Unlikelihood of blood-borne pathogens transmission, obviate volume constraints of FFP administration, reduces time for administration and achieving adequate hemostasis.

	Excessive INR with and without bleeding in patients on warfarin ■ INR <5.0: Lower dose *or* omit next warfarin dose. ■ INR 5.0–9.0: Discontinue warfarin for several doses, high risk (e.g., age, recent hemorrhage, alcoholism, hepatic or renal impairment, and NSAID use) omit next warfarin dose *and* administer oral vitamin K_1 1.0–2.5 mg *or* IV vitamin K_1 0.5–1.0 mg. ■ INR 9.0–20.0: Oral vitamin K_1 3.0–5.0 mg. ■ INR >20.0: IV vitamin K_1 10 mg and PCC or FFP or rFVIIa *and* repeat vitamin K_1 doses every 12 h as needed.		
Methyl bromide ■ Neurologic: Vomiting, headache, gait disturbance, vertigo, visual disturbance (premonitory stage); "Jerkiness," intentional tremors, action myoclonus, seizures, delirium, acute mania (cerebral irritation stage); hallucinations, apathy, amnesia, aphasia, incoordination (recovery stage, may last years).	Supportive care.	Remove all clothing and wash skin with soap and water to eliminate potential methyl bromide residues. Early hemodialysis associated with improving mortality.	Serum bromide concentration: ■ Poor surrogate for methyl bromide. ■ May confirm, but does not correlate with severity of exposure. ■ Significantly elevated concentrations may be seen as an elevated chloride level. Spectrophotometric method may be more useful in detecting methyl bromide in biological fluid matrix.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
■ Respiratory: Dyspnea; bronchitis; pulmonary edema; pneumonitis; respiratory failure. ■ GU: Proteinuria; hematuria; renal failure. ■ Liver: Jaundice; liver function test abnormalities. ■ Skin: Burns (underlie clothes and gloves where methyl bromide gas is trapped).			
N-3-Pyridylmethyl-N′-p-nitrophenylurea (PNU; Vacor Rat-Killer) ■ Nausea, vomiting, abdominal pain, perforation (corrosive effects); hypoglycemia followed by hyperglycemia and ketoacidosis accompanied by severe postural hypotension and	Known or suspected PNU exposure: IV or IM niacinamide (nicotinamide) 500 mg followed by 100–200 mg every 4 h for up to 48 h, increased to every 2 h if signs of toxicity develop, maximum total dose 3 g/d for adult (Peds: One-half of adult dose); when patient able to take oral medications 100 mg 3–5 times daily for 2 wk.	GI decontamination consideration (after patient stabilized, assessing GI tract integrity, and precautionary measures to minimize aspiration): Gastric lavage (see Box I.) in patients presenting soon after a serious ingestion followed by activated charcoal 1–2 g/kg.	Administer niacin as a substitute when niacinamide (nicotinamide) is unavailable: Vasodilatory effects may exacerbate hypotensive effects of PNU; causes and exacerbates glucose intolerance; less effective than niacinamide; niacinamide in capsule form may be found at nutritional supplement outlets.

sensorimotor peripheral and autonomic neuropathies.	Postural hypotension: Limited response to oral fludrocortisone 0.3 mg/d and elastic stockings.		Monitor serum glucose closely and treat hypoglycemia with glucose supplementation; management of subsequent hyperglycemia and ketoacidosis same as diabetes mellitus and diabetic ketoacidosis.
N,N-Diethyl-m-toluamide (diethyltoluamide, or DEET) ■ Neurologic: Anxiety; behavioral changes; tremors; lethargy; ataxia; confusion; seizures; coma. ■ Skin: Irritation, contact dermatitis, urticaria; skin necrosis. ■ Immunologic: Anaphylactic reactions with cutaneous application.	Supportive care. Seizures: IV BZD, progress to barbiturate.	Decontamination consideration: Remove all clothing and meticulously wash skin with soap and water.	
Organochlorine (e.g., dichlorodiphenyl trichloroethane [DDT] and related agents, hexachlorocyclohexanes, the cyclodienes [e.g., chlordane, heptachlor, endrin, aldrin, and dieldrin], and toxaphenes)	Seizures: IV BZD, progress to barbiturate, neuromuscular paralysis and general anesthesia; phenytoin not effective and may exacerbate seizures.	Decontamination consideration: ■ Precautionary measures to pevent secondary contamination; completely disrobe, remove all jewelry/accessories, meticulously wash entire body with soap and water including hair and fingernails; discard all wash water in a secure manner; place	Systemic toxicity by ingestion, dermal absorption, or inhalation. Chlorinated hydrocarbons are radiopaque, and directly related to the number of chlorine atoms per molecule.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
■ GI: Nausea, vomiting, and diarrhea especially if petroleum distillate additives/vehicles. ■ Respiratory: Aspiration resulting in tachypnea, respiratory distress; pulmonary edema; hypersensitivity pneumonitis following inhalation of organochlorine mixed with pyrethrins. ■ Neurologic: Psychomotor agitation; CNS depression; opisthotonos; slurred speech; muscle tremors; weakness; seizures with or without a prodrome and may be delayed following ingestion or dermal absorption. ■ CV: Cardiac dysrhythmias. Acute DDT exposures presents with tremors, nausea, vomiting, muscle weakness, and confusion, progressing to seizures.	Bronchospasm: Humidified oxygen and nebulized bronchodilators; parenteral adrenergic amines may potentiate myocardial irritability.	clothing and leather goods in a plastic bag labeled "bio-hazard" for disposal. ■ Chlordecone: Oral/nasgastric cholestyramine 4 g every 6 h.	

Organophosphate (cholinergic agents). ■ HEENT: Miosis; lacrimation; rhinorrhea, salivation. ■ Respiratory: Bronchial muscle spasm; pulmonary edema; respiratory failure. ■ CV: Hypertension/hypotension; dysrhythmias. ■ GI: Diarrhea, vomiting; abdominal pain; pancreatitis. ■ Neurologic: Seizures; coma; delirium; Cheynes-Stokes respiration. ■ Musculoskeletal: Fasciculations; dystonias; choreoathetoid movements; paralysis. ■ Skin: Diaphoresis. ■ Metabolic: Hyperglycemia/ hypoglycemia. ■ Intermediate syndrome: Associated with severe organophosphate toxicity; conscious patient without fasciculation or other cholinergic signs (apparent recovery from acute cholinergic crisis) developing marked	Seizures: IV atropine and BZD (e.g., diazepam 0.2–0.4 mg/kg or lorazepam 0.05 mg/kg) *or* phenobarbital 18 mg/kg. Cholinergic crisis: ■ Respiratory support; intubate/ventilate. *and* ■ IV atropine 1–4 mg (Peds: 0.05 mg/kg), double the dose every 5–10 min as needed until pulmonary secretions are controlled (tachycardia is *not* a contraindication to atropine); once stablized start atropine infusion (10%–20% of total dose for stablization per hour) and then titrated back the infusion; restart atropine at the first signs of cholinergic excess. *and* ■ IV pralidoxime 30 mg/kg over 30 min followed by a continuous infusion 8–10 mg/kg/h with empiric dose adjustment based on clinical response, continue until atropine has not been required for 24–48 h and patient extubated; restart pralidoxime if recurrent signs/symptoms. Agitation: Review atropine dosing; IV BZD Review respiratory function frequently after atropine/pralidoxime/extubation: Intubate/ventilate if tidal volume <5 mL/kg, vital capacity <15 mL/kg, apneic events, or Pao_2 <60 mm Hg on Fio_2 >60%.	Decontamination consideration: Precautionary measures to prevent secondary contamination; completely disrobe, remove all jewelry/accessories, meticulously wash entire body with soap and water including hair and fingernails; discard all wash water in a secure fashion; place clothing and leather goods in a plastic bag labeled "bio-hazard" for disposal.	Cholinergic poisoning is a *clinical diagnosis* base on a history of exposure, presence of a cholinergic toxidrome, and clinical improvement after appropriate antidotal therapy; plasma (pseudocholinesterase) and red blood cell cholinesterase activity to confirm clinical diagnosis. Atropine has no effect on muscle weakness or paralysis and will not affect acetylcholinesterase regeneration rate; pralidoxime regenerates acetylcholinesterase and is most effective when initiated early; respiratory muscles are the *last* to recover. Succinylcholine use may result in prolonged (hours to days) paralysis. Carbamates and other reversible cholinesterase inhibitors: Signs/ symptoms should resolve within 24 h; atropine *and* pralidoxime is use to treat acutely ill patients with carbamate toxicity unless carbaryl (Sevin) is known to be involved, then just atropine and supportive care. Latent onset toxicity following fenthion, parathion, dichlofenthion, leptophos poisoning; recurrence of cholinergic crises (release of fat soluble organophosphorus from

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
weakness of neck flexion and varying degree of motor cranial nerve, proximal limb muscle (e.g., shoulder abduction, hip flexion), and respiratory muscle weakness 24–96 h after poisoning, lasting 5–18 days.	Intermediate syndrome: Regularly assess flexor neck strength by asking patient to lift their head off the bed and hold it while pressure is applied to their forehead; any weakness suggests at risk of developing respiratory failure; check respiratory function at least every 4 h, and intubate/ventilate if tidal volume <5 mL/kg, vital capacity <15 mL/kg, or Pao_2 <60 mm Hg on FIo_2 >60%.		fat stores) days to weeks after ingestion will need retreatment with atropine and pralidoxime.
Pentachlorophenol ■ Tachycardia, tachypnea; sweating; altered consciousness; hyperthermia; seizures; pulmonary edema; intravascular hemolysis; pancreatitis; jaundice; acute renal failure.	Supportive care and vigorous management of hyperthermia. Known or symptomatic pentachlorophenol poisoning: Urine alkalinization with IV sodium bicarbonate 2 mmol/kg bolus followed by continuous sodium bicarbonate infusion (150 mmol mixed in 1,000 mL D5W) starting at 1.5 to 2.0 times maintenance rate, adjusted to maintain urinary pH 8.0 and arterial pH <7.55; reassess clinical status/laboratory parameters	Maximize GFR: IV NS target urine output 2–4 mL/kg/h. Decontamination consideration: Remove all clothing and wash skin with soap and water; gastric lavage (after patient stabilized and precautionary measures to minimize aspiration) in acutely sick patients (see Box I.); oral/nasgastric cholestyramine 4 g every 6 h.	There is no antidote for pentachlorophenol poisoning and insufficient clinical evidence to mandate routine urine alkalinization or cholestyramine use.

	(e.g., electrolytes, acid-base, urine pH) hourly; terminate when clear clinical-biochemical recovery.	Exchange transfusion used successfully in infants with severe toxicity.	
Pyrethroid ■ Neurologic: Paresthesias; fasciculations; coma; seizures. ■ Acute hypersensitivity reactions (e.g., anaphylaxis). ■ Respiratory: Hypersensitivity pneumonitis following inhalation of organochlorine mixed with pyrethrins.	Seizures: See Organochlorine. Bronchospasm: See Organochlorine.		Systemic toxicity by ingestion, dermal absorption, or inhalation.
Sodium monofluoroacetate (compound 1080) and sodium fluoroacetamide (compound 1081) ■ GI: Nausea, vomiting; abdominal pain. ■ Neurologic: Anxiety; verbosity; irritability, agitation, hyperactivity; muscle spasm; stupor; seizures; coma. ■ CV: Tachycardia; hypotension; ventricular dysrhythmias. ■ Respiratory: Respiratory distress. ■ GU: Acute renal failure. ■ Metabolic: Metabolic acidosis; hypocalcemia.	Known, suspected, or symptomatic monofluoroacetate exposure: Oral ethanol (96%) 40–60 mL, followed by IV ethanol (10% solution in D5W) 10 mL/kg over 1 h and 1.5 mL/kg/h for the next 6–8 h. Seizures: IV BZD, progress to barbiturates.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (see Box I.) in acutely sick patients; activated charcoal 1–2 g/kg.	

(continued)

TABLE 102-1 **Continued**

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
Strychnine ■ Diffuse/severe muscle contractions and spasms; facial muscle spasms (i.e., risus sardonicus, "sardonic smile"), trismus; opisthotonos; abdominal muscle contractions; tonic movements of the extremities; extensor muscles more affected than flexor muscles; contractions triggered or exacerbated by auditory, tactile, or visual stimuli; respiratory failure; metabolic acidosis; rhabdomyolysis; hyperthermia.	Symptomatic patients ■ Respiratory support; intubate/ventilate. ■ IV propofol 1–2.5 mg/kg then 3–12 mg/kg/h (Peds: 2.5–3.5 mg/kg then 7.5–15 mg/kg/h) *or* IV diazepam 0.1–0.5 mg/kg; IV pentobarbital 2–4 mg/kg (adult 100–200 mg), general anesthesia and neuromuscular blockade with nondepolarizing agent as necessary.	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (see Box I.) in acutely sick patients; activated charcoal 1–2 g/kg.	
Sedative hypnotic General: Ataxia; nystagmus; slurred speech; CNS depression (e.g., lethargy; coma; respiratory/cardiovascular/thermoregulatory centers); apnea; hypotension; myocardial depression; hypothermia; cardiovascular collapse; (non)cardiogenic pulmonary edema/ARDS.	Supportive care.		

Barbituate ■ Atonic gut, ileus, may progress to bowel necrosis; tense, clean, bullous skin lesions over pressure points surrounded by erythema, bullae fluid has detectable amounts of barbiturate, not pathognomonic for barbiturate poisoning.		Activated charcoal 1–2 g/kg followed by hourly, every 2 h, *or* every 4 h at a dose equivalent to 12.5 g/h (Peds: 10–25 g) for 12–24 h; not in patients with decreased bowel sounds/ileus. Urine alkalinization (long-acting barbiturates e.g., phenobarbital) enhance elimination: IV sodium bicarbonate 1–2 mmol/kg bolus followed by continuous sodium bicarbonate infusion (150 mmol in 1,000 mL D5W) starting at 1.5 to 2.0 times maintenance, adjusted to maintain urinary pH >7.5; monitor urine pH hourly; potassium supplement as needed. Extracoporeal support consideration: Cardiovascular instability unresponsive to conservative measures; phenobarbital: hemoperfusion clearance 100–300 mL/min, hemodialysis clearance 60–75 mL/min; hemodialysis especially effective with activated charcoal treatment; repeat hemodialysis/hemoperfusion if serum drug levels rebound.	Barbituates: Suppress brain activity and isoelectric EEG not indicator of poor prognosis; prolonged coma; rhabdomyolysis.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
Benzodiazepine ■ Slurred speech; ataxia; nystagmus; lethargy, stupor, coma; loss of deep tendon reflexes; apnea (massive overdose); rare cases of cardiac arrest, ARDS, pulmonary edema.	Inadequate spontaneous ventilation or airway protection: Intubation/ventilation. Flumazenil diagnostic aid in lethargy, stupor, coma: IV flumazenil 0.1–0.2 mg followed by 0.1 to 0.2 mg every minute (max 2 mg) until awake, failure to respond makes BZD unlikely cause.		Flumazenil: Half-life 1–2 h; reverses sedative/anxiolytic effects, inconsistent in reversing BZD-induced respiratory depression; precipitate abrupt BZD withdrawal syndrome; unmask epileptogenic effects of polypharmacy overdoses.
Nonbenzodiazepine nonbarbiturate sedative-hypnotic Baclofen ■ Oral: Latent toxicity 2–6 h; Unreactive pupils; CNS (mimic brainstem lesion)/respiratory/CV depression; autonomic instability; hypotonia/flaccidity, areflexia; myoclonic jerking; seizures; coma; hallucinations; hypothermia; cardiac conduction abnormalities.	Prolonged respiratory support (e.g., 3–7 d).		Overdose >200 mg may be predictive of developing delirium, coma, seizures, prolonged hospital admission.

■ Intrathecal: Same as Oral except latent period.	Respiratory support; empty pump reservoir and record amount; may consider IV/IM physostigmine 0.02 mg/kg at ≤0.5 mg/min (adult 0.5–1.0 mg at ≤1 mg/min) may repeat every 5–10 min (max 2 mg) to desired response. Reduce CSF drug burden: Withdraw 30–40 mL CSF by catheter access port/lumbar puncture and replace equal volume NS (instructions on withdrawing CSF through the catheter access port contact Medtronic Inc Technical Services 800-707-0933); closely monitor for symptom recurrence; notify patient's intrathecal baclofen (ITB) therapy physician.		Physostigmine: Insufficient evidence to mandate routine use. Contacts: Medtronic, Inc., Technical Services and Physician Consultants (intrathecal device manufacturer) 800-707-0933; Novartis Pharma AG, Technical Services (drug manufacturer) 888-669-6682.
Carisoprodol ■ Similar to meprobamate.	Supportive care.		Carisoprodol is metabolized to meprobamate.
Chloral hydrate ■ GI irritation (e.g., gastritis, perforation); CNS depression; miosis; hypothermia; hypotension; respiratory depression; paradoxical CNS excitation (pediatric); myocardial depression; ventricular dysrhythmia; pulmonary edema; delayed dermal exfoliation; renal tubular necrosis; hepatotoxicity.	Ventricular dysrhythmia: IV beta-blocker (e.g., propanolol 1 mg).	Hemodialysis consideration: Prolonged coma, persistent hypotension/dysrhythmias, cardiovascular instability; hypotension and poor clinical condition are not contraindications for hemodialysis; repeat session(s) for rebound in serum levels.	Chloral hydrate is radio-opaque.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
Ethchlorvynol ■ CNS depression; prolonged coma (>a week); hypothermia; respiratory depression; hypotension; bradycardia; seizures; aromatic pungent odor similar to a new plastic shower curtain on victim's breath.	Supportive care.	Hemoperfusion consideration: Prolonged coma; repeat session(s) for rebound in serum levels.	Ethclorvynol: Isoelectric EEG during coma.
Gamma hydroxybutyrate (GHB), 1,4-butanediol, gamma butyrolactone ■ Coma; respiratory depression; hypothermia; bradycardia; hypotension; seizures.	Supportive care; respiratory support; may be consider IV physostigmine 0.02 mg/kg at ≤0.5 mg/min (adult 0.5–1.0 mg at ≤1 mg/min) may repeat every 5–10 min (max 2 mg) to desired response.		GHB: Low quality of evidence for physostigmine use, no evidence physostigmine improves outcome, insufficient evidence to mandate routine use.
Glutethimide ■ Thick/tenacious bronchial secretions; fluctuating level of consciousness; seizures; profound and prolonged	Supportive care.	GI decontamination consideration: (after patient stabilized and precautionary measures to minimize aspiration): Activated charcoal 1-2 g/kg followed by hourly, every 2 h,	

coma; hypotension; hypothermia; persistent acidosis; anticholinergic effects.		*or* every 4 h at a dose equivalent to 12.5 g/h (Peds: 10-25 g) for 12-24 h; not in patients with decreased bowel sounds/ileus; late activated charcoal administration may be beneficial.	
Meprobamate ■ CNS and respiratory depression; hypotension; dysrhythmias; bezoar formation.	Supportive care.	Activated charcoal 1–2 g/kg followed by hourly, every 2 h, or every 4 h at a dose equivalent to 12.5 g/h (Peds: 10–25 g) for 12–24 h; not in patients with decreased bowel sounds/ileus. Hemodialysis consideration: Serum meprobamate >20 mg/dL. Gastroscopy consideration: Suspected bezoar (e.g., relapsing conscious level, prolonged/erratic drug absorption, persistently elevated serum drug levels); gastrotomy as indicated.	Meprobamate is a metabolite of carisoprodol. Potential for gastric concretion formation following large ingestions.
Sympathomietic Amphetamine ■ Same as cocaine; in particular anxious, (paranoid) psychosis, volatile, aggressive, life-threatening agitation, visual/tactile hallucinations.	Agitation/delirium/hallucinations: IV diazepam 10 mg (or equivalent) rapidly titrated to effect (cumulative dose may be >100 mg). Seizures, hyperthermia, hypertension, hypotension: See Cocaine.		Amphetamine complications: See Cocaine. PMA: Tachycardia, hyperthermia, coma, seizures, dysrhythmias, IVCD, hypoglycemia, hyperkalemia.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
Cocaine ■ Sympathetic hyperactivity with CNS excitation and peripheral sympathetic stimulation (e.g., mydriasis, hypertension, tachycardia, tachypnea, pyrexia, diaphoresis, headache, anxious, psychomotor agitation, confusion, psychosis, tremor, hyperreflexia, seizures, visual/tactile hallucinations); preterminal events: bradycardia, hypotension, cardiovascular collapse. ■ Metabolic: Metabolic acidosis; hypokalemia, hyperglycemia.	Anxiety/psychomotor agitation: IV diazepam 5–10 mg (or equivalent) rapidly titrated to effect. Seizures: IV BZD, propofol or barbiturate. Sinus tachycardia: IV diazepam 5–10 mg (or equivalent) titrated to effect. SVT: Cardioversion if hemodynamically unstable; IV diazepam 5–10 mg (or equivalent); IV diltiazem 20 mg or IV verapamil 5–10 mg; IV adenosine 6 mg or 12 mg. Ventricular dysrhythmias: Defibrillate if hemodynamically unstable; IV sodium bicarbonate 1–2 mmol/kg; IV lidocaine 1.5 mg/kg bolus followed by 2 mg/min infusion; IV diazepam 5–10 mg (or equivalent). ACS: Current guidelines, IV diazepam 5–10 mg (or equivalent). Hypertension: Rapid control of psychomotor agitation with IV diazepam or equivalent; IV phentolamine 1 mg, repeat in 5 min; IV nitroglycerin or nitroprusside infusion titrated to effect.		Cocaine complications (acute, hours, days after use): ACS, AMI, IVCD, dysrhythmias; CVA, SAH, intracerebral hemorrhage; organ ischemia/infarction, aortic dissection, vasculitis; acute lung injury/pulmonary edema/ARDS, pneumonitis ("crack lung"), pneumothorax, pneumomediastinum; rhabdomyolysis; infections (e.g., endocarditis, hepatitis, pneumonia, epidural abscess); placentae abruptio; BADS: decrease level of consciousness, profound lethargy, similar to a prolonged postictal period, normal thought content, normal sleep postures, can be aroused to orientation.

	Hyperthermia: Rapid control of psychomotor agitation with IV diazepam or equivalent; external cooling. Pulmonary edema: IV nitroglycerin infusion titrated to blood pressure; IV furosemide 20–40 mg; IV morphine sulfate 2 mg every 5 min titrated to pain relief or respiratory status. Hypotension: IV norepinephrine or epinephrine (avoid dopamine).		
Systemic asphyxiant Carbon monoxide (CO) ■ Headache, dizziness; nausea and vomiting; progressive impairment of consciousness; hyperventilation; hypotension; increased muscle tone, hyper-reflexia, clonus, Babinski positive; skin blistering over pressure areas; metabolic acidosis with normal oxygen tension and reduced oxygen saturation; delayed neuropsychiatric sequelae.	Known or suspected CO toxicity, severe and unexplained anion gap metabolic acidosis: ■ Ventilate and oxygenate patient with 100% oxygen. ■ HBO considerations: Unconscious any time after CO exposure, neurological or psychiatric features (e.g., coma, seizures, focal deficits, GCS < 15), pregnancy, cardiac ischemia, carboxyhemoglobin (COHgb) >20%.		Pulse oximetry reading over estimates oxyhemoglobin. COHgb: Determination of venous blood sample by CO-oximeter; high levels confirm CO exposure; specific levels not necessarily predictive of symptoms or outcome; COHgb can return to normal or be zero if oxygen treatment before obtaining blood test.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
Cyanogens (e.g., cyanide (CN) ■ Anxiety; dizziness; palpitations; headache; weakness; pulmonary edema; respiratory failure; dysrythmias; cardiovascular collapse; CNS dysfunction; loss of consciousness; seizures; coma; metabolic acidosis. Nitroprusside-induced CN toxicity: Tachycardia, need for escalating nitroprusside doses to maintain blood pressure control (tachyphylaxis), metabolic acidosis with increase in serum lactate concentration, a narrowing of difference in oxygen content of arterial and venous blood, and acute unexplained CNS dysfunction.	Known or suspected CN toxicity (e.g., occupation, fire in an enclosed space), severe and unexplainable anion gap metabolic acidosis: ■ Ventilate and oxygenate patient with 100% oxygen. ■ IV dicobalt edetate 300 mg (Peds: 10 mg/kg) over 1–5 min *if* certain of the diagnosis particularly when patient is unconscious with deteriorating vital signs; repeat 1–2 dose base on clinical response; adverse events include hypotension, cardiac dysrhythmias, angioedema. *or* ■ IV hydroxocobalamin 5 g over 15–30 min, repeat 1–2 doses base on clinical response; transient pink discoloration of mucous membranes, skin, urine; may interfere with colorimetric determinations of serum iron, bilirubin, creatinine concentration. *or* ■ Cyanide antidote kit: Amyl nitrite (broken in gauze and held close to the nose and	GI decontamination consideration (after patient stabilized and precautionary measures to minimize aspiration): Gastric lavage (see Box I.) soon after ingestion followed by activated charcoal 1–2 g/kg. HBO considerations: CN toxicity complicated by coincidental carbon monoxide poisoning.	CN toxicity is a *clinical diagnosis*; plasma lactate ≥72 mg/dL (8 mmol/L) sensitive surrogate for whole blood CN ≥1.0 μg/mL (39 μmol/L) and significant toxicity; death ≥3.0 μg/mL (117 μmol/L); whole blood CN concentration to confirm clinical diagnosis. An abnormal percent saturation gap (difference between percent oxyhemoglobin reported by cooximeter and percent saturation calculated by blood gas analysis) does not suggest cyanide poisoning. Cyanogen exposure: Thermal decomposition of polyurethane foams in furniture, contributor to mortality in smoke inhalation; latent onset (> 12 h) of toxicity following acetonitrile (e.g., artificial nail removers) ingestion; prolonged or excessive

	mouth of spontaneously breathing patients, or can be placed into the face mask lip or inside the resuscitation bag) should be inhaled for 30 seconds of each min with a fresh pearl used every 3–4 min *and* IV sodium nitrite 300 mg (10 mL of a 3% solution) over 5–20 min [Peds: Based on hemoglobin (Hgb) concentration; See Caveat] *and* IV sodium thiosulfate 12.5 g (50 mL of a 25% solution) [Peds: 0.41 mg/kg (1.65 mL of 25% solution/kg), max 12.5 g (50 mL)] over 10 min; repeat 1–2 doses of sodium nitrite and thiosulfate base on clinical response. *or* ■ IV 4-dimethylaminophenol (4-DMAP) 3–5 mg/kg; precise extent of induced methemoglobinemia may not be predictable. When diagnosis is uncertain and patient is conscious, administer IV sodium thiosulfate Preventive nitroprusside toxicity: Add 1 g (10 mL of 10%) sodium thiosulfate to each 100 mg bag of sodium nitroprusside (i.e., 10:1 ratio).		therapeutic use of nitroprusside; ingestion of the cyanogenic glycoside amygdalin (vitamin B_{17}) found in kernels of fruits (e.g., almonds, apples, apricots, cherries, peaches, plums). *Pediatric IV sodium nitrite dosing:* Hgb (g/dL) — 3% Sodium nitrite (mL/kg) 7.0 — 0.19 8.0 — 0.22 9.0 — 0.25 10.0 — 0.27 11.0 — 0.30 12.0 — 0.33 13.0 — 0.36 14.0 — 0.39

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
			Excessive methemoglobinemia resulting from nitrite or 4-DMAP: IV methylene blue 1 mg/kg (onset of action ≤30 min); repeat doses based on clinical response.
Hydrogen sulfide (HS) ■ Altered mental status; respiratory distress; pulmonary edema; cyanosis; seizures; coma; delayed neuropsychiatric sequelae; blackening of copper and silver coins in patient's pocket or darkening of jewelry.	Known or suspected HS toxicity (e.g., rapidly loses consciousness "knockdown," rotten eggs odor, rescue from sewer or manure pit, multiple victims with sudden death syndrome, cardiac arrest in previously healthy worker at work site), severe and unexplainable anion gap metabolic acidosis: ■ Ventilate and oxygenate patient with 100% oxygen. ■ IV sodium nitrite: See Cyanogens, Cyanide antidote kit, sodium nitrite component. ■ Consider HBO.		

Withdrawal syndrome Baclofen ■ Oral: Similar to ethanol (sedative hypnotic) withdrawal. ■ Intrathecal: Latent onset 1–3 d; tachycardia, hypotension/labile blood pressure, hyperthermia, altered/depressed consciousness, hallucinations, muscular spasticity/rigidity, seizures, priapism.	Oral: IV BZD and titrate to desired effects, administer oral/enteral baclofen (patient's prescribed dosing before withdrawal). Intrathecal: Administer baclofen (oral or enteral) ≥120 mg/d in 6–8 divided doses (safety not established <12 y of age) early in clinical course; restore intrathecal baclofen (ITB) therapy through programmed bolus through catheter access port, by lumbar puncture, or through externalized intrathecal catheter; IV BZD infusion titrated to effect until ITB therapy is restored. Consult physician experienced in ITB management; interrogate pump status using manufacturer's programming device, perform biplane or CT imaging of pump/catheter system to identify problems (e.g., catheter leak, break, kink, dislodgement, etc.); depending on results, experienced physician should empty pump reservoir, refill with baclofen solution at proper concentration, and expeditiously perform system trouble-shooting to determine cause of ITB therapy interruption.		Baclofen: Muscular rigidity may progress to fatal rhabdomyolysis; oral dosing not reliable as sole treatment.

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
Gamma hydroxybutyrate (GHB), 1,4-butanediol, gamma butyrolactone ■ Withdrawal syndrome may progresses over 2 to 3 d; insomnia, tremor, vomiting, tachycardia, hypertension, tremor, diaphoresis, auditory/visual hallucinations, anxiety, confusion, disorientation, delirium, agitation, rapid fluctuations in sensorium, seizures.	IV BZD titrated to sedation, normalization of vital signs and sensorium. Severe withdrawal (delirium or autonomic instability) or high-dose benzodiazepine (e.g., cumulative lorazepam dose 0.4–1 mg/kg during a 6 h period) does not control agitation and tachycardia: IV pentobarbital 1–2 mg/kg every 30 to 60 min titrated sedation, normalization of vital signs and sensorium.		Pentobarbital may be more effective than benzodiazepines at controlling delirium in patients with abnormal vital signs, paranoid delusions, and hallucinations; premature pentobarbital tapering may result in recrudescence of delirium.
Opioid ■ Mydriasis, lacrimation, rhinorrhea, diaphoresis, yawning, piloerection, anxiety, restlessness; tachycardia, hypertension, myalgias, vomiting, diarrhea, anorexia, abdominal pain, dehydration; intense drug craving; not life-threatening (i.e., do not have altered mental status,	Clinical opioid withdrawal: IM methadone 10 mg, repeat in 1 h if no significant relief or oral clonidine 0.1–0.2 mg every 4–6 h × 5–10 d and slowly tapered by 0.2 mg/d.		IM methadone 10–20 mg will block most physiologic manifestations of withdrawal, 20–40 mg daily or divided every 12 h may be required to avoid psychologic withdrawal; after acute medical illness is stabilized heroin-dependent patients may be tapered with methadone over 1 wk; methadone-dependent patients

hyperthermia, seizures) except neonatal withdrawal and may involve seizures.			require ≥4 wk of gradually decreasing dosages. Clonidine: Hypotension especially with first dose; tachyphylaxis to antiwithdrawal effects may develop by 10–14 d. Complications: Dehydration, electrolyte disturbances, hyperthermia, rhabdomyolysis, seizures, aspiration); withdrawal treatment (e.g., CNS/respiratory depression, aspiration); underlying illness (e.g., infection, nutritional deficiencies, trauma).
Sedative-hypnotics (e.g., ethanol, benzodiazepine, barbiturate, non-benzodiazepine non-barbiturate sedative-hypnotic): ■ Tremors, vomiting, anorexia, anxiety, and insomnia, seizures (status epilepticus rare), delirium tremens (i.e., altered sensorium with pathologic autonomic and CNS hyperactivity e.g., tachycardia, hypertension, hyperpyrexia,	Determine need for sedation using CIWA scale (a numbered grading system based on mental status e.g., reported anxiety, hallucinations, disorientation); goal is to control agitation: IV diazepam every 5–10 min until patient quietly sleeping-yet easily awaken, start with 5 mg (2.5 mg/min), if not effective repeat dose, if second dose not effective administer 10 mg for the third and fourth doses, if not effective administer 20 mg for the fifth and subsequent doses until sedation is achieved, administer 5–20 mg every hour as needed to maintain light somnolence, may require >1 g in 24 h or IV lorazepam 1–4 mg every 5–15 min or IM		Sedative-hypnotics: Anticipate/recognize early withdrawal to allow timely treatment and prevent serious manifestations (e.g., seizures, hyperthermia, delirium); long-acting BZD with active metabolites (e.g., diazepam, chlordiazepoxide) offer prolonged therapeutic effect without need for frequent dosing; risk of respiratory depression with barbituates; phenothiazines (e.g., prochlorperazine, chlorpromazine) and butyrophenones (e.g.,

(continued)

TABLE 102-1 Continued

Agent target organ systemic effect	Action alert critical laboratory value clinical intervention	Adjunct therapy extracorporeal support	Caveat complication
diaphoresis, mydriasis, disorientation, global confusion, hallucinations, delusions, mumbling speech, psychomotor agitation).	lorazepam, 1–40 mg every 30–60 min until calm, then every hour as needed to maintain light somnolence. If unresponsive to BZD, IV propofol 1–2.5 mg/kg stat then 3–12 mg/kg/h or pentobarbital 1–2 mg/kg every 30–60 min. Neuroleptic agents may be considered *in conjunction with BZD* when agitation, perceptual disturbances, or disturbed thinking not adequately controlled; IV/IM haloperidol 0.5–5 mg every 30–60 min or oral haloperidol 0.5–5 mg every 4 h as needed for severe agitation.		haloperidol) lower seizure threshold, induce hypotension, impair thermoregulation; taper drug dose over 2–4 wk by 10–20% every 3 days.

ACS, acute coronary syndrome; AMI, acute myocardial infarction; APL, acute promyelocytic leukemia; ARDS, adult respiratory distress syndrome; AST/ALT, aspartate aminotransferase or alanine aminotransferase; BADS, biogenic amines depletion syndrome; BAL, dimercaprol, 2,3-dimercapto-1-propanol, British anti-Lewisite; BZD, benzodiazepine; C, celsius; CaEDTA, calcium disodium edetate; CAVH, continuous arteriovenous hemodiafiltration; CIWA, Clinical Institute Withdrawal Assessment; CNS, central nervous system; CPR, cardiopulmonary resuscitation; Cr, creatinine; CT, computed tomography; CV, cardiovascular; CVA, cerebrovascular accident; CVVH, continuous venousvenous hemodiafiltration; d, day; DMSA, 2,3-dimercaptosuccinic acid; D5W, dextrose 5% water; DKA, diabetic ketoacidosis; ECG, electrocardiogram; EEG, electroencephalogram; FHF, fulminant hepatic failure; GI, gastrointestinal; GFR, glomerular filtration rate; GU, genitourinary; h, hours; HBO, hyperbaric oxygen; ICH, intracranial hemorrhage; ICU, intensive care unit; IM, intramuscular; IVCD, intraventricular conduction delay; INR, international normalized ratio; IV, intravenous; max, maximum; mo, months; 4MP, 4 methylpyrazole; MPPP, methyl-phenyl-propionoxypiperidine; msec, milliseconds; NAC, *N*-acetylcysteine; NS, normal saline; NSAID, nonsteroidal antiinflammatory drugs; OLT, orthotopic liver transplant; Peds, Pediatrics; PEG, polyethylene glycol (solution); PMA, paramethoxyamphetamine; PT, prothrombin time; QTc, corrected QT interval; RaVR, terminal R wave in lead aVR; R/SaVR, R-wave/S-wave ratio in lead aVR; SAH, subarachnoid hemorrhage; SC, subcutaneous; SIADH, syndrome of inappropriate anti-diuretic hormone; SIRS, systemic inflammatory response syndrome; SVR, systemic vascular resistance; WBI, whole bowel irrigation; wks, weeks; yr, years.

Box I. Gastric lavage.

Endotracheal or nasotracheal intubation should precede gastric lavage in the comatose patient; place oral airway between teeth; place patient in left lateral/head down position (20 degree tilt); measure and mark length of tube (mouth to stomach) with rounded end that is sufficiently firm to be passed into the stomach through the mouth, yet flexible enough not to cause mucosal damage (adult: at least 36–40 French [external diameter12–13.3 mm], Peds: at least 24–28 French gauge [external diameter 7.8–9.3 mm]); lubricate tube with a hydroxyethylcellulose jelly and pass the tube without excessive force; check tube placement either by air insufflation while listening over stomach and/or by aspiration with pH testing of the aspirate; lavage is carried out using 200–300 mL aliquots of warm fluid (e.g., normal saline, tap water), Peds: warm normal saline 10 mL/kg; volume of lavage fluid returned should approximate amount administered; continue lavage until recovered lavage solution is clear of particulate matter.

A negative or poor lavage return does not rule out a significant ingestion.

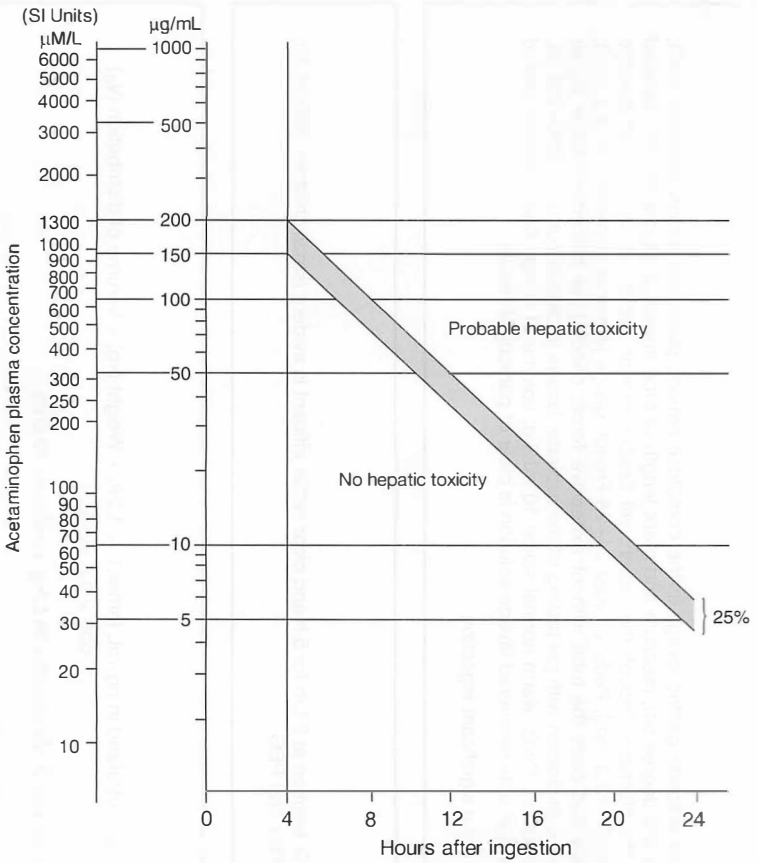
Box II. Whole bowel irrigation.

Insert nasogastric/oral tube and administer PEG solution at 2 L/h for 5 h and clear rectal effluent is evident (small children: 500 mL/h); doubtful patients would be cooperative or tolerate oral PEG.

Box III. Digoxin antibody dosing calculator.

$$\text{Number of vials} = \frac{\text{Digoxin body burden to be neutralized in ng/mL (nmol/L} \times 1.28) \times \text{Weight (kg)} \times \text{Volume of distribution } (V_d)}{1{,}000 \times 0.6 \text{ mg/vial}}$$

V_d: Adults 8 L/kg, children 2–10 years 13 L/kg, infants 2–24 months 16 L/kg, neonates 10 L/kg



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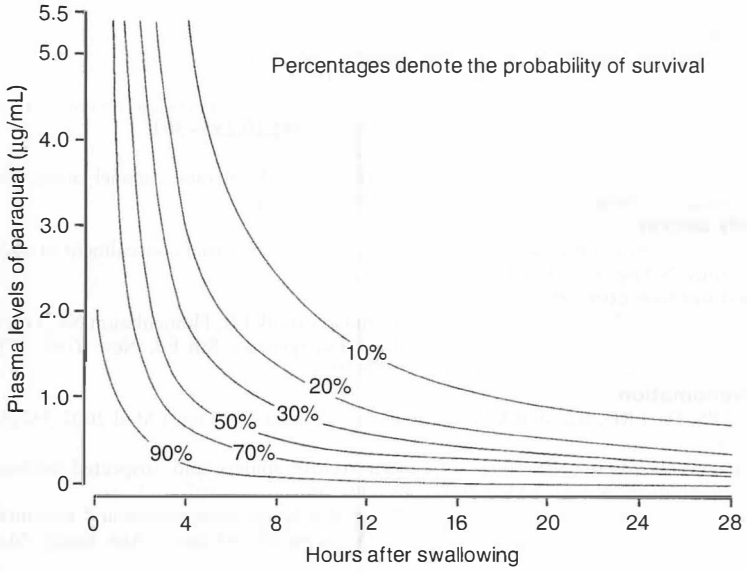

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Surgical Problems in the Intensive Care Unit

X

EPISTAXIS

103

Sewit Amde

I. GENERAL PRINCIPLES

A. Epistaxis is a common clinical problem that is usually mild and self-limited. However, epistaxis can become a severe and life-threatening emergency.

B. Understanding the blood supply anatomy to the nose is essential.

1. The nose, like the rest of the face, has an abundant blood supply. The arterial supply to the nose may be principally divided into:

a. Branches from the internal carotid, namely the branches of the anterior and posterior ethmoid arteries from the ophthalmic artery

b. Branches from the external carotid, namely the sphenopalatine, greater palatine, superior labial, and angular arteries.

2. Internally, the lateral nasal wall is supplied by the sphenopalatine artery posteroinferiorly and by the anterior and posterior ethmoid arteries superiorly.

3. The nasal septum also derives its blood supply from the sphenopalatine and the anterior and posterior ethmoid arteries with the added contribution of the superior labial artery (anteriorly) and the greater palatine artery (posteriorly).

4. The Kiesselbach plexus represents a region in the anteroinferior third of the nasal septum, where all three of the primary sources of perfusion to the internal nose converge.

5. Anterior bleeding is most common and usually originates from Kisselbach's plexus.
6. Posterior bleeding usually originates from the sphenopalatine artery.

II. ETIOLOGY

A. Direct trauma to nasal mucosa is the most common cause of epistaxis.
1. Digital trauma (nose picking)
2. Nasogastric and feeding tube placement
3. Nasotracheal intubation

B. Primary and secondary coagulopathies are important considerations.
1. Nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulants
2. Von Willebrand disease
3. Hemophilia
4. Leukemia
5. Liver disease
6. Idiopathic thrombocytopenic purpura

C. Other factors that may increase risk of epistaxis:
1. Hypertension
2. Deviated septum or bony deformity
3. Rhinitis and upper respiratory infections
4. Dry air/unhumidified oxygen (dries mucosa)
5. Overuse of nasal decongestants and cocaine use desiccate mucosa
6. Nasal mass
7. Posterior bleeds are more common in elderly

III. DIAGNOSIS

A. A thorough history and examination of nasal cavity with speculum/rigid scope, suction, and adequate lighting should be performed.
1. Anterior versus posterior bleed should be established for appropriate management.
2. Imaging is rarely indicated, unless tumor is suspected.

IV. TREATMENT

A. Most epistaxis is self-limited.
1. Usually ceases with digital pressure for 10 minutes
2. If maneuver fails, topical vasoconstrictors, cautery, and nasal packing may be necessary. Care must be taken not to perforate the septum.
3. Clear view of bleeding site is necessary for the use of cautery method.
4. Adequately anesthetize the nose before packing.
   a. Anterior packing: various self-expanding/inflatable devices exist with or without vasoconstrictive agents.
   b. Posterior packing: patients may need to be sedated for standard posterior packing with rolled gauze. Foley catheter can also be passed to nasopharynx, inflated then retracted to wedge balloon snugly in posterior choana.
   c. Packs can be left in place for 2 to 5 days. Prophylactic antibiotics should be given due to risk of sinusitis and toxic shock syndrome.

B. In cases of severe or uncontrolled epistaxis:
1. Airway is a priority and intubation may be required.
2. Monitor vital signs, check blood count, type/screen and coagulation studies.
3. Gastric decompression will minimize aspiration of blood.

C. If epistaxis is recurrent or refractory to sufficient packing, arterial ligation or selective embolization is necessary.
1. Anterior nasal bleeding is abated by ligation of the ethmoidal arteries.
2. Posterior bleeding is controlled by ligation of internal maxillary artery.
3. In cases of diffuse bleeding without identification of bleeding location, both internal maxillary and ethmoid artery should be ligated.

4. Angiographic embolization is a viable option in treatment of intractable epistaxis.

D. For patients in intensive care setting, prevention is important.

1. Rotate and inspect nasal tubes regularly.
2. Use lubricating agents when inserting tubes.
3. Humidified oxygen in essential to prevent mucosal desiccation.
4. Hypertension and coagulopathies should be treated immediately.

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104 ESOPHAGEAL PERFORATION AND ACUTE MEDIASTINITIS

Olga Ivanov, Fred A. Luchette, and Robert M. Mentzer

I. ESOPHAGEAL PERFORATION

A. Definitions. Esophageal perforation can be a result of multiple pathophysiologic stresses

1. Spontaneous perforation due to increased wall tension
2. Penetrating injuries
   a. Owing to intraluminal causes
   b. Owing to extraluminal causes

B. Etiology

1. Spontaneous rupture
   a. Owing to intraluminal pressure increase that is greater than tolerated by the esophagus (i.e., Boerhaave's syndrome, blunt trauma)
   b. Esophageal cancer perforation from the intrinsic necrosis
   c. Inflammatory esophageal lesions: tuberculosis, Barrett's esophagus, idiopathic eosinophilic esophagitis
2. Extraluminal perforation
   a. Penetrating trauma from stabs or gunshot wounds
   b. Primary esophageal surgery: resection or esophagomyotomy
   c. Adjacent surgical procedures: cervical procedures, pneumonectomy, echoendoscopy, laparoscopic Nissen fundoplication, aortic surgery, atrial fibrillation procedures through surgical or percutaneous approach, and tube thoracostomy
3. Intraluminal perforation
   a. Instrumentation
      i. Leading edge of a stricture is a point most likely to rupture.
      ii. More common with rigid rather than flexible endoscopy.
   b. Esophageal stent placement, especially in cases of prior radiation and chemotherapy
   c. Congenital anomalies (esophageal atresia) from nasogastric (NG) tube placement
   d. Transesophageal echocardiography—very rare
   e. Endotracheal intubation
   f. Ingested foreign bodies
   g. Chemical burns from alkali or strong acids, resulting in mucosal damage and stricture

C. Clinical presentation

1. Tachycardia—earliest sign of mediastinitis
2. Tachypnea and shallow respirations
3. Emphysema of soft tissues of the face and chest
4. Pain: precordial, epigastric, or scapular due to diaphragmatic irritation
5. Fever
6. Dysphagia and odynophagia
7. Hoarseness and cervical tenderness in cervical esophageal perforations

D. Diagnosis

1. Chest radiography (CXR): mediastinal air, hydropneumothorax

2. Contrast esophagogram—most sensitive diagnostic test; avoid water-soluble contrast due to pulmonary complications
3. Computed tomography (CT) scan: extraluminal air, periesophageal fluid, wall thickening, extraluminal contrast

E. Treatment

1. Early (i.e., <12 hours from the time of perforation):
   a. Primary closure and with subsequent drainage of the region
   b. Reinforcement of repair with a flap of parietal pleura, intercostal muscle flap, or an omental patch
2. Late (i.e., >12 hours or extensive inflammation):
   a. Esophageal diversion
   b. Generous drainage
   c. Broad spectrum antibiotics
3. Perforations limited to the mediastinum. Antibiotics, NG drainage, and total parenteral nutrition (TPN)
4. Persistent esophagomediastinal fistulas. Controlled with esophageal stents or fibrin glue.
5. Endoluminal esophageal stents effectively seal malignant perforations.

II. ACUTE MEDIASTINITIS

A. Etiology

1. Associated with sternotomy and intrathoracic procedures
2. Predisposing factors include advanced age, severe obesity, emergency surgery, lower preoperative ejection fraction, prolonged cardiopulmonary bypass, postoperative bleeding and need for reoperation, diabetes mellitus, use of bilateral internal mammary artery grafts, and immunosuppression as seen in heart transplant recipients
3. Rarely could be due to spread of periodontal disease to mediastinum
4. Cervical and thoracic esophageal perforation
5. Extension of primary pulmonary infections into the mediastinal planes
6. Complications from central lines
7. Morbidity and mortality of mediastinitis
   a. Poststernotomy mediastinitis seen in 1% to 4% of patients
   b. Threefold increase in mortality in patients with mediastinitis
   c. Up to 5% mediastinitis rate in postheart transplant patients

B. Clinical presentation

1. Fever
2. Pain localized to the chest or radiating to the neck
3. Tachycardia
4. Subcutaneous emphysema
5. Postoperative infection
   a. Occurs 3 days to 4 weeks after resection
   b. Characterized by tachycardia, leukocytosis, increasing sternal pain, and sternal drainage with sternal instability

C. Diagnosis

1. CXR: air tracking in the mediastinum, retrosternally, or between the leaves of the sternum
2. CT scan: may not be very helpful within days of surgery due to disruption of natural tissue planes by surgical dissection and presence of air and fluid after any recent sternotomy

D. Treatment

1. Obtain blood and mediastinal fluid cultures
2. Broad spectrum antibiotics
3. Resuscitate to maintain adequate cardiac output and oxygen delivery

4. Drain or debride fluid collections or necrotic tissue
5. Open-window thoracostomy for bronchopleural or esophagopleural fistulas
6. Irrigation and sternal debridement with rewiring for early exploration
7. Irrigation catheter in cases of gross purulence
8. Unilateral or bilateral pectoralis major, omental, or rectus abdominal muscle flap closure after radical sternal debridement for postoperative infections
9. Vacuum-assisted closure (VAC) therapy for drainage, closure, and increased blood supply to the area

E. Complications

1. Late failure of internal mammary arterial bypass graft in postoperative mediastinitis
2. Free right ventricular wall rupture on sternal mobilization during delayed closure or on spontaneous cough or movement

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105 DIAGNOSIS AND MANAGEMENT OF INTRA-ABDOMINAL SEPSIS

Mary M. Wolfe

I. GENERAL PRINCIPLES

- **A.** Intra-abdominal infections are commonly encountered in the intensive care unit (ICU) setting.
- **B.** The presentation and causes are varied.
  - **1.** The largest group of patients is those having undergone a recent procedure or intervention in whom abscess must be ruled out.
  - **2.** A second group of patients is those in the ICU with clinical findings suggestive of infection without obvious source.
    - **a.** Prophylactic antibiotic usage is decreasing occurrence of postoperative infections.
    - **b.** May be unrelated to primary problem.
    - **c.** May present as ileus without signs of infection elsewhere. Can be seen with bowel ischemia, cholecystitis, pseudomembranous colitis, pancreatitis, and diverticulitis.

II. ETIOLOGY

- **A.** Pathogenesis is secondary to spontaneous causes or to contamination of the peritoneal cavity by perforated viscus that causes breakdown of peritoneal defense mechanisms.
- **B.** Peritoneal defense mechanisms provide a system for rapid clearance of foreign particulates and solutes from the intraperitoneal space.
  - **1.** Resident peritoneal macrophages, neutrophils, and monocytes ingest microorganisms and secrete proinflammatory molecules.
  - **2.** Lymphatic channels provide entry of peritoneal fluid with bacteria and proinflammatory mediators into the venous system.
  - **3.** Inspiration, especially positive pressure ventilation, causes a pressure gradient favoring fluid movement out of the abdomen.
  - **4.** Entry of proinflammatory substances into the vascular space would be expected to produce many of the hemodynamic and respiratory findings of severe sepsis.
- **C.** Pathogens include mixed flora—aerobic, anaerobic, and facultative gram-negative organisms are common pathogens.
  - **1.** Facultative and aerobic gram-negative organisms release endotoxin and endotoxin-associated proteins.
  - **2.** Cytokines and leukocyte-derived inflammatory mediators give rise to systemic response including tachycardia, fever, peripheral vasodilatation, hypotension, decreased cardiac output.
  - **3.** Host defenses can be suppressed by bacterial synergy that inhibits complement activation and leukocyte migration.

III. DIAGNOSIS

- **A.** The initial therapeutic goal should focus on resuscitation, diagnosis, and control of contamination.

B. History and physical are key to the diagnosis of intra-abdominal sepsis in the patient in the ICU.
  1. Timing and evolution of symptoms—fever, localized abdominal pain/tenderness, hypotension
  2. Laboratories—leukocytosis, electrolyte abnormalities, increased liver enzymes, amylase, acute renal failure

C. Radiology
  1. Plain radiographs
    a. Perforation/pneumoperitoneum
    b. Bowel obstruction
    c. Pneumatosis intestinalis
    d. Pneumonia
    e. Portal venous air
  2. Ultrasound (US)
    a. Noninvasive and can be done at bedside to localize extraluminal fluid collection
    b. Can be used for drainage
    c. Limited by body habitus, bowel gas, retroperitoneum
  3. Computed tomography (CT)
    a. Noninvasive identification of pathology not identified on physical examination, plain radiographs, or US
    b. Can be used to guide and drain abscess

IV. TREATMENT

A. Resuscitation
  1. Rapid volume expansion to counter vasodilation should be done before surgical or radiologic intervention and should continue during radiologic, diagnostic, and therapeutic efforts. In addition, appropriate monitoring should be utilized including central venous pressure, urine output, and abdominal compartment pressures.
  2. Once patients have undergone intervention, resuscitation should be maximized, employing pressors to increase cardiac output or high inspired oxygen concentrations to maintain adequate arterial oxygen saturation and restore tissue perfusion.

B. Institution of appropriate antibiotics should be done as soon as diagnosis of intra-abdominal sepsis is made to hasten the elimination of infecting microorganism, minimize the risk of recurrent intra-abdominal infection and shorten the clinical manifestations of infection (Table 105-1).
  1. Appropriate coverage must anticipate pathogens most likely to be encountered at the site of infection. Initial empiric antibiotics should cover enteric gram-negative facultative and obligate anaerobic bacilli.
  2. Proximal small bowel has gram-positive aerobic and gram-negative anaerobic organisms that are generally susceptible to β-lactam antibiotics.
  3. Distal small bowel and colon perforations cause contamination with gram-negative facultative organisms and obligate anaerobes that should be covered with broad-spectrum antibiotics.
    a. Carbapenems, cephalosporins, penicillins plus β-lactamase inhibitors, and quinolones
  4. Reevaluation of antibiotic coverage is imperative after culture results are conclusive.

C. Percutaneous drainage can be used if there is no sign of diffuse peritonitis. Percutaneous drainage is preferable to open surgical intervention when

TABLE 105-1 Bacteria Commonly Encountered in Intra-Abdominal Infections

Facultative gram-negative bacilli	Obligate anaerobes	Facultative gram-positive cocci
Escherichia coli	*Bacteroides fragilis*	Enterococci
Klebsiella species	Bacteroides species	Staphylococcus species
Proteus species	Fusobacterium species	Streptococcus species
Morganella morganii	Clostridium species	
Other enteric gram- negative bacilli	Peptococcus species	
Aerobic gram-negative bacilli	Peptostreptococcus species	
Pseudomonas aeruginosa	Lactobacillus species	

feasible because of the initial deterioration that almost always occurs following operative manipulation of intra-abdominal infection.

1. US guided—portable but has limitations
2. CT guided—best modality for patients who are hemodynamically stable

D. Surgery is indicated if perforation or diffuse peritonitis exists or there is large solid tissue component. Operative management involves immediate evacuation of all purulent collections, debridement of necrotic tissue, and control of the septic source.

1. Bowel resections should be done, with end ostomy if necessary.
2. Primary closure of the wound is controversial and must take into consideration abdominal wall edema and aggressive resuscitation in order to avoid abdominal compartment syndrome.
3. Second-look laparotomy may be necessary to achieve complete evacuation of infection.
   a. Fascial prostheses can be used for wound closure with planned relaparotomy and definitive closure of the abdomen once edema resolves.

V. SPECIFIC INFECTIONS

A. Acute pancreatitis

1. Infections superimposed on acute pancreatitis are among the most difficult intra-abdominal infections to manage.
2. See Chapter 106.

B. Biliary infections

1. Ascending cholangitis is biliary obstruction with secondary bacterial infection that presents with Charcot's triad of abdominal pain, fever, and jaundice.
   a. US or CT diagnosis shows biliary ductal dilatation, wall thickening, pericholecystic fluid, and stones.
   b. Laboratory findings include hyperbilirubinemia, leukocytosis, and elevated alkaline phosphatase.
   c. Treatment includes antibiotics and drainage with endoscopic retrograde cholangiopancreatography/percutaneous transhepatic cholangiography (ERCP/PTC).
   d. Initial antibiotic therapy should be monotherapy with a β-lactam/β-lactamase inhibitor or metronidazole with third-generation cephalosporin or fluoroquinolone.
2. Acute cholecystitis
   a. Acalculous cholecystitis is most common in ICU secondary to microvascular and mucosal dysfunction and presents as occult sepsis ± right upper quadrant (RUQ) tenderness.

   b. US/CT shows wall thickening, pericholecystic fluid, and sludge.
   c. Treatment includes antibiotics and percutaneous cholecystostomy tube for high-risk patients who do not respond to antibiotic therapy.
   d. Initial therapy should be monotherapy with β-lactam/β-lactamase inhibitor for those patients without previous broad spectrum antibiotic therapy, otherwise metronidazole with third-generation cephalosporin or fluoroquinolone.

C. Intestinal ischemia
   1. Arterial or venous occlusion or low flow states are causative factors. Thromboembolic events must be taken into consideration if there is an arrhythmia.
   2. Plain radiographs to evaluate for severe ischemia in form of pneumatosis, portal venous gas.
   3. Angiography is used to identify site and cause of ischemia.
   4. CT is useful to evaluate those with less specific symptomatology and early changes such as bowel dilatation, transmural thickening with inflammatory changes in the perienteric fat can be seen. CT can also identify strangulation of closed loop obstruction or perforation with abscess formation.

D. Postoperative intra-abdominal infections
   1. Postoperative peritonitis generally is due to anastomotic leak/dehiscence.
   2. It must be considered in patients with signs of sepsis who have undergone gastrointestinal (GI) anastamosis or who manifest diffuse abdominal tenderness.
   3. US/CT will reveal fluid which should lead to aspiration of fluid for diagnostic purposes.
   4. Surgical treatment should include resection with reanastamosis or end colostomy.
      a. Antibiotic therapy should be targeted toward specific enteric pathogens and tailored to culture results.

E. Enteric fistulas
   1. Small intestine is most common source, followed by colon, stomach, duodenum, biliary tract, and pancreas.
   2. Recognition of fistula is key to management as only 26% of fistulas were identified at the time of initial drainage. Fistulogram or other study must be performed to demonstrate and evaluate fistula.
   3. Fistulas can present as occult sepsis or sudden change in character or amount of drainage from wound.
   4. Management includes control by adequate drainage, skin protection, nutritional support, and formation of a mature tract formation, and exclusion of downstream obstruction.

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ACUTE PANCREATITIS

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106

I. DEFINITIONS

- **A.** Clinically acute pancreatitis: process of rapid onset associated with pain and alterations in exocrine function
- **B.** Clinically chronic pancreatitis: repeated episodes of pain associated with diminished exocrine function
- **C.** Morphologically acute pancreatitis: occurs in a gland that was and will be functionally normal before and after the attack
- **D.** Morphologically chronic pancreatitis: involves the pancreas that was morphologically or functionally abnormal before the attack and may remain abnormal after the attack
- **E.** Pathologically acute pancreatitis:
  - **1.** Mild: associated with interstitial edema, intrapancreatic, or peripancreatic acute necrosis
  - **2.** Severe: associated with focal or diffuse acinar cell necrosis, thrombosis of intrapancreatic vessels, intraparenchymal hemorrhage, and abscess formation
- **F.** Pathologically chronic pancreatitis: associated with scarring, fibrosis, and acinar tissue atrophy

II. ETIOLOGY

- **A.** Biliary tract stone disease
  - **1.** Along with ethanol abuse, it accounts for 60% to 80% of patients with acute pancreatitis.
  - **2.** Demographic distribution: Affluent groups have more attacks due to stones, and poorer patients due to ethanol abuse.
  - **3.** Three theories of gallstone pancreatitis:
    - **a.** "Common channel"—stones create a common biliopancreatic channel proximal to the stone-induced obstruction and allow bile to reflux into the pancreatic ducts, triggering pancreatitis.
    - **b.** "Duodenal reflux"—incompetent sphincter of Oddi due to the stone passage permits reflux of duodenal juice containing activated digestive enzymes into the pancreas.
    - **c.** "Pancreatic duct obstruction"—the only theory currently supported by clinical models—after duct obstruction lysosomal hydrolases activate digestive enzymes within pancreatic acinar cells, leading to their injury.
- **B.** Ethanol abuse
  - **1.** Mean ethanol consumption is 150 to 175 g/day for 18 years for men and 11 years for women before the first attack.
  - **2.** Mechanism for acute or chronic pancreatitis is not clear.
- **C.** Drugs
  - **1.** Most commonly seen in patients with acquired immunodeficiency syndrome (AIDS) receiving dideoxyinosine and pentamidine or transplant or inflammatory bowel disease (IBD) patients receiving azathioprine.

2. Historically, diuretics: thiazides, ethacrynic acid, and furosemide have high association with pancreatitis.
3. H_2-blockers and steroids are not currently believed to be capable of causing acute pancreatitis.

D. Pancreatic duct obstruction
1. Tumors: duodenal, ampullary, biliary tract, or pancreatic
2. Inflammatory lesions: peptic ulcer, duodenal Crohn's disease, periampullary diverticulitis
3. Pancreatic cysts, pseudocysts, and periampullary diverticula
4. Ductal strictures
5. Parasites: *Ascaris* and *Clonorchis*

E. Miscellaneous causes of acute pancreatitis
1. Traumatic
2. Postoperative: duct exploration, sphincteroplasty, distal gastrectomy, endoscopic retrograde cholangiopancreatography (ERCP) and procedures associated with hypoperfusion or atheroembolism of the pancreatic circulation

F. Idiopathic pancreatitis
1. Affects 5% to 10% of population
2. Possible etiologies are biliary sludge, familial (mutation on chromosome 7), nonclassic cystic fibrosis mutations, and autoimmune basis

III. CLINICAL PRESENTATION

A. Symptoms: epigastric abdominal pain of rapid onset, nausea, vomiting that may result in Mallory–Weiss syndrome

B. Physical examination
1. Tachycardia, tachypnea, diaphoresis, hyperthermia, restlessness, and jaundice (20% incidence)
2. Abdominal tenderness with voluntary and involuntary guarding, rebound, distension, epigastric mass, and diminished or absent bowel sounds
3. Flank ecchymoses (Grey Turner sign) or other evidence of retroperitoneal bleeding (Cullen sign)
4. Chest examination may reveal evidence of atelectasis and left pleural effusion

IV. DIAGNOSIS

A. Routine blood tests
1. Increased hemoglobin, hematocrit (HCT), blood urea nitrogen (BUN), creatinine, bilirubin, white blood cells (WBCs), glucose, and triglycerides
2. Decreased calcium, albumin
3. In severe cases—thrombocytopenia, decreased fibrinogen levels, and prolonged prothrombin time and partial thromboplastin time

B. Amylase
1. May be normal in 10% of patients with lethal pancreatitis.
2. Levels increase 2 to 12 hours after attack onset, normalize after 3 to 6 days.
3. May be elevated due to processes other than pancreatitis: acute cholecystitis, perforated gastric or duodenal ulcers, and intestinal obstruction.
4. Usually elevated to levels >1,000 IU/L.

C. Other enzyme assays and blood tests: urine amylase and serum lipase may remain elevated for days after the attack.

D. Routine radiography
1. Chest radiograph: left pleural effusion, basal atelectasis
2. Plain frontal supine radiograph of the abdomen: pancreatic calcifications in chronic pancreatitis, ileus, retroperitoneal air if pancreatic abscess is formed

E. Ultrasonography: detection of gallbladder stones or bile duct dilatation, or both

F. Computed tomography (CT):

1. Mild pancreatitis—normal or slightly swollen pancreas with streaking of retroperitoneal or transverse mesocolic fat
2. Severe pancreatitis—peripancreatic or intrapancreatic fluid collections
3. Dynamic CT—areas of pancreatic necrosis that fail to enhance with contrast administration

G. Differential diagnosis

1. Perforated hollow viscus
2. Cholecystitis/cholangitis
3. Bowel obstruction
4. Mesenteric ischemia/infarction

V. PROGNOSIS

A. Mild self-limited pancreatitis in 90% to 95% of patients

B. Approximately 5% to 10% will have severe attack associated with 40% morbidity and mortality

C. Ranson's prognostic signs

1. On admission: age older than 55 years; WBC >16,000/mm^3; glucose >200 mg/dL; lactate dehydrogenase (LDH) >350 IU/L; glutamic-oxaloacetic transaminase (GOT) >250 U/dL
2. During initial 48 hours: HCT decrease >10%; BUN rise >5 mg/dL; serum calcium <8 mg/dL; Pao_2 <60 mm Hg; base deficit >4 mEq/L; fluid sequestration >6 L
3. Less than three criteria: mild pancreatitis—1% mortality
4. Seven or eight criteria: severe pancreatitis—90% mortality

D. APACHE-2—another useful system to evaluate severity of an attack

E. Peripancreatic fluid collections on CT scan

1. Two or more fluid collections—61% incidence of late pancreatic abscess
2. One fluid collection—12% to 17% incidence of pancreatic abscess
3. Pancreatic enlargement only—zero incidence of pancreatic abscess

VI. TREATMENT OF ACUTE PANCREATITIS

A. Initial management

1. Sometimes impossible to establish diagnosis without exploratory laparotomy
2. However, laparotomy may increase incidence of septic complications

B. Treatment of pain. Demerol is the drug of choice; it relaxes the sphincter of Oddi, whereas morphine contracts it.

C. Fluid and electrolyte replacement

1. Initially—hypochloremic alkalosis due to vomiting and decreased fluid intake
2. Later—metabolic acidosis due to hypovolemia and poor tissue perfusion
3. Hypomagnesemia and hypoalbuminemia due to preexisting malnutrition in chronic alcoholics
4. Hypocalcemia may lead to tetany and carpopedal spasm
5. Hemodynamics in severe attacks resemble shock: increased heart rate, cardiac output, cardiac index (CI), arterial-venous oxygen difference; decreased pulmonary vascular resistance (PVR); hypoxemia

D. Other treatments

1. Intravenous imipenem or meropenem for 14 days may be of benefit in patients with infected pancreatitis by reducing mortality and morbidity.
2. Fluconazole decreases the emergence of resistant fungi.

3. Unclear value of nasogastric suction and agents that reduce pancreatic function, inhibit inflammatory or cytotoxic responses, inhibit digestive enzymes or platelet-activating factor antagonist lexipafant.
4. Use of early enteral nutrition (initiated within 36 hours of symptom onset) has shown benefit over parenteral nutrition in terms of duration of hospital stay, infectious morbidity, and need for surgery.
5. Probiotic prophylaxis does not reduce the risk of infectious complications and is associated with an increased risk of mortality.

E. Role of surgery and endoscopy in gallstone pancreatitis
1. Mild pancreatitis—no early surgical or endoscopic intervention
2. Severe gallstone pancreatitis—early surgical or endoscopic intervention warranted
3. Recurrent attacks of gallstone pancreatitis should be prevented by cholecystectomy combined with surgical or endoscopic duct clearance

VII. TREATMENT OF SYSTEMIC COMPLICATIONS

A. Aggressive fluid and electrolyte therapy may be the most effective method of preventing pulmonary and renal failure.

B. Pulmonary toilet and monitoring of pulmonary function with arterial blood gas measurements.

C. Prophylaxis with either antacids or H_2-blockers may prevent stress-induced bleeding of gastroduodenal lesions.

VIII. LOCAL COMPLICATIONS OF PANCREATITIS

A. Definitions
1. Acute pancreatic and peripancreatic fluid collections. Occur early, in or near the pancreas, lack of wall
2. Pancreatic necrosis. Either sterile or infected area of nonviable pancreatic tissue, diffuse or focal, associated with peripancreatic fat necrosis
3. Pancreatic pseudocyst
   a. Occurs 4 to 6 weeks after the attack, nonepithelialized wall of fibrous or granulation tissue enclosing a collection of pancreatic juice rich in digestive enzymes.
   b. Leakage into peritoneal cavity or chest leads to pancreatic ascites or pancreatic-pleural fistula, respectively.
4. Pancreatic abscess. Circumscribed intra-abdominal collection of pus close to the pancreas without necrosis.

B. Diagnosis
1. Dynamic contrast-enhanced CT—identifies and quantitates areas of pancreatic necrosis or abscess based on extraintestinal gas, poor enhancement, or Gram stain of CT-guided fine-needle aspirate
2. ERCP—determines communication of fluid collections with the main pancreatic duct and/or localizes the point of duct rupture

C. Management
1. Acute fluid collections—resolve spontaneously, no treatment.
2. Sterile pancreatic necrosis—mostly nonoperative management, unless clinical deterioration despite aggressive nonoperative treatment.
3. Infected necrosis—aggressive and repeated surgical debridement and drainage and antibiosis; stable patients with infected necrosis can be managed more electively and conservatively.
4. Pseudocysts—treat only if symptomatic, regardless of size, with internal surgical drainage (cystogastrostomy, cystoduodenostomy, Roux-en-Y cystojejunostomy), endoscopic drainage (cystogastrostomy, cystoduodenostomy), or percutaneous drainage with or without administration of somatostatin.

5. Pancreatic ascites or pancreatic-pleural fistula—bowel rest, nutrition, somatostatin; most will require ERCP for identification of ductal disruption with subsequent distal pancreatectomy, Roux-en-Y pancreatojejunostomy or endoscopic stent placement.
6. Pancreatic abscess—percutaneous or surgical drainage.

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107 MESENTERIC ISCHEMIA

Raymond L. Candage and Peter E. Rice

I. GENERAL PRINCIPLES

- **A.** Defined as a compromise of intestinal mesenteric arterial or venous flow, which may occur acutely or over the course of several weeks.
- **B.** Intestine is deprived of blood and oxygen leading to ischemia, acidosis, leukocytosis, and the development of sepsis and multiple organ failure.
- **C.** Mortality in excess of 80% to 95% for acute arterial occlusion with a somewhat more optimistic prognosis for patients with venous occlusive disease.
- **D.** Risk factors include advanced age, atrial arrhythmias, history of congestive heart failure or recent myocardial infarct, and valvular heart disease.
- **E.** Early diagnosis is the key factor to a favorable outcome.

II. ETIOLOGY

- **A.** Approximately 50% of cases of acute mesenteric ischemia are due to arterial embolic events, 25% of cases are the result of arterial thrombosis, 20% to 30% of cases are due to nonocclusive mesenteric ischemia (NOMI), and fewer than 10% of cases are the result of mesenteric venous thrombosis (MVT).
- **B.** Mesenteric arterial embolism and thrombosis involve the superior mesenteric artery (SMA) almost exclusively. Most individuals have preocclusive atherosclerotic disease in other locations including the visceral vessels.
- **C.** Emboli from a cardiac source typically lodge at the first branch point of the SMA. Arterioarterial emboli tend to be smaller and lodge in the more distal mesenteric circulation.
- **D.** Thrombosis usually develops at or near the origin of vessels or areas of concurrent atherosclerotic stenoses.
- **E.** NOMI is caused by primary splanchnic vasoconstriction resulting in a low flow state to the mesenteric vascular bed.
- **F.** MVT is a rare disorder resulting from a variety of acquired and inherited hypercoagulable states. MVT usually involves the superior mesenteric and splenic veins and less commonly the inferior mesenteric and portal veins.

III. PATHOPHYSIOLOGY

- **A.** Acute arterial obstruction will rarely present with acute mesenteric ischemia at normotensive pressures due to excellent collateral circulation of the gut.
- **B.** Ischemic times as short as 3 hours can produce significant damage to the intestinal mucosa.
- **C.** Reduction of blood flow initiates a cascade of events including an acute inflammatory response, reperfusion injury through oxygen derived free radicals, hypovolemia, and multisystem organ dysfunction.
  1. Prolonged ischemic time leads to bowel necrosis with resultant leukocytosis, acidosis, hypotension, or bloody diarrhea.
  2. Bowel necrosis is ultimately complicated by perforation, sepsis, multisystem organ failure, and death.
- **D.** Acute arterial occlusion usually results from emboli or thrombosis.
  1. Emboli are usually cardiac in origin, lodge at an arterial branch point, and spare the proximal branches of the SMA.

2. Thrombosis generally occurs at or near the origin of the SMA and is generally the result of a systemic abnormality (e.g., diabetes, hypercoagulable state).

E. Nonocclusive ischemia is the result of mesenteric vasospasm, usually in the distribution of the SMA.

1. Homeostatic mechanism attempts to maintain cardiac and cerebral perfusion at the expense of visceral and peripheral organs.
2. NOMI is associated with cardiopulmonary bypass, shock states, and certain medications (e.g., α-adrenergic agents, digitalis, vasopressin).

IV. DIAGNOSIS

A. Clinical presentation

1. Hallmark of acute mesenteric ischemia—pain out of proportion to the physical examination.
2. Onset of pain may be accompanied by gut emptying—vomiting, bowel movement, or diarrhea.
3. Physical examination may reveal abdominal tenderness, which is not well localized and hypoactive to absent bowel sounds. With progression of disease to bowel infarction and perforation, the patient will develop peritoneal findings.
4. High index of suspicion in patients with preexisting cardiac disease and critically ill patients with a shock state from trauma, burns, and sepsis.

B. Laboratory

1. Elevation of serum amylase concentration
2. Elevation of serum lactate, often implies severe ischemia or bowel infarction
3. Most common laboratory abnormality is a persistent and profound leukocytosis; in excess of 15,000 cells/mm^3
4. Electrolyte derangements from dehydration and acidosis seen in the advanced stages of intestinal infarction

C. Imaging

1. Plain radiographs typically demonstrate no abnormalities until late in the clinical course. Late findings include distended bowel loops with air fluid levels, bowel wall thickening, gas within the mesenteric venous circulation, and free air.
2. Duplex ultrasonography. Results are best when the patient has fasted before examination. Highly operator dependent.
3. Computed tomography (CT) using an intravenous (IV) contrast agent.
4. Angiography remains the "gold standard" for imaging of mesenteric occlusion.

V. TREATMENT

A. SMA embolism

1. Arteriotomy with embolectomy. Can close arteriotomy site primarily or with a patch angioplasty with autologous vein.
2. Perform bowel resection after revascularization unless faced with an area of frank necrosis or perforation and peritoneal soilage. Second look laparotomy within 48 hours.
3. Endovascular approaches with thrombolysis, angioplasty, and stenting are typically reserved for high-risk patients in an elective setting.

B. SMA thrombosis

1. SMA bypass. Often a prosthetic bypass conduit is best for patients with chronic mesenteric ischemia. In patients with obviously infarcted bowel or bowel perforation, autogenous vein is the preferred conduit.
   a. Retrograde bypass (iliac artery inflow)
   b. Antegrade bypass (proximal aortic inflow)

2. Thrombolytics. Best candidates are those with angiographic findings of good collateral circulation and no evidence of bowel compromise.

C. NOMI
1. Expedient management of cardiac events and shock states are essential. Systemic vasoconstrictors should be avoided and replaced by vasodilators that diminish cardiac preload and afterload.
2. Pharmacologic treatment may involve selective intra-arterial infusion of papaverine into the SMA.
3. If peritoneal signs develop or abdominal pain persists despite papaverine infusion, emergent exploratory laparotomy is indicated.

D. Mesenteric venous thrombosis
1. Conservative management with bowel rest and anticoagulation (heparin, warfarin).
2. Surgery reserved for complications (e.g., intestinal infarction). Management involves bowel resection and venous thrombectomy.

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COMPARTMENT SYNDROME OF THE ABDOMINAL CAVITY

Gerard J. Abood, Dietmar H. Wittmann, and Fred A. Luchette

108

I. GENERAL PRINCIPLES

A. Overview

1. Abdominal cavity considered as single compartment enclosed by apeuronotic envelope with limited compliance.
2. First coined by Kron et al. in 1984 when they described the pathophysiologic changes following a ruptured abdominal aortic aneurysm.
3. Elevated intra-abdominal pressure (IAP) can impair blood flow and normal organ function.
4. Once critical threshold volume is reached, small increments in tissue volume lead to exponential increases in intraperitoneal pressure. May result in multiorgan failure and death if not reversed promptly.

B. Definitions

1. Compartment syndrome: increased pressure in confined anatomic space that adversely affects function and viability of tissue within compartment.
2. Abdominal compartment syndrome (ACS): acutley increased and sustained pressure within abdominal wall, pelvis, diaphragm, and retroperitoneum adversely affecting function of organs and tissue within and adjacent to abdominal cavity. Usually requires operative decompression.
3. Abdominal hypertension (AH): sustained (>6 hours) increase in IAP that may or may not require operative decompression.
4. On the basis of the consensus statement of the World Society of the Abdominal Compartment Syndrome, intra-abdominal hypertension (IAH) was defined as IAP $\geq$12 mm Hg and ACS as a sustained IAP $\geq$20 that is associated with new organ dysfunction or failure (as measured at the level of the midaxillary line).
   a. Normal abdominal pressure: 10 mm Hg
   b. Mild AH: 10 to 15 mm Hg; usually not clinically significant
   c. Moderate AH: 16 to 35 mm Hg; operative intervention may be required
   d. Severe AH: sustained pressures >35 mm Hg; operative decompression always warranted

II. PATHOPHYSIOLOGY

A. Causes. Most AH is caused by peritoneal, mesenteric, or retroperitoneal edema impinging on fascial envelope of abdominal compartment.

1. Total surface area of peritoneum is 1.8 m^2, which is approximately equal to entire surface area of skin. Theoretically, 1 mL of peritoneal thickening may contain 15 to 18 L of fluid.
2. Expanding edema can quickly exceed compensatory elasticity of abdominal fascia and diaphragm and lead to organ function compromise.
3. Increased venous outflow resistance results in reduction in effective perfusion of the capillary beds, leading to tissue ischemia and inflammatory mediator activation.

B. Table 108-1 lists variety of causes of IAP.

TABLE 108-1 Causes of Abdominal Hypertension

Peritonitis, trauma, burns	Retroperitoneal hematoma
Fluid overload: hemorrhage or septic shock	Peritoneal operative trauma
Bowel edema, reperfusion injury, acute pancreatitis	Ileus, bowel obstruction
Intra-abdominal mass	Abdominal closure under tension
Ascites, intra-abdominal fluid collection	Laparoscopic abdominal insufflation
	Weight lifting up to >200 mm Hg (physiological abd. hypertension)

III. DIAGNOSIS

A. Clinical presentation

1. The key to diagnosis includes identifying patients at risk, recognizing salient clinical features, and remaining proactive in carrying out diagnostic measures to confirm the diagnosis.

2. Patients typically present with a tense abdominal wall, shallow respirations, low urinary output, and increased central venous pressure.

3. Physiologic impairments in all systems observed.

a. Cardiac: Output initially rises as a result of increased venous return from intra-abdominal veins, but diminishes as pressure rises above 10 mm Hg.

i. Decreased preload, result of pooling in lower extremities and functional narrowing of vena cava

ii. Afterload increased and ventricular function decreased as cardiac compliance and filling pressures were negatively affected by increased IAP.

b. Pulmonary: Decrease in diaphragmatic excursion resulting in atelectasis, pneumonia, and ventilation-perfusion mismatch. Positive end-expiratory ventilation to maintain alveolar patency worsens intrathoracic pressure and cardiac output.

c. Renal: Impaired as a result of decreased cardiac output, compression of both renal inflow and outflow, and direct compression of kidney parenchyma; development of "renal compartment syndrome."

d. Hepatic: Reduction in blood flow affecting production of acute-phase proteins, immunoglobulin, and factors of the other host defense system.

e. **Gastrointestinal** (GI): Splanchnic hypoperfusion possibly affecting mucosal pH, bacterial translocation, and bowel motility.

B. Measurement of IAP

1. Direct method: intraperitoneal catheter is connected to a pressure transducer to take direct measurements. This is the preferred method for most experimental studies.

2. Indirect method: Less invasive, relies on pressure transduction to inferior vena cava, stomach, or, most commonly, the bladder. Transvesical technique: bladder behaves as passive diaphragm when volume is between 50 and 100 mL; abdominal pressure can be measured transvesically.

a. Instill 50 to 100 mL of sterile saline into empty bladder through Foley catheter. Tubing drain clamped and 16-gauge needle advanced through aspiration port and connected to pressure transducer or manometer.

b. Recordings correlated with direct measurements in range of 5 to 70 mm Hg.

IV. TREATMENT

A. Conservative and nonsurgical measures

1. The best treatment for ACS is prevention.

2. Early recognition of patients at increased risk prompts the institution of early corrective/preventative measures before full-blown ACS develops.

3. Nonsurgical treatment options include:
   a. Gastric and rectal decompression
   b. Sedation and neuromuscular blockade
   c. Body positioning
   d. Diuretics, venovenous hemofiltration/ultrafiltration
   e. Paracentesis

B. Decompression
1. Nonoperative decompression reserved for distension caused by ascites
2. Operative decompression: Opening abdominal cavity in operating room or intensive care unit once intravascular fluid deficits, temperature, and coagulation abnormalities are corrected.
   a. Postdecompression compensation has been reported: Systemic vascular resistance falls markedly after decompression, surpassing the increase in cardiac output.
   b. Careful monitoring, volume resuscitation before decompression, and judicious use of vasoconstrictors postoperatively may be of most benefit.

C. Closure
1. Abdomen can be reapproximated by a variety of methods.
2. Type of closure dependent on degree of decompression; abdomen can be reclosed when fascia can be reapproximated without undue tension.
   a. Synthetic fascial materials that are sutured to the fascial edges, which can be approximated slowly, offer another reliable option (Artificial Burr, Wittmann Patch); all meshes help to decompress the abdomen, fascial reapproximation and final closure, however, is difficult.
   b. Leaving fascia open and closing only skin with sutures or towel clips to protect bulging viscera has been recommended; this method has become obsolete because temporary fascial expansion, reapproximation and final closure is available (see a).

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109 NECROTIZING FASCIITIS AND OTHER SOFT TISSUE INFECTIONS

Julie L. Barone, David H. Ahrenholz, and Fred A. Luchette

I. OVERVIEW

A. General principles

1. Skin provides a barrier to infection; therefore, any break in skin allows bacteria to invade.
2. Risk factors for infection include trauma, edema, hematoma, ischemia, and foreign body.
3. Virulent infections occur when host defenses are weak (i.e., diabetes, cancer, malnutrition, immunosuppression, advanced age, and major trauma).

B. Pathophysiology

1. Group A, B-hemolytic *Streptococcus pyogenes*: highly virulent; cellulitis; erysipelas with demarcated borders; ecthema contagiosum; *streptococcal lymphangitis*; seen in necrotizing fasciitis; exotoxins result in cytokine release causing hypovolemia (toxic shock syndrome). See Sections II and III.
2. *Staphylococcus aureus*: most common cause of skin infection; purulence; folliculitis (dermis); superficial abscess (soft tissue); carbuncle (burrowing infection); pyomyositis (hematogenous spread to intramuscular hematoma); seen in necrotizing fasciitis. Also produces toxic shock syndrome. See Sections II and IV.
3. *Clostridium perfringens, Clostridium novyi*, and *Clostridium septicum*: gram-positive, spore forming obligate anaerobes; most common in ischemic muscle; exotoxins cause myonecrosis and sepsis. See Section V.
4. *Eikenella corrodens*: human bite wounds; treat with cephalosporins or penicillin.
5. *Pasteurella multocida*: animal bites or scratches; treat with cephalosporins, penicillin, tetracycline, trimethoprim–sulfamethoxazole + clindamycin.
6. *Vibrio vulnificus*: aggressive disease; more common in alcoholics; due to immunologic defect; aggressive debridement and treat with doxycycline.
7. *Escherichia coli, Klebsiella*: abscess of perineal area; usually arising from infected pilonidal cyst or laceration of rectal mucosa causing a perirectal abscess; can occur in other areas; initially treat with drainage and fluoroquinolones when indicated.
8. *Cryptococcus neoformans* and other fungi can mimic cellulitis due to group A streptococcus. See Section II.
9. *Bartonella*: gram-negative bacteria previously classified as rickettsiae; cause several uncommon diseases: cat-scratch disease, an acute febrile anemia, a chronic cutaneous eruption, and disseminated disease in immunocompromised hosts; treat with gentamicin and a second antibiotic depending on the *Bartonella* species and severity of the disease process.
10. Actinomycosis: chronic localized or hematogenous infection due to *Actinomyces israelii*; local abscess with multiple draining sinuses; seen more commonly in adult males as cervicofacial (lumpy jaw) abscess, portal of entry is decayed teeth; treat with surgical excision followed by cephalosporins.

II. CELLULITIS AND SUBCUTANEOUS INFECTIONS

A. Etiology

1. Most common organisms: *S. aureus* and group A streptococci causing a diffuse cutaneous infection; nonpyogenic; starts with a minor break in skin, such as an insect bite, puncture limited to skin, and subcutaneous tissues; infections spread through tissue facilitated by toxins and enzymes
2. In the extremity: presents with lymphadenitis or lymphangitis involving dermal lymphatics
3. High-risk cellulitis when infection involves the face or extremities of immunocompromised patients
4. Folliculitis: nontoxic pyodermas centered in hair follicles
5. Subcutaneous abscess (complicated cellulitis): most common soft tissue infection
6. Hidradenitis suppurativa: Chronic burrowing infection of groin or axilla involving infected hair follicles; more commonly seen in diabetic or very obese patients
7. Community-acquired methicillin-resistant *Staphylococcus* aureus (MRSA): increasing cases of MRSA soft tissue infections

B. Diagnosis

1. Presents with progressive erythema and edema; may cause tenderness over the involved area
2. Low diagnostic yield on cultures of tissue or aspirate

C. Treatment

1. Uncomplicated cellulitis: treatment antibiotics and elevation; surgery not indicated unless joints or tendon sheath involved
2. β-Lactams (penicillins, nafcillin, cephalosporins, carbapenams), clindamycin, clindamycin + vancomycin until causative microorganisms are identified and sensitivities determined

D. Complications

Recurrent cellulitis of the upper extremities is most commonly seen after a modified radical mastectomy or axillary lymph node dissection; it is seen in the lower extremities after saphenous vein harvesting for coronary artery bypass grafting surgery; it is best treated with long-term antibiotics targeting group A streptococcus.

III. NECROTIZING FASCIITIS

A. Definition

1. A severe and progressive infection that spreads rapidly along fascia planes with minimal cutaneous signs
2. Typically occurs after trauma or surgery in immunocompromised patients (i.e., those with peripheral vascular disease, diabetes, or malignancy)
3. Fournier's gangrene: a rapidly spreading scrotal skin infection
4. Requires prompt surgical debridement and parenteral antibiotics; if not treated aggressively, necrotizing fasciitis can result in death

B. Etiology

1. B-Hemolytic streptococcus comprises 90% of necrotizing fasciitis cases; anaerobic gram-positive cocci, aerobic gram-negative bacilli and bacteriodes; often a combination of bacteria; most commonly occurs in immunocompromised patients or those who have atherosclerotic vascular disease, diabetes, or malignancy; begins at site of minor wound or contaminated abdominal wounds after primary closure; enteric organisms are common in perineum
2. Has been reported after treating cellulitis with β-lactams secondary to rapid release of exotoxins
3. Hematogenous seeding of contusion after blunt trauma

4. Varicella infection in children can be complicated by streptococcal skin infections leading to necrotizing fasciitis

C. Diagnosis

1. Pain, edema, fever, leukocytosis with a left shift
2. Erythema and dermal necrosis are rare
3. Streptococcal necrotizing fasciitis: typical symptoms plus tachycardia, localized erythema, edema, and watery drainage; positive blood cultures; blistering of skin, which turns dusky after cutaneous vascular thrombosis
4. A diagnosis is made at time of surgical exploration. Plain radiographs/computed tomography scan may show gas fluid but can be misleading because it may only show tissue edema. If necrotizing fasciitis is suspected, surgical exploration is mandatory.

D. Treatment

1. Surgical debridement after fluid resuscitation; preoperative antibiotics to cover facultative and anaerobic organisms (cefoxitin, cefotetan, ampicillin/sulbactam, ticarcillin/clavulanate, piperacillin/tazobactam, imipenem/cilastatin).
2. Intraoperative wound cultures to determine postoperative course of antibiotics.
3. Pack wound with antiseptic soaked gauze after debriding nonviable tissue.
4. Wound can then heal by secondary intention or can be skin grafted.
5. Amputation of the extremity is sometimes necessary to control the spread of infection.
6. Intravenous (IV) immunoglobulins for streptococcal toxic shock syndrome.
7. Diverting colostomy reduces perineal soiling but is not mandatory for Fournier's gangrene.
8. Aggressive nutritional support: treatment is similar to burned patient (1.5 × basal metabolic expenditure).
9. Whirlpool debridement with daily dressing changes; vacuum-assisted closure on clean tissue to promote wound granulation.

E. Complications

1. Delayed diagnosis or incomplete debridement can result in profound sepsis.
2. Intra-abdominal sepsis following postoperative treatment of necrotizing fasciitis.
3. Overall mortality is 38%; there is a worse prognosis with increasing age, female gender, delay in first debridement, elevated serum lactate levels, and organ failure. More recent data suggest a mortality about 20% (see http://www.ncbi.nlm.nih.gov/pubmed/18807667).

IV. NONCLOSTRIDIAL MYONECROSIS

A. Etiology. Same as necrotizing fasciitis; rarely *Aeromonas hydrophilia* or *Bacillus cereus.*

B. Diagnosis. Similar signs and symptoms of necrotizing fasciitis; radiographs show gas outlining muscles; debridement reveals muscle and fascia necrosis; differs from clostridial myonecrosis as there are mixed organisms on Gram stain and fewer systemic effects.

C. Treatment. Excision of all necrotic tissue including muscle, fascia, and skin.

D. Complications. Overall mortality is 76%; same complications as necrotizing fasciitis.

V. CLOSTRIDIAL MYONECROSIS

A. Definition

1. Necrotizing muscle infection often with *C. perfringens* exotoxins; requires debridement and sometimes amputation.

2. *Gas gangrene*: term describing clostridial myonecrosis; gas is seen in both clostridial abscess and nonclostridial myonecrosis.
3. Gram stain shows large number of gram-positive rods, few polymorphonuclear leukocytes (PMNs) are found in the exudates, and free fat globules are demonstrated with Sudan stain.

B. Etiology

1. Associated with war injuries, farm machinery accidents, or deep tissue wounds exposed to soil organisms
2. Also surgical manipulation, irrigation with pressure devices, injection and air, and disruption of the esophagus or trachea
3. Occurs when wound is inadequately debrided; and occupation into surgical wounds after a gastrointestinal or biliary tract surgery; C. *perfringens* most common toxin

C. Diagnosis

1. Severe systemic toxicities; mental status changes, woody edema, gram-positive rods; cardiovascular collapse secondary to exotoxins
2. Muscle changes from a lusterless pink to deep red then gray–green/mottled purple; muscle does not contract on stimulation
3. Other causes of dermal necrosis: ischemic dermal necrosis (dry gangrene); ulcerating skin lesions (Meleney cutaneous gangrene); also seen in disseminated intravascular coagulation after septicemia (purpura fulminans), streptococcal necrotizing fasciitis

D. Treatment

1. Surgical emergency: wide debridement of nonviable fascia and muscle.
2. Wound is packed open.
3. Penicillin G 12 to 20 million units/day or clindamycin.
4. Hyperbaric oxygen therapy may be helpful particularly in extremities, as a supplement to antibiotics and surgery, but should not delay surgical debridement.

E. Complications. Worst prognosis if hematuria is present

VI. TOXIC SHOCK SYNDROME

A. Etiology

1. Usually exotoxin-producing strains of *S. aureus* and *S. pyogenes*
2. Disease progression stems from a superantigen toxin that allows the nonspecific binding of major histocompatibility complex (MHC) II with T-cell receptors, resulting in polyclonal T-cell activation.
3. *S. aureus* commonly colonizes skin and mucous membranes in humans.
4. Associated with use of tampons in women and complications of skin abscesses or surgery.

B. Diagnosis

1. Characterized by sudden onset of fever, chills, vomiting, diarrhea, muscle aches, and rash.
2. It can rapidly progress to severe and intractable hypotension and multisystem dysfunction with involvement of three or more organ systems:
   a. Renal failure (serum creatinine >2 times normal)
   b. Hepatic inflammation (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] >2 times normal)
   c. Thrombocytopenia (platelet count $<100{,}000/mm^3$)
   d. Central nervous system (CNS) involvement
   e. Desquamation, particularly on the palms and soles, can occur several weeks after onset of the illness

C. Treatment

1. The severity of this disease warrants hospitalization.
2. IV fluid administration and antistaphylococcal antibiotics, such as cephalosporins, penicillinase-resistant semisynthetic penicillins or vancomycin.

3. Streptococcal toxic shock–like syndrome treatment consists of penicillin and clindamycin.
4. With proper treatment, patients usually recover in 2 to 3 weeks. The condition can be fatal within hours.

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PRESSURE ULCERS: PREVENTION AND TREATMENT

110

Sewit Amde

I. EPIDEMIOLOGY

A. In an acute care setting, pressure sores develop in 3% to 11% of admissions.

B. Residents in chronic care facilities are the group at highest risk for the development of pressure sores.

C. Patients with spinal cord injury and patients in the intensive care unit often have multiple risk factors for the development of this problem.

II. PATHOPHYSIOLOGY

A. Pressure sores form as the end result of unrelieved pressure exerted on tissue over bony prominences.

B. Normal arterial capillary blood pressure closes at 32 mm Hg and weight-bearing prominences (sacrum, buttocks, heels, and occiput) are subject to this critical pressure while a patient is in the supine position.

C. Prolonged exposure to ischemia results in tissue necrosis; however, differing tissues exhibit different sensitivities to ischemia.

1. Muscle has much poorer tolerance to pressure than does skin or subcutaneous tissue.
2. Muscle and subcutaneous tissue infarction without skin necrosis is the "tip of the iceberg" phenomenon.
3. Studies have shown that ischemic necrosis can be prevented with intermittent restoration of blood flow.

D. Complicating the ischemic skin breakdown in critically ill patients are other factors such as malnutrition, hypotension, impaired mobility and sensation, and fecal or urinary incontinence.

III. PREVENTION

A. Prevention of pressure sores begins with education and dedicated care.

1. The tenets of prevention include pressure reduction over bony prominences, alteration of weight-bearing surfaces, good skin hygiene, and adequate nutrition.
2. Pressure dispersion techniques include foam mattress, air mattress, low air loss beds, air-fluidized beds, and oscillating support surfaces.
3. Patients with acute traumatic injuries and a decreased level of consciousness should be removed from backboards and cervical collars as soon as safely possible.

IV. WOUND CLASSIFICATION

A. Stage I: nonblanchable erythema of the skin with the lesion being limited to the epidermis and dermis

B. Stage II: full-thickness ulceration of the skin extending through to the subcutaneous adipose tissue

C. Stage III: ulceration extending to the underlying muscle

D. Stage IV: ulceration extending through muscle and involving bone

V. WOUND MANAGEMENT

- **A.** Management strategies entail identification, debridement, wound dressings, pressure dispersion, and maximization of overall health status.
  - **1.** Most stage 1 and 2 ulcers respond well to these measures.
  - **2.** Stage 3 and 4 ulcers may require sharp or enzymatic debridement, then wet to moist dressings are recommended to provide optimal wound environment for healing.
  - **3.** Negative pressure wound therapy in clean wounds has been shown to improve wound healing.
  - **4.** An occlusive hydrocolloid dressing can be used as an alternative in a well-debrided wound with minimal dead space.
  - **5.** Deeper ulcers also respond better if air-fluidized pressure dispersion is used.
- **B.** With appropriate care, up to 80% of pressure sores heal without surgery.
- **C.** Operative treatment is reserved for patients whose wounds have plateaued in healing despite maximal conservative (including nutritional) therapy.
  - **1.** Surgery is less frequently required in the ambulatory patient.
  - **2.** Spasticity must be medically addressed as part of treatment for pressure ulcer in spinal cord injured patients.
  - **3.** At operation, all devitalized tissue is removed and bony prominences partially reduced.
  - **4.** A variety of muscular advancement flaps are used, depending on the wound location.
  - **5.** Care is taken to avoid hematoma formation and tension on the closure.
- **D.** Postoperatively, it is critical to avoid compression on the flap vascular pedicle and minimize tension or shearing forces.
  - **1.** A special air or fluid mattress is important for the first 3 weeks.
  - **2.** Gradually, a program of weight bearing is used for the following 6 to 8 weeks.
  - **3.** The greatest challenge is to minimize future risks of pressure sore development.

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PAIN MANAGEMENT IN THE CRITICALLY ILL

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111

I. OVERVIEW. Pain, discomfort, restlessness and agitation are major problems for critically ill patients. Effectiveness of analgesia is related to correct usage of drugs, rather than to their analgesic properties. Fears of depressing spontaneous ventilation, inducing opioid dependence, and precipitating cardiovascular instability are frequent causes for inadequate relief of pain. Appropriate pain resolution facilitates recovery. In fact, evidence suggests that the appropriate usage of a combination of analgesics and sedatives may help ameliorate the detrimental effect that the stress response to pain might have on the recovery of the critically ill patient. Pain and anxiety are difficult to measure, because they constitute subjective phenomena. The clinician should therefore not judge the appropriateness of pain, but should concentrate on managing it appropriately.

II. GENERAL PRINCIPLES. Successful management of pain is based on:

- **A.** Identifying the etiology of pain.
- **B.** Determining a baseline before starting treatment and assessing the degree of pain in an objective manner with the help of validated scales and instruments.
- **C.** Understanding other components such as anxiety, ethnocultural factors, situational meaning, and prior experience.
- **D.** Establishing and maintaining drug levels at active sites for appropriate analgesia and anxiolysis and determining the end point of treatment so as to know when to stop management.
- **E.** Understanding that therapy is an iterative process in which measurements are made, therapeutic actions are taken, effectiveness is reevaluated, and the action is repeated until the desired clinical outcome is reached.

III. DEFINITIONS AND PATHOGENESIS

- **A.** *Pain* is an unpleasant sensory and emotional experience that can be associated with actual or potential tissue damage. *Pain-related behavior* is the only manifestation that can make the observer conclude that pain is being experienced. *Acute pain* has an identifiable temporal and causal relationship to an injury, in contrast to *chronic pain*, which persists beyond the healing process and that may not have an identifiable cause. *Nociception* is the detection and signaling of the presence of a noxious stimulus.
- **B.** Acute pain begins with damage to skin and/or deeper tissues. Locally produced and released algogens (prostaglandins, small peptides) sensitize or stimulate peripheral nociceptors, whose fibers propagate the signal into the dorsal horn of the spinal cord or the sensory nuclei in the brainstem. Before reaching pain-specific areas in deep brain structures or cortex, the signal is modulated (amplified or attenuated), which can increase or decrease the response to painful stimuli. These responses are either beneficial (e.g., withdrawal from noxious stimulus) or deleterious (e.g., sympathetic discharge that increases oxygen consumption from elevated muscle tone or spasm and tachycardia and increased cardiac work). Reflex hypothalamic stimulation leads to increased release of catabolic stress hormones and decreased anabolism, which may prolong or worsen the postsurgical catabolic state.

IV. DIAGNOSIS

A. Location: It should be determined whether the location is appropriate with the type of injury sustained or the surgery performed or whether it is entirely different. Look for unrecognized sources of pain, such as missing injuries. Pain can be neuropathic in nature, or it might be chronic or as a result of malpositioning during surgery. Underlying medical conditions such as chronic pain, arthritis, history of alcohol or other substance abuse, and psychiatric illness can influence medication selection and dosages.

B. Intensity: Visual or verbal analog scales aid the patient in quantifying her or his own pain, thereby providing a baseline for the evaluation of the response to treatment. The most widely used scale is the visual analog scale (VAS), where a spectrum of pain from "no pain" to "the worst pain I've ever had" is depicted as a scale from 0 to 10. The patient points to the corresponding level of pain. Modified versions using pictures of smiling/crying faces can be used in children or adults who do not understand the conventional VAS.

In patients who are unable to communicate (e.g., are intubated), markers of sympathetic activity such as restlessness, sweating, tachycardia, lacrimation, pupillary dilation, and hypertension can be graded as signs of pain intensity. It is important to identify reliable and valid tools for evaluating pain in the noncommunicative patient in the intensive care unit (ICU). Parameters such as facial expression, upper limb movement, compliance with mechanical ventilation, among others, may be important factors that can help the clinician determine if the patient is in distress secondary to pain.

C. Quality of sensation: Pain can be sharp if it is due to direct nociception (e.g., incision), dull or aching if it arises from deeper structures, or pulling or tugging in nature if it is related to the presence of sutures or visceral stimulation. Pain manifested as tingling, stinging, or buzzing sensations is usually related to abnormal neural function, secondary to either recovery from regional anesthesia or reestablishment of neural function after neural compression. Painful dysesthesias occur in conjunction with peripheral neuropathy.

D. Delirium, a transient disorder of attention and cognition, is common in critically ill patients. There are active (intermittent agitation, hallucinations, disruptive behavior) and hypoactive forms. The type and potential cause should be identified (including delirium induced by sedative or analgesic medications).

E. The concept of patient-focused sedation and analgesia stresses the importance of individual assessment of patients, and periodic reevaluation due to the changing needs in an individual patient for sedation and analgesia over time. The clinician should also identify all the therapeutic interventions and measures that may be causing or contributing to pain-related distress, for example, suctioning, intubation, placement of nasogastric tubes, blood withdrawal or placement of invasive lines for monitoring or intravenous (IV) access.

F. Monitoring the degree of sedation is also very important. There are a number of numerical scales that can be followed to help guide the appropriate dosage of analgesic/sedative medication based on the depth of sedation. The most popular is the 6-point Ramsay Scale, which is based on motor responsiveness, ranging from 1 = anxious or restless or both, to 6 = no response to stimulus. Other scales include the Sedation–Agitation Scale and the Motor Activity Assessment Scale. More sophisticated monitoring techniques currently being used in the operating room, like the bispectral index (BIS), provide objective data based on cortical and subcortical interactions, but are still in the process of being included in the clinical practice guidelines.

V. TREATMENT. Interference at various levels of the pain pathway by different techniques:

A. Periphery: nonsteroidal anti-inflammatory drugs (NSAIDs), local anesthetic infiltration, and peripheral nerve blockade. NSAIDs provide analgesia through the nonselective, competitive inhibition of cyclooxygenase (COX), thereby interfering with the production of prostaglandins and other mediators of the inflammatory cascade, which produce hyperalgesia and induce an inflammatory response. Ketorolac is the only IV NSAID available in the United States. It has been shown to provide additional analgesia when used in conjunction with opioid analgesics, without compromising respiratory drive. Side effects of ketorolac include nausea, peptic ulceration, and inhibition of platelet function. Severe bronchospasm can occur in patients with asthma, nasal polyposis, and allergy to NSAIDs. Ketorolac is contraindicated in acute or chronic renal failure and in the presence of hypovolemia. It should not be given for >5 days, and the renal function should always be monitored. Local infiltration with anesthetics is useful in the management of postoperative pain. Studies show that the analgesic effect persists for at least 48 hours. This prolonged effect is termed *preemptive analgesia*, and it was shown to be superior to spinal or general anesthesia in the control of postoperative pain after hernia repair. Repeated intermittent intercostal nerve blocks have been used to provide analgesia for thoracic injuries and surgery. Nerve blocks provide analgesia without sedation or respiratory depression. The need for repeated injections, the risk for pneumothorax, and the risk for systemic toxicity are disadvantages of this procedure. Paravertebral nerve blockade provides analgesia over several dermatomes by bathing several intercostal nerves with anesthetic, either with a single injection or by continuous infusion through a catheter. Intrapleural analgesia with bupivacaine is useful for analgesia in the thorax and upper abdomen. Unfortunately, this technique loses effectiveness in the presence of a thoracostomy tube (anesthetic is drained out of the pleural space) or if the pain is bilateral (increased absorption and toxicity and bilateral sympathetic blockade). Contraindications to this technique include fibrosis of the pleura, inflammation/infection with or without blood or fluid in the pleural space, and anticoagulation or infection at the site of injection. Other regional blocks include brachial plexus blocks and femoral nerve or lumbar plexus blocks for the upper and lower extremities.

B. Spinal cord (first integration): epidural and intrathecal infusions of local anesthetics or opioids, transcutaneous electrical nerve stimulation (TENS). By means of high frequency (80 to 100 Hz), low-intensity stimulation through sterile skin electrodes, and in combination with other methods of analgesia, TENS down modulates the afferent nociceptive signal at the spinal cord and brainstem levels, thereby controlling postoperative (periincisional) pain. It is associated with reduced rates of complications (nausea, vomiting, atelectasis, ileus). Afferent conduction can be blocked at the nerve root or spinal cord level with local anesthetics, and nociceptive signals can be down modulated centrally by intraspinal opioids acting on specific opioid receptors in the dorsal horn. Regional analgesia techniques include subarachnoid and epidural administration of local anesthetics, opioids, or mixtures thereof, with intermittent dosing or continuous infusion. Continuous subarachnoid analgesia with local anesthetics is used to manage postoperative pain. However, it requires continuous monitoring at bedside because of the potential for profound sympathectomy and hemodynamic instability. It has been associated with central nervous system infection, but current techniques are safe for at least 48 hours. Continuous epidural infusion of local anesthetics allows for prolonged analgesia, frequently associated, however, with hypotension due to sympathetic blockade. This side effect can usually be managed with intravascular volume expansion or small doses of an α-adrenergic agent. The opioid

most commonly used for epidural blockade is morphine, which, because of its low lipid solubility, tends to stay dissolved in the cerebrospinal fluid. Systemic absorption and rostral spread after administration may be responsible for side effects such as nausea, pruritus, urinary retention, and early (1 hour after administration) or late respiratory depression (6 to 12 hours), which is usually preceded by progressive sedation rather than decreased respiratory rate. Naloxone is used in divided doses to treat significant respiratory depression. Epidural catheters usually remain in place for 2 to 3 days, at which time patients can take oral pain medications. They can, however, be left in place indefinitely as long as there are no signs of infection or inflammation. Newer approaches recommend the use of combinations of local anesthetics with opioids for continuous epidural infusion because of fewer side effects and increased effectiveness in postoperative pain management.

C. Higher orders of integration throughout the nervous system: systemic opioids by depot injections (intramuscular [IM] or subcutaneous [SC]), transdermal delivery systems, bolus or continuous IV infusions, or patient-controlled analgesia (PCA). Inhaled anesthetic agents have a limited role in critically ill patients because of complications resulting from prolonged exposure, such as toxicity and bone marrow suppression. They are useful only during short, painful procedures such as dressing changes in burn patients. Sedatives such as benzodiazepines, barbiturates, phenothiazines, and butyrophenones are given in conjunction with opioids and are used for anxiolysis, sedation, and production of amnesia. These medications have the potential for depressing consciousness and respiratory effort. They are useful in patients who need prolonged mechanical ventilation and in patients who require sedation for the first 24 to 48 hours postoperatively. Systemic opioid analgesia is usually given through IM or SC injections. It, however, has limited use in ICU patients due to extreme delay in attaining therapeutic drug levels. Small IV doses are more effective. An alternative is the use of a transdermal fentanyl patch. These patches have various rates of delivery and have a delayed onset of action of 12 to 16 hours. The potential complications with this technique come from choosing the wrong dose, particularly in opioid naive patients. The effects will gradually worsen and will persist longer than expected, depending on skin blood flow. Continuous IV infusion of opioids is a relatively simple technique, as long as the loading dose and the rate of infusion are calculated correctly to maintain therapeutic levels. Most opioids have a half-life of 3 hours. The dose required to maintain a level of analgesia is one half the loading dose used to achieve analgesia in the first place. This is divided by 3 to calculate the hourly requirements. When patients experience breakthrough pain, it must be addressed as new-onset pain and the new infusion rate titrated to effect. PCA is a technique for the administration of small doses of opioid IV on a demand basis. When establishing the upper limit for PCA (1- to 4-hour dosage limit), a fivefold increase in need during the early postoperative period must be considered, from what was originally calculated for an hourly requirement. Maintenance doses should generally not exceed 0.02 mg of morphine per kg, or 1.5 mg per dose in most adults. The lockout interval (5 to 10 min) accounts for the time required for an adequate concentration of the opioid to be established at the active site before another dose is given. PCA is useful for maintaining established analgesia but not for establishing it in the first place. Overdose with PCA is rare because patients tend to titrate themselves into the therapeutic range. Most patients actually choose not to eliminate pain entirely. Overdose is a significant risk if a basal infusion rate is administered. Accumulation tends to occur if the rate is set too high. Basal rate should not exceed half the estimated hourly requirement. Lack of adequate analgesia results from inadequate dosing secondary to the patient failing to understand

the technique or equipment malfunction/programming errors. An unusual problem is parent- or spouse-controlled PCA. PCA requires that patients are awake and cooperative. PCA has also been used to give epidural medications (patient-controlled epidural analgesia [PCEA]) with considerable safety and efficacy.

VI. SELECTION OF DRUGS

A. Analgesics: Morphine is the first-line opioid recommended for use in the ICU. It is water-soluble, has a delayed peak effect. It also causes venodilation and decrease in the heart rate. It has a propensity to cause respiratory depression, nausea, ileus, spasm, pruritus and contraction of the sphincter of Oddi. Fentanyl is a good choice in patients with hemodynamic instability or in patients with morphine allergy. It is 80 to 100 times more potent than morphine and it has a short duration of action when administered in small doses. Hydromophone is an alternative to morphine that is approximately 5 to 10 times more potent. It has minimal hemodynamic effects. Methadone, is a synthetic opioid that can be given enterally or parenterally. It is the drug of choice in patients that have prolonged mechanical ventilation requirements and recovery times. It can also be used to wean patients of infusions of other opioid analgesics. Ketamine is a short-acting phencyclidine compound that can be used for short, painful procedures such as dressing changes in the burn ICU.

B. Sedatives: Lorazepam is the preferred agent for the prolonged treatment of anxiety in the critically ill adult. The effects are similar to diazepam, but lorazepam is 5 to 10 times more potent. Its onset of action is relatively slower but it is longer acting. Lorazepam is administered with propylene glycol, which makes it precipitate in IV lines and can cause metabolic acidosis and acute tubular necrosis. Midazolam is a short-acting benzodiazepine, which has a short duration of action. It is frequently combined with propofol and used for short-term treatment of anxiety in the critically ill adult. Midazolam can cause hypotension and respiratory depression. Diazepam is a weaker alternative that can be used in patients with prolonged hospital courses and recovery times. Propofol is a lipid-soluble alkylphenol that is prepared as a lipid infusion and has excellent sedative and hypnotic effects. It does not provide analgesia. Its mechanism of action is not completely known. Rapid levels of sedation can be quickly achieved and controlled, and discontinuation leads to rapid recovery, which makes it a popular choice for general anesthesia induction and maintenance. Haloperidol (Haldol) is used for the treatment of delirium in the ICU. It has the potential for causing arrhythmias, lowering seizure thresholds and causing extra-pyramidal reactions.

VII. COMPLICATIONS.

Under-treated pain and anxiety can lead to complications secondary to physiological responses. Constant stimulation of the autonomic nervous system and the release of humoral factors as part of the stress response to injury, infection/sepsis or surgery can lead to hemodynamic instability and increased demands on the heart, with ensuing myocardial ischemia or even infarction. The stress response also causes insulin resistance, increased metabolic rate and protein catabolism, together with immunosuppression. Adequate pain management can curb these once-considered physiologic responses and accelerate the recovery after surgery or trauma.

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This article provides a focused approach on pain management in critically ill patients.

MANAGEMENT OF THE OBSTETRIC PATIENT IN THE INTENSIVE CARE SETTING

112

Frank P. Schubert and John G. Gianopoulos

I. OVERVIEW

- **A.** General principles
  - **1.** Maternal physiologic adaptation to pregnancy
    - **a.** Cardiovascular
      - **i.** Increased: cardiac output, blood volume
      - **ii.** Decreased: peripheral vascular resistance
    - **b.** Respiratory
      - **i.** Increased: tidal volume, respiratory rate
      - **ii.** Decreased: total lung capacity, functional residual capacity
      - **iii.** No change: pulmonary artery pressure
    - **c.** Hematologic
      - **i.** Increased: blood volume, pH, coagulability
      - **ii.** Decreased: hematocrit
    - **d.** Renal
      - **i.** Increased: renal artery perfusion, glomerular filtration rate (GFR), creatinine clearance, renal clearance of medications, urinary stasis, risk of urinary tract infection (UTI)
      - **ii.** Decreased: blood urea nitrogen (BUN), serum creatinine, serum uric acid
    - **e.** Gastrointesinal
      - **i.** Increased: gastroesophageal reflux, aspiration risk with intubation
      - **ii.** Decreased: motility
  - **2.** Diagnostic radiation exposure
    - **a.** There is a small risk of oncogenesis at all gestational ages.
    - **b.** In early pregnancy 10 cGy exposure will cause fetal death.
    - **c.** In the first 12 weeks, 5 to 10 cGy exposure is concerning for teratogenicity.
    - **d.** Abdominal/pelvic shielding when possible.
    - **e.** Single-shot films expose the fetus to minimal radiation/risk.
    - **f.** Computed tomography (CT) delivers 5 to 10 cGy; use with caution if result will significantly alter the patient's management.
    - **g.** Significant fetal effects with >10 cGy.
    - **h.** Magnetic resonance imaging (MRI) is considered a safe alternative to CT.
  - **3.** Medications and pregnancy
    - **a.** Analgesics
      - **i.** Short courses of opiates are tolerated.
      - **ii.** Codeine is teratogenic in the first 12 weeks.
    - **b.** Nonsteroidal anti-inflammatory drugs (NSAIDs): should be avoided due to possible premature closure of the ductus arteriosus
    - **c.** Antibiotics
      - **i.** No known fetal effect: penicillins, cephalosporins, erythromycin, clindamycin, vancomycin
      - **ii.** Streptomycin and kanamycin: ototoxicity
      - **iii.** Gentamicin can be used if life threatening; monitor levels closely

iv. Sulfonamides: avoid in third trimester because it is associated with kernicterus in the infant when used in the third trimester
v. Tetracycline is teratogenic

d. Anticoagulants
i. Coumadin: teratogenic in first trimester, later it carries risk of fetal bleeding
ii. Heparin: does not cross placenta, anticoagulant of choice
iii. Low molecular weight heparin: safe, change to unfractionated in third trimester because low molecular weight heparin has been associated with epidural hematoma with regional anesthesia

e. Antihypertensives
i. Avoid angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers as they are associated with fetal renal dysfunction and oligohydramnios. (Why?)
ii. Sodium nitroprusside can lead to fetal thiocyanide poisoning.

f. Pressors
i. Phenylephrine for epidural/spinal anesthesia–related hypotension
ii. Dopamine or is recommended for the critically ill patient

g. Tocolytics
i. Multiple classes: β-adrenergic, NSAID, calcium channel blockers, magnesium sulfate
ii. Limited efficacy
iii. All have been associated with pulmonary edema—use continuous pulse-oximetry, avoid multiple agents as this increases the risk, treat with diuretics and supplemental oxygen, intubation or continuous positive airway pressure (CPAP)

II. HYPERTENSIVE DISORDERS OF PREGNANCY (PREECLAMPSIA)

A. General principles: eight percent to 10% of pregnancies. Leading cause of morbidity/mortality
B. Classification: chronic, gestational, preeclampsia/eclampsia, chronic with superimposed preeclampsia
C. Etiology: unknown
D. Pathophysiology: arteriolar vasospasm with intravascular volume depletion is the primary pathophysiologic alteration in preeclampsia
1. Peripheral vascular resistance increases → hypertension (HTN) Proteinuria →
2. Decreased albumin in blood → decreased oncotic pressure
E. Diagnosis:
1. Mild: sustained blood pressure >140 mm Hg systolic and/or 90 mm Hg diastolic developing after 20 weeks' gestation and proteinuria (>300 mg in a 24-hour collection).
2. Severe: one or more of the following: blood pressure >160 mm Hg systolic and/or 100 mm Hg diastolic (twice/6 hours apart). Greater than 5 g proteinuria. Less than 500 mL urine output in 24 hours. Cerebral or visual disturbances. Pulmonary edema or cyanosis. Epigastric or right upper quadrant pain. Impaired liver function. Thrombocytopenia ($<100{,}000/mm^3$). Fetal growth restriction.
F. Treatment: definitive treatment: delivery. Remote from term expectant management if mild disease. Bed rest, intravenous (IV) fluids, treatment of HTN (labetalol or hydralizine), steroids for fetal lung maturity (before 34 weeks), magnesium sulfate (seizure prophylaxis). Monitor labs: complete blood count (CBC), liver enzymes, 24-hour urine protein/creatinine clearance, coagulation studies, uric acid, metabolic profile. Monitor fetal status (ultrasound and external fetal heart rate monitoring).

G. Complications: hemolysis, elevated liver enzymes, low platelets (HELLP), pulmonary edema, premature delivery, renal failure, abruption, hypertensive encephalopathy. Eclamptic seizure is treated with IV magnesium.

III. OBSTETRIC HEMORRHAGE

A. General principles: significant cause of maternal morbidity, mortality, and fetal loss; 500 to 600 mL/minute flow to uterus at term; always localize the placenta by ultrasound before digitally examining the cervix.

B. Etiology: placenta previa, placental abruption, uterine atony, retained placental, urogenital lacerations, unrecognized coagulopathies.

C. Pathogenesis: previa—implantation of placenta over the cervix, abruption—separation of the placenta from the uterus before delivery of the fetus, atony—after delivery, the bleeding from the raw myometrial surface is halted by uterine contraction. Hemorrhage occurs when this fails to occur.

D. Diagnosis:

1. Third trimester bleeding : previa—painless vaginal bleeding, ultrasound shows placenta over cervical os. Abruption—painful vaginal bleeding, no previa on ultrasound.
2. Postpartum: loss >500 mL (vaginal delivery) or 1,000 mL (cesarean section), palpate for uterine tone, explore for retained placenta, examine for laceration, red top tube for clotting time.

E. Treatment:

1. Previa: bed rest, blood replacement, hospitalization near term, cesarean section.
2. Abruption: IV fluid and blood products, Kleihaur–Betke (a test for fetal hemoglobin in the maternal circulation) to assess for fetal maternal hemorrhage, delivery at term, expectant management and steroids if stable and remote from term.
3. Postpartum: uterine massage, uterotonics (pitocin, methergine [contraindicated with HTN], prostaglandins), uterine curettage, laceration repair.

F. Complications: fetal loss, placental percreta (growth into the myometrium), hysterectomy, maternal hypotension with cerebral ischemia.

IV. AMNIOTIC FLUID EMBOLISM

A. General principles: sudden and acute cardiovascular and respiratory collapse at or around the time of delivery

B. Etiology: entry of amniotic fluid into maternal circulation

C. Pathogenesis: unknown

D. Diagnosis: primarily clinical diagnosis of exclusion. Fetal squamous cells may be present in the maternal blood

E. Treatment: early intubation and ventilation, inotropic and vasoconstrictive agents, invasive right-sided cardiac monitoring

F. Complications: maternal death (>50%), disseminated intravascular coagulation (DIC)

V. HEMOLYTIC UREMIC SYNDROME (HUS)/THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

A. General principles: rare in pregnancy, can be mistaken for preeclampsia

B. Diagnosis:

1. HUS: renal failure, thrombocytopenia, and hemolysis
2. TTP: HUS with neurologic changes

C. Treatment: high-dose IV steroids, plasmapheresis

D. Complications: maternal mortality

VI. BURN INJURIES

A. General principles: pregnancy does not alter the acute management of the burn victim. Fetal loss rate is correlated with severity of burn and development of complications.

B. Treatment: if remote from term—steroids for fetal lung maturity. If preterm labor and <30% burn—tocolytics. Broad spectrum antibiotics, tetanus toxoid, and immunoglobulin therapy are not contraindicated.

C. Complications: fetal loss—if maternal burn is >50% then loss approaches 100%.

VII. TRAUMA

A. General principles: most common cause of death in pregnancy. Maternal physiology may delay the manifestations of shock. Uterus is particularly susceptible to blunt and penetrating trauma in the third trimester. Fetal compromise may occur early after trauma. When evaluating hypotension place pregnant patient in left lateral decubitus position to optimize blood return from the lower extremities.

B. Treatment:

1. Blunt trauma: fetal assessment using ultrasound and continuous fetal monitoring (4-hour minimum, longer if abdominal pain, vaginal bleeding, or contractions). Kleihaur-Betke (fetal maternal hemorrhage). Rh immunoglobulin for Rh-negative mothers. Treat maternal injuries appropriately.

2. Penetrating trauma: uterus protects other maternal abdominal organs. Fetal injury is common in abdominal penetrating injury (66%) with high fetal mortality (40% to 70%). Management is controversial. Most advocate surgical exploration, but conservative management (imaging/observation) may be considered.

C. Complications: abruption, fetal compromise or demise, fetal injury.

VIII. OTHER PREGNANCY-RELATED PROBLEMS

See Chapter 47 for other causes of acute respiratory failure in pregnancy and Chapter 95 for discussion of HELLP syndrome.

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XI Shock and Trauma

113 SHOCK: AN OVERVIEW

Kevin M. Dwyer

I. GENERAL PRINCIPLES

A. Definition

Shock is a multifactorial syndrome leading to systemic and localized tissue hypoperfusion resulting in cellular hypoxia and multiple organ dysfunction.

B. Description

1. Perfusion may be decreased systemically with obvious signs such as hypotension.
2. Perfusion may be decreased because of maldistribution as in septic shock where systemic perfusion may appear elevated.
3. Signs of malperfusion may be subtle and lead to significant organ damage.
4. Prognosis is determined by degree of shock, duration of shock, number of organs affected, previous organ dysfunction, and possibly some genetic predisposition.

II. ETIOLOGY CLASSIFICATION OF SHOCK

A. Hypovolemic shock

1. Loss of circulating intravascular volume and decrease in cardiac preload.

TABLE 113-1 Classification of Hypovolemic Shock

Hypovolemic shock (based on a 70-kg patient)	Class I	Class II	Class III	Class IV
Blood loss (mL)	Up to 750	750–1,500	1,500–2,000	>2,000
Blood volume (%)	Up to 15	15–30	30–40	>40
Pulse rate	<100	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Capillary refill	Normal	Decreased	Decreased	Decreased
Respiratory rate	Normal	20–30	30–40	Distress
Urinary output (mL/h)	>30	20–30	5–15	<10
Mental status	Mild anxiety	Anxiety	Confused	Lethargic
Fluid replacement	Crystalloid	Crystalloid	Crystalloid + blood	Crystallolid + blood

2. May be from hemorrhage such as with trauma, gastrointestinal bleeding, nontraumatic internal bleeding (such as aneurysm, ectopic rupture), or vaginal bleeding.
3. May be from nonhemorrhagic fluid loss from the gastrointestinal tract (vomiting, diarrhea, fistula), urinary losses (hyperglycemia with glucosuria), evaporative loss (fever, hyperthermia), and internal fluid shifts (third spacing as with a bowel obstruction).
4. Most common form of shock.
5. All forms of shock have some component of decreased preload.
6. Clinical signs depend on volume lost (Table 113-1). Symptoms include tachycardia, hypotension, decreased urine output, mental status changes, and tachypnea.
7. Treatment is with volume resuscitation with crystalloid solution, and, in addition, blood if from hemorrhage. Colloid infusion has no value in hypovolemic shock.

B. Obstructive shock

1. Caused by a mechanical obstruction to normal cardiac output (CO) with a decrease in systemic perfusion.
2. Consider cardiac tamponade and tension pneumothorax. Clinical signs of these include jugular venous distension, muffled heart sounds (tamponade), and decreased breath sounds unilaterally (pneumothorax).
3. Other causes are massive pulmonary embolism and air embolism.
4. Treatment is maximizing preload and relief of the obstruction.

C. Cardiogenic shock

1. Caused by myocardial (pump) failure.
2. Most common cause is extensive myocardial infarction.
3. Other causes are reduced contractility (cardiomyopathy, sepsis induced), aortic stenosis, mitral stenosis, atrial myxoma, acute valvular failure, and cardiac dysrhythmias.
4. Treatment is maximizing preload, cardiac performance, and reducing afterload.

D. Distributive shock

1. Caused by systemic vasodilatation from an inciting cause (infection, anaphylaxis) resulting in systemic hypotension, and increased or decreased CO.

2. The systemic inflammatory response syndrome (SIRS) is the most common cause of distributive shock. The endothelial toxicity and diffuse vasodilation is enhanced by messengers of the inflammatory response such as tissue necrosis factor α (TNF-α)
3. Most common cause of SIRS is sepsis, and SIRS used to be classified as "septic shock." Sepsis is caused by a systemic infection and is characterized by a high CO with systemic hypotension.
4. Septic shock is enhanced by the inflammatory response. Despite a high CO, there is cellular hypoxia likely from disruption of mitochondrial function.
5. Other causes of SIRS include posttraumatic shock and pancreatitis.
6. Treatment of shock secondary to SIRS is with massive volume to supplement preload, augmentation of blood pressure (BP) with vasoconstrictors as necessary, and treatment of underlying cause.
7. Other causes of distributive shock are anaphylaxis, severe liver dysfunction, and neurogenic shock.
8. Neurogenic shock is due to cervical spinal cord injury with loss of sympathetic vascular tone. There is no inflammatory response. The patient has hypotension, bradycardia, and warm extremities. Treatment is with volume and a vasoconstrictor.

E. Endocrine shock

1. Caused by hypothyroidism, hyperthyroidism with cardiac collapse, and adrenal insufficiency. Treatment is treating the underlying disease.
2. Adrenal insufficiency may be a contributor to shock in critically ill patients. Patients unresponsive to treatment should be tested for adrenal insufficiency.

III. PATHOPHYSIOLOGY

A. The result of shock is decreased tissue perfusion and cellular hypoxia.
B. Cellular hypoxia leads to cellular ischemia. Ischemic cells are primed by alterations of calcium and adenosine 3′,5′ cyclic monophosphate (cAMP), and creation of superoxide radicals.
C. Endothelial cells under hypoxic conditions will have enhanced vascular permeability and less control over membrane transport functions.
D. Reperfusion will result in release of oxygen radicals that cause further cell damage.
E. These processes activate neutrophils and the release of proinflammatory cytokines.
F. The inflammatory response results in further cellular damage, third spacing, and activation of the coagulation system, leading to microcirculatory thrombosis, collapse, and further ischemia.
G. In septic shock and SIRS, the initial event is the inflammatory response.
H. Microcirculatory collapse leads to multiple organ failure.

IV. DIAGNOSIS

A. Vital signs. Heart rate (HR), Blood Pressure (BP), temperature, urine output, and pulse oximetry are traditional measures to determine shock, and most clinicians still rely on these. However, 50% to 85% of patients with normal or near-normal vital signs are still in shock.

1. HR
   a. Tachycardia is an early sign of significant volume loss in shock.
   b. The HR in young patients or those on β-blockers may not increase.
   c. Bradycardia after prolonged hypotension precludes cardiovascular collapse.

2. BP
   a. Hypotension and narrowed pulse pressure is a sign of severe volume loss and shock.
   b. Mean arterial pressure (MAP) is a better guide to therapy then systolic BP.
3. Temperature
   a. Hyperthermia, normothermia, or hypothermia may be present in shock.
   b. Hypothermia is a sign of severe hypovolemic and septic shock.

B. Urine output
1. Early guide of hypovolemia and end organ response (renal) to shock.
2. This is a delayed vital sign as time (1 to 2 hours) is needed to measure the output.

C. Pulse oximetry
1. Continuously measured and early indicator of hypoxemia. May be invalid on the hypothermic patient.

V. INVASIVE HEMODYNAMIC MONITORING

A. Indwelling arterial catheters give continuous BP measurements.

B. A central venous catheter gives continuous central venous pressure (CVP) measurements.

C. Pulmonary arterial catheters (PAC) (introduced by Swan and Ganz in 1970) can measure CVP, right atrial pressure, pulmonary artery pressure, pulmonary arterial occlusion pressure (PAOP or wedge pressure), and CO. A PAC will help guide aggressive resuscitation in patients with severe shock. Hemodynamic variables are listed in Table 113-2

D. Cardiac preload

1. Left ventricular end-diastolic volume (LVEDV) is proportional to left ventricular end-diastolic pressure (LVEDP). Increasing LVEDV (preload) will increase myocardial fiber length and therefore increase CO to a patient specific optimal level (Frank–Starling law).
2. PAOP will reflect LVEDP in a patient without mitral valve disease and with stable ventricular compliance.
3. Increases in PAOP will increase CO to an ideal "wedge pressure."
4. Ventricular compliance is not stable in patients with severe shock.
5. Therefore in patients in shock, the measured PAOP is not accurate, but the trend of PAOP will reflect the ideal preload for optimal cardiac function.
6. Measurement of PAOP will guide resuscitation and volume status.

E. Cardiac flow variables

1. CO or cardiac index (CI) reflects cardiac function and can be directly measured by a PAC. Some PACs measure CO continuously.
2. Optimizing CI is a goal of resuscitation. CI can be increased by increasing preload, increasing contractility, and/or decreasing afterload.
3. Systemic vascular resistance index (SVRI) can be derived from the PAC measurements of CO (CI) and PAOP. The SVRI, which is a factor in cardiac afterload, will help guide volume, pressor, and vasodilator therapy.
4. Patients with hypovolemic, obstructive, cardiogenic and end-stage septic shock have a high SVRI and a low CI. Patients with early septic shock have a low SVRI and a high CI.
5. Left ventricular stroke work index (LVSWI) can be derived by the change in pressure × the change in volume and will also reflect the response to therapy. LVSWI = (MAP − PAOP) × stroke volume index (SVI = CI/HR) (0.0136).
6. Specialized PACs measure right ventricular ejection fraction (RVEF) which can calculate right ventricular end-diastolic volume (RVEDVI). (RVEDVI = SVI/RVEF). RVEDVI is a more accurate measure of true volume status.

TABLE 113-2 Hemodynamic Variables

Variable (abbreviation)	Unit	Normal range
Measured variables		
Systolic blood pressure (SBP)	mm Hg	90–140
Diastolic blood pressure (DBP)	mm Hg	60–90
Systolic pulmonary blood pressure (PAS)	mm Hg	15–30
Diastolic pulmonary blood pressure (PAD)	mm Hg	4–12
Pulmonary artery occlusion pressure (PAOP)	mm Hg	2–12
Central venous pressure (CVP)	mm Hg	0–8
Heart rate (HR)	Beats/min	50–100
Cardiac output (CO)	L/min	4–6
Right ventricular ejection fraction (RVEF)	Fraction	0.4–0.6
Calculated variables		
Mean arterial pressure (MAP)	mm Hg	70–105
Mean pulmonary artery pressure (MPAP)	mm Hg	9–16
Cardiac index (CI)	L/min/m^2	2.8–4.2
Stroke volume (SV)	mL/beat	Varies
Stroke volume index (SVI)	mL/beat/m^2	30–65
Systemic vascular resistance index (SVRI)	dynes × s/cm^5	1,600–2,400
Pulmonary vascular resistance index (PVRI)	g × m/m^2	250–340
Left ventricular stroke work index (LVSWI)	g × m/m^2	45–62
Right ventricular stroke work index (RVSWI)	mL/m^2	7–12
Right ventricular end-diastolic work index (RVEDWI)		60–100
Body surface area (BSA)	m^2	Varies

7. Methods for measuring CO other than with a PAC have been devised. Examples are analysis integration of the area beneath the arterial wave form, and noninvasive chest impedance.

VI. OXYGEN TRANSPORT ASSESSMENT

A. Shock is a decrease of cellular oxygen perfusion or the delivery of oxygen to the tissues is inadequate to meet the cellular oxygen demand or consumption.

B. Oxygen delivery index (DO_2) is the arterial oxygen content × the CI.

$$DO_2 = CaO_2 \times CI \times 10dL/L$$

C. Arterial oxygen content is % saturated Hgb × the biding coefficient (1.34) + the oxygen dissolved in the plasma (a clinically insignificant amount and is disregarded).

$$CaO_2 = (1.34 \times Hgb \times SaO_2) + (PaO_2 \times 0.003)$$

D. Venous oxygen content is the % saturated venous Hgb × 1.34 + oxygen dissolved.

$$CvO_2 = (1.34 \times Hgb \times SvO_2) + (PvO_2 \times 0.003)$$

E. Oxygen consumption index (VO_2) is the $(CaO_2 - CvO_2) \times CI \times 10$ dL/L

$$VO_2 = (1.34 \times Hgb \times SaO_2 - SvO_2) \times CI \times 10dL/L$$

F. The oxygen extraction ratio (OER) is VO_2/DO_2 or approximately 25% normally.

G. If the consumption is increased, the OER increases and there is an oxygen demand. If the DO_2 is low, there will not be enough oxygen to meet the demand.

H. Oxygen transport determines if DO_2 is adequate to meet VO_2. The cornerstone of treatment is to increase DO_2 either by increasing Hgb or by increasing CI.

I. Transfusion of blood to increase Hgb beyond 7 to 8 is only necessary with active hemorrhage.

J. Supranormal oxygen delivery has been supported by some literature. Other literature suggests the achievement of supranormal DO_2 is only a marker of survival, and does not increase survival. Therefore, normal or above normal oxygen delivery is associated with increased prior to survival.

K. Continuous measurement of SvO_2 (available with a specialized PAC) will detect early increases of VO_2 (a low SvO_2) and the need for an increase of DO_2.

L. A high SvO_2 is indicative of early sepsis, SIRS, and or cirrhosis and may reflect the derangement of O_2 utilization at the cellular (mitochondrial) level.

VII. RESUSCITATION ENDPOINTS

A. Lactic acid production

1. Cells with inadequate oxygen will switch to anaerobic metabolism.
2. Lactic acid is a byproduct of anaerobic metabolism.
3. Elevation of serum lactate is a measure of the severity of shock. Elevated lactate is a global measure of hypoperfusion, and may not be elevated with regional hypoperfusion. Lactate may be elevated in liver or kidney failure and may be of less value as an absolute number.
4. The rate of clearance of lactate is a better marker of adequate resuscitation rather then the absolute value.

B. Base deficit

1. Base deficit is the amount of base required to titrate whole blood to a normal pH.
2. The presence of an elevated base deficit correlates with the severity of shock.
3. Base deficit is easily obtained with an arterial blood gas.
4. The correction of the base deficit is a guide to further resuscitation.

C. Intramucosal pH monitoring

1. With the mesenteric hemodynamic response to shock, the mesenteric organs will have earlier and greater hypoperfusion than other organ systems.
2. Gastric tonometry measure intramuscular pH and is an early indicator of hypoperfusion in shock, and correlates with mortality. Technical difficulties with the monitoring have mitigated its usage.

VIII. TREATMENT

A. Rapid recognition and restoration of perfusion is the key to preventing multiple organ dysfunction and death with shock. In all forms of shock, rapid restoration of preload with infusion of fluids is the first treatment. Crystalloid is first infused and then blood if shock is secondary to hemorrhage. Shock must be treated while identifying its cause. Further treatment of shock will depend upon its etiology.

IX. HYPOVOLEMIC SHOCK

A. Rapid infusion of multiple liters of crystalloid is the treatment of hypovolemic shock. Large-bore venous access is needed, and central access may be necessary.

B. If the cause is hemorrhage, then after 2 to 3 L of crystalloid, blood is transfused. Coagulapathy will persist until the source of bleeding is controlled.
C. Recent data from resuscitation of severe hemorrhagic shock from war wounds supports the use of massive transfusion of blood and coagulation factors (fresh frozen plasma [FFP] and platelets) in a 1:1:1 ratio.
D. Factor VIIa may assist in coagulation during the resuscitation of hemorrhagic shock until the bleeding is controlled.
E. Resuscitation is not complete until the base excess or serum lactate has decreased to an acceptable level. Patients with severe hypovolemic shock will have third space fluid with resuscitation.
F. Vasoconstrictors are rarely needed with pure hypovolemic shock.
G. A PAC may be helpful in guiding resuscitation in patients with severe shock.

X. OBSTRUCTIVE SHOCK

A. The cause of the obstruction must be identified and relieved early.
1. Pericardiocentesis or pericardiotomy for a cardiac tamponade
2. Needle decompression and tube thoracostomy for tension pneumothorax
3. Ventilatory and cardiac support, possibly thrombolytics in addition to heparin for pulmonary embolism (see Chapter 48).

XI. CARDIOGENIC SHOCK

(see Cardiac Section of this manual)
A. Optimize preload with infusion of fluids.
B. Optimize contractility with inotropes as needed, balancing cardiac oxygen demand. Consider dobutamine, amrinone, or milrinone.
C. Adjust afterload to maximize CO. This may involve using a vasoconstrictor if a patient is hypotensive with a low SVR. Patients with cardiogenic shock may need vasodilatation to decrease their SVR and resistance to flow from a weak heart. Consider nitroprusside or nitroglycerin.
D. A B-type natriuretic peptide (BNP) level will be elevated in patients with congestive heart failure. Diureses may be indicated in patients.
E. A PAC is recommended to guide therapy in these patients.
F. The underlying cardiac cause needs to be treated if possible.

XII. DISTRIBUTIVE SHOCK

A. In SIRS and sepsis, shock is due to toxin or mediator-induced vasodilation. See Chapter 123.
B. Treatment is with aggressive fluid resuscitation (see Chapter 123). Once adequate volume status is established, pressors can be used to augment BP. Frequently, pressors are started during resuscitation. However, tissue perfusion will not be optimized unless optimal preload augmentation is achieved.
1. Dopamine is frequently used because of its splanchnic vasodilatation. However, this effect may be insignificant, and dopamine's initial effect is an increase in HR. Dopamine has no effect on mortality from septic shock.
2. Norepinephrine is a good vasoconstrictor and is the recommended pressor in septic shock once adequate volume is achieved.
3. Vasopressin has been used effectively in profound septic shock, especially when norepinephine is not working. There is evidence that natural vasopressin stores are low in patients in shock.
4. Low-dose steroids can be considered in patients with adrenal insufficiency.
C. A PAC is highly recommended for patients with shock from SIRS.
D. Treatment of the underlying cause of SIRS is essential. Many clinical trials have been conducted to identify pharmaceuticals to interrupt the inflammatory response. Only activated protein C has been approved for treatment for patients with septic shock. In theory, it interrupts the microcirculatory thrombosis.

Suggested Reading

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Choi PTL, Yip G, Quinonez LG, et al. Crystalloids versus colloids in fluid resuscitation: a systematic review. *Crit Care Med* 1999;27:200–210.
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Committee on Trauma of the American College of Surgeons. *Advanced trauma life support program for physicians.* Chicago: American College of Surgeons, 1997.
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Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 2003;348:727–734.
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Davis JW, Shackford SR, Mackersie RC, et al. Base deficit as a guide to volume resuscitation. *J Trauma* 1988;28:1464–1467.
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Marik PE, Pastores SL, Annane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med* 2008;36:1937–1949.
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Sharshar T, Blanchard A, Pallard M, et al. Circulating vasopressin levels in septic shock. *Crit Care Med* 2003;31:1526–1531.
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Waxman K. Shock: ischemia, reperfusion, and inflammation. *New Horiz* 1996;4(2): 153–160.
This entire journal is a good review of the pathophysiology of shock.

HEMORRHAGIC SHOCK AND RESUSCITATION

114

Christopher P. Michetti

I. GENERAL PRINCIPLES

A. Definition

1. Shock is a condition in which the amount of oxygen delivered to tissues is inadequate to maintain normal cellular function, that is, aerobic metabolism.

2. Hemorrhagic shock (HS) results from tissue hypoperfusion due to hypovolemia from blood loss.

B. Epidemiology

1. Hemorrhage is second only to brain injury as a cause of early death after traumatic injury.

2. Trauma is the leading cause of death in the United States from ages 1 to 44.

C. Outcome

1. Outcome is proportional to the duration and severity of shock.

2. Rapid identification of shock and initiation of treatment before hypotension occurs is essential to minimize morbidity.

3. Trauma patients with HS have improved outcomes when treated at a level I trauma center (highest level) as soon as possible after injury.

II. PATHOPHYSIOLOGY

A. Physiologic alterations

1. Hypoperfusion after hemorrhage leads to tissue ischemia, a shift from aerobic to anaerobic metabolism, production of lactate and inorganic phosphates, and metabolic acidosis.

a. Depletion of adenosine triphosphate (ATP), oxygen radical formation, and other processes of anaerobic metabolism result in cellular injury and eventually cell death.

2. The hypothalamic-pituitary-adrenal axis is activated by shock and results in release and elevation of several hormones.

a. Increased cortisol leads to hyperglycemia and insulin resistance, muscle breakdown, and lipolysis.

b. Release of vasopressin causes sodium and water retention.

c. Activation of the renin-angiotensin system produces angiotensin II, a vasoconstrictor.

3. Activation of the systemic inflammatory response results in release of proinflammatory mediators that can cause cell and organ dysfunction.

a. Ischemia and reperfusion of tissues, especially gut, activate systemic inflammatory response.

b. Cytokines such as tumor necrosis factor, interleukins-1 and -6 are released.

c. Complement system is activated.

d. Endothelial cells allow adhesion of activated neutrophils and their transmigration into tissues, where they cause tissue injury by releasing oxygen radicals and proteolytic enzymes.

B. Fluid shifts
  1. Triphasic response
    a. Initial phase: response to bleeding is fluid shift from the interstitial space into capillaries to compensate for lost intravascular volume.
      i. Lasts from start of bleeding until bleeding controlled
    b. Second phase: with resuscitation, fluid shifts from the intravascular space back to the interstitial space (the "third space").
      i. Lasts 1 to several days.
      ii. Interstitial space sequesters large amounts of fluids ("capillary leak" phenomenon).
      iii. Patients become severely edematous and *simultaneously* intravascularly depleted.
      iv. Fluid intake markedly exceeds output.
      v. Fluid sequestration and resultant edema are obligatory and necessary in resuscitation from HS.
    c. Third phase: a natural diuresis occurs as fluid moves from the interstitial space to the intravascular space, and is filtered through the kidneys.
      i. Starts 3 to 5 days after injury
      ii. Key sign of recovery from shock
  2. Common mistake among those inexperienced in shock resuscitation is to misinterpret the edema and highly positive fluid balance of shock patients as signs of increased hydrostatic pressure from congestive heart failure.
    a. Fluid intake/output balance is irrelevant in acute HS resuscitation.
    b. Tissue edema and increased body water are the natural result of successful HS resuscitation.
    c. Forced diuresis exacerbates tissue hypoperfusion by depleting intravascular volume.

III. DIAGNOSIS

A. Classifications of HS
  1. Class I
    a. Loss of up to 15% of total blood volume (0 to 750 mL in a 70-kg person)
    b. Characterized by normal vital signs and urine output, slight tachypnea, slight anxiety
  2. Class II
    a. Loss of 15% to 30% of total blood volume (750 to 1,500 mL)
    b. Characterized by normal blood pressure (BP), tachycardia, mild tachypnea, decreased urine output, and mild anxiety
  3. Class III
    a. Loss of 30% to 40% of total blood volume (1,500 to 2,000)
    b. Characterized by hypotension, tachycardia, tachypnea, decreased urine output, and anxiety and confusion
  4. Class IV
    a. Loss of >40% of total blood volume (>2,000 mL)
    b. Characterized by severe hypotension and tachycardia, tachypnea, negligible urine output, and lethargy
  5. Note that BP is *normal* until significant blood loss occurs (Class III)
  6. Tachycardia is the earliest reliable sign of shock

B. Sources of hemorrhage
  1. There are only five locations of blood loss that can result in HS.
    a. Thorax
      i. Hemothorax (blood in pleural cavity)
      ii. Diagnosis by chest radiograph or computed tomography (CT) scan
      iii. Ninety percent of thoracic injuries can be treated with thoracostomy tube alone

- **b.** Abdomen
  - **i.** Usually due to liver or spleen injury.
  - **ii.** Gastrointestinal (GI) bleeding is common nontraumatic etiology.
  - **iii.** Diagnosis by ultrasound, CT scan, diagnostic peritoneal lavage, or visible GI bleeding.
  - **iv.** Physical examination is *not adequate* to exclude bleeding in the abdomen.
  - **v.** Significant injuries and hemoperitoneum may be present with a normal abdominal examination.
- **c.** Pelvis and retroperitoneum
  - **i.** Exsanguination can result from pelvic fractures, especially posterior fractures.
  - **ii.** Renal or major vascular injuries, or ruptured aortic aneurysms can result in significant retroperitoneal blood loss.
  - **iii.** Diagnosis of fractures by pelvic radiograph; CT scan best test for retroperitoneum.
- **d.** Long bone fractures
  - **i.** Can lose up to 1,500 mL of blood in each thigh from femur fractures
  - **ii.** Can lose up to 750 mL of blood from humerus or tibia fracture
  - **iii.** Diagnosis by radiography
- **e.** External sites
  - **i.** Bleeding from scalp lacerations, deep soft tissue wounds, or major vascular injuries can result in HS.
  - **ii.** Diagnosis by history (from scene) and physical examination of all wounds.
  - **iii.** Wounds should be carefully explored and never blindly probed (to avoid dislodging a hemostatic clot and rebleeding).

2. Intracranial bleeding or brain injuries do not cause shock.

IV. TREATMENT

A. Management of HS involves two goals: hemostasis and fluid resuscitation

1. Both goals usually pursued simultaneously

B. Hemostasis

1. Control of the source of bleeding is an absolute necessity in HS management.

2. The method of hemostasis depends on the cause and source of bleeding. Options include:

- **a.** Surgery
- **b.** Endovascular techniques and embolization
- **c.** Application of direct pressure
- **d.** Correction of coagulopathy to allow hemostasis to occur on its own
  - **i.** This option usually not applicable when bleeding is from major blood vessel

3. In some cases, resuscitation is delayed until hemorrhage control is achieved.

- **a.** Only applies to situations where surgery is already planned as immediate definitive treatment
  - **i.** For example, penetrating trauma, ruptured abdominal aortic aneurysm

C. Pitfalls in hemostasis

1. Delay in surgery

- **a.** Hypotension from bleeding is an indication for immediate surgical consultation since it indicates significant blood loss and such patients have a high risk of requiring surgery.
- **b.** Avoid attempts at interventional radiology or endovascular hemostasis in the setting of hypotension or prolonged bleeding.

2. Not correcting hypothermia
   a. Hypothermia is a common and often overlooked contributor to coagulopathy.
   b. Standard coagulation tests do not uncover hypothermia-induced coagulopathy since blood is warmed in the laboratory before performing the tests.
3. Not correcting coagulopathy
   a. Frequent assessment of coagulation function should accompany any HS resuscitation.

D. Resuscitation
1. The first priority for any bleeding patient is to ensure a patent, secure airway. The second priority is to ensure adequate breathing and ventilation. Hemostasis and fluid resuscitation are the third priority.
   a. In clinical practice, all assessed and treated nearly simultaneously
2. Resuscitation from HS includes stopping the bleeding and replacing the volume loss.
   a. Direct localized pressure should be applied to any visible bleeding points.
      i. Use of tourniquets discouraged because of global ischemia distal to tourniquet
      ii. Direct pressure allows hemostasis with preserved collateral flow
   b. Resuscitation encompasses replacing volume loss and restoration of normal end-organ perfusion
3. Fluid resuscitation:
   a. Warm lactated Ringer's or normal saline (crystalloid) solution are the preferred resuscitation fluids for HS, with initial rapid bolus of 2 L.
   b. If hypotension persists after 2-L bolus of crystalloid, packed red blood cells should be transfused and crystalloid infusion continued.
   c. Crystalloid should be infused to replace the initial volume lost, and ongoing fluid infusion to resuscitate the *interstitial space fluid deficit* resulting from HS.
      i. General rule of HS resuscitation is to replace three times the volume of blood lost with crystalloid (e.g., 1 L of blood loss should be replaced with 3 L of crystalloid).
         (a) The 3-to-1 rule comes from classic experiments in the 1960s and 1970s, in which HS was noted to result in large extracellular fluid deficit.
         (b) Mortality for resuscitation with shed blood alone was 80%, shed blood plus plasma was 70%, lactated Ringer's plus shed blood (in a 3:1 ratio) 30%.
   d. Replacement of hemorrhage with blood only, or less than the required ratio of crystalloid to blood loss, results in persistent hypoperfusion and acidosis, and increased mortality.
   e. Fluid resuscitation of the interstitial space is *obligatory* in HS. The resultant edema and fluid retention is the expected result, not a harmful side effect, of proper HS resuscitation. Since this space needs to be filled to several times its original volume, a larger volume of fluid than the original volume lost must be infused (3:1 rule).
      i. The interstitial space volume in a 70-kg male is approximately 10 L.
4. Response to resuscitation
   a. Rapid response
      i. "Responders" become hemodynamically normal after the initial fluid bolus and remain so without continued boluses.
      ii. Early surgical consultation is necessary due to the possible need for operative intervention.
   b. Transient response
      i. These patients respond to the initial fluid bolus, but again become hemodynamically unstable or show signs of decreased perfusion.

Continued fluid infusion and blood transfusion are required to maintain normal hemodynamics.

ii. These patients most often require rapid surgical intervention.

c. No response

i. Patients who show no response to fluid boluses and blood transfusion have continued hemorrhage and require immediate surgical intervention to stop bleeding.

ii. Must keep in mind nonhemorrhagic causes of shock such as tension pneumothorax, cardiac tamponade, spinal cord injury, cardiogenic shock, and septic shock.

5. Endpoints of resuscitation

a. The goal of HS resuscitation is restoration of end-organ perfusion.

b. Traditional endpoints (normalization of BP, heart rate, urine output, capillary refill) are inadequate.

i. BP does not equal cardiac output (CO), and therefore may not reflect normal perfusion.

ii. Increased systemic vascular resistance (SVR) may raise BP, with no change in perfusion.

iii. Patients with shock but normal BP are referred to as being in "compensated shock," since they are able to maintain BP despite bleeding and hypoperfusion.

c. Even experienced practitioners can be fooled by patients in compensated shock.

d. Failure to recognize compensated shock can result in under-resuscitation and its sequelae.

e. Normalization of acidosis and oxygen consumption are best current indicators of adequate resuscitation at cellular level.

i. Base deficit (on arterial blood gas) and lactate level are good indicators of tissue perfusion.

ii. Oxygen delivery and consumption are calculated using pulmonary artery catheter.

E. Pitfalls in resuscitation

1. Albumin and other colloids

a. Colloids have no benefit over crystalloids in terms of outcome or complication rate in resuscitation for any condition.

b. The majority of evidence shows higher mortality with use of albumin in trauma and HS.

c. In normal volunteers, colloids remain in intravascular space and increase colloid oncotic pressure, drawing fluid into intravascular space and raising BP. This physiology is not applicable to HS, in which colloids leak into the interstitial space, retain fluid and increase organ edema.

d. Lower-volume resuscitation, a proposed benefit of colloid use, opposes the physiologic need for resuscitation of the interstitial space with fluid per the 3:1 rule.

e. Albumin shown to decrease glomerular filtration and urine output, increase sodium retention, worsen oxygenation, and increase coagulopathy when used for HS.

f. National warning from U.S Food and Drug Administration (FDA) in 1996 warned of potential harm of albumin solutions.

g. Colloid use in HS or critical care hard to justify considering lack of evidence for benefit, and high cost.

2. Vasopressors

a. Vasopressors increase SVR and raise BP, according to formula BP = CO × SVR. However, increased BP does not mean increased perfusion. Since normal tissue perfusion is the goal of shock resuscitation, vasopressors may have opposite effect of worsening perfusion through vasoconstriction.

- **b.** Must ensure adequate intravascular volume status before vasopressor therapy.

3. Diuretics
- **a.** Well-resuscitated patients mobilize third space fluids naturally 3 to 5 days after resuscitation.
- **b.** Induced diuresis (e.g., with furosemide) is unnecessary, and may be harmful if it reduces intravascular volume and perfusion.
- **c.** Since normal edema resulting from proper shock resuscitation is the result of an inflammatory response (not cardiogenic failure) and is obligatory, it is not reversible in the early stages of shock.
  - **i.** For example, one could not prevent or treat edema in a sprained ankle (result of inflammation) with diuretics, but could do so for ankle edema from congestive heart failure (result of increased hydrostatic pressure).
- **d.** Intravascular volume status should be estimated by measurements of central venous pressure or pulmonary capillary wedge pressure; overall fluid balance and physical examination are not accurate measures of intravascular volume status

4. Bicarbonate
- **a.** Bicarbonate combines with hydrogen ion to form water and carbon dioxide.
  - **i.** CO_2 diffuses into cells and worsens intracellular acidosis.
- **b.** It is not indicated for lactic acidosis from HS.
- **c.** Best treatment of acidosis from HS is restoring perfusion to ischemic tissues through volume resuscitation.

F. Investigational strategies

1. These strategies for HS resuscitation have been well tested in animals, but less so in controlled clinical human trials. None have proven superiority over the standard treatment described earlier and are not considered standard of care, but may be used by experienced practitioners in specific circumstances.

2. Hypertonic saline:
- **a.** Provides restoration of BP with low volume
- **b.** Has anti-inflammatory properties
- **c.** Sometimes used in prehospital setting or in hypotensive brain injured patients

3. Delayed resuscitation:
- **a.** Entails limiting fluids and accepting low BP until definitive control of hemorrhage achieved, to avoid disrupting hemostatic plugs with normal BP
- **b.** Only one prospective human trial involving only penetrating chest and abdominal trauma
- **c.** Used only in patients planned for immediate surgery
- **d.** Contraindicated in brain injuries; unproven in blunt trauma

4. Hemoglobin-based oxygen carriers
- **a.** Solution of polymerized or crosslinked hemoglobin molecules
- **b.** Able to carry and deliver oxygen
- **c.** Universally compatible
- **d.** Decreased immunomodulatory and infectious risks compared to blood
- **e.** May decrease need for blood transfusion
- **f.** Clinical trials in humans indicate these products may be a safe alternative to traditional red blood cell transfusion

V. COMPLICATIONS

A. Multiple organ failure (MOF)

1. Patients who survive HS but die in the hospital later usually die of MOF or sepsis.

2. MOF results from the systemic inflammatory response.

3. Duration and severity of HS correlate with incidence of MOF.
4. Patients who get >6 units of packed red blood cells in the first 12 hours of HS resuscitation have a higher risk of MOF.

B. Coagulopathy
1. Hypothermia
   a. Most common cause of coagulopathy in HS
   b. Significant coagulopathy begins at core body temperature <34°C
   c. Undetectable on laboratory tests of coagulation; blood warmed to 37°C before testing
      i. Treat with warmed fluids and external rewarming
2. Platelet dysfunction and deficiency
   a. Second most common cause of coagulopathy in HS.
   b. Hypothermia causes platelet dysfunction.
   c. Thrombocytopenia is common with massive HS.
   d. Degree of thrombocytopenia does not correlate directly with volume of blood loss.
   e. Platelet transfusion is indicated for platelet dysfunction (presence of microvascular bleeding or diffuse oozing) or platelet count <100,000/mm^3 with active bleeding.
   f. Platelet transfusion is not based on number of blood transfusions given.
3. Factor dysfunction and deficiency
   a. Factor dysfunction in HS usually due to hypothermia (slows enzymatic reactions of coagulation).
   b. Dilution of factors is possible with massive resuscitation.
   c. Treat with normalizing body temperature, and fresh frozen plasma transfusion if prothrombin time is abnormal.

Suggested Reading

Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomized controlled trials. *Br Med J* 1998; 317:235–240.
Large review of all randomized trials prior to 1998 using albumin for multiple conditions, including hemorrhagic shock.

Committee on Trauma of the American College of Surgeons. *Advanced trauma life support course for doctors*, 6th ed. Chicago: American College of Surgeons, 1997: 97–117.
Standard reference on the initial diagnosis and management of hemorrhagic shock.

Davis JW, Shackford SR, Mackersie RC, et al. Base deficit as a guide to volume resuscitation. *J Trauma* 1988;28:1464–1467.
Reference on base deficit as an endpoint in resuscitation.

Forsythe SM, Schmidt GA. Sodium bicarbonate for the treatment of lactic acidosis. *Chest* 2000;117:260–267.
Review on rationale for lack of efficacy of sodium bicarbonate use in lactic acidosis.

Lucas CE. The water of life: a century of confusion. *J Am Coll Surg* 2001;192:86–93.
An excellent brief review of hemorrhagic shock pathophysiology and fluid shifts.

Moore EE. Blood substitutes: the future is now. *J Am Coll Surg* 2003;196:1–17.
Excellent reference on pathophysiology, development, and uses of hemoglobin-based oxygen carriers.

The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004;350:2247–2256.
A prospective randomized blinded trial in almost 7,000 patients showing no difference in outcomes between saline and albumin in critically ill patients.

Velanovich V. Crystalloid versus colloid fluid resuscitation: a meta analysis of mortality. *Surgery* 1989;105:65–71.
Early meta-analysis on fluids and mortality.

115 TRAUMA: AN OVERVIEW

Christoph R. Kaufmann

I. THE PROBLEM

- **A.** Trauma is the leading cause of death between the ages of 1 and 44 in the United States and is estimated to kill 160,000 annually.
- **B.** Two million injured Americans are hospitalized and 27 million are treated in emergency departments on an annual basis.
- **C.** Trauma, as a disease of the young, is responsible for more years of life lost than cancer and heart disease combined.
- **D.** The leading cause of trauma deaths in the United States is the motor vehicle, which accounts for 45,000 deaths annually. Motor vehicles are predicted to become the third largest cause of death and disability worldwide by 2020.
- **E.** Prevention of gun violence remains a public health challenge as gun-related deaths are the second leading cause of trauma death in the United States.

II. LESSONS LEARNED IN TRAUMA CARE ARE FROM MILITARY EXPERIENCE

- **A.** The Edwin Smith Papyrus, recognized as the earliest example of medical literature, describes 48 trauma cases and their treatment.
- **B.** Ambroise Paré, a French military surgeon of the 1500s, introduced several modern wound care concepts including ligation of arteries.
- **C.** Dominique Jean Larrey, Napoleon's chief surgeon, developed the concept of the "ambulance volante" or flying ambulance to rapidly evacuate the wounded from the battlefield.
- **D.** The last 100 years have seen additional improvements in trauma care through military experience.
  - **1.** Resuscitation fluids
  - **2.** Vascular surgery
  - **3.** Helicopter transport
- **E.** Recent experience of military surgeons in Iraq and Afghanistan has lead to the use of new hemostatic agents and reevaluation of ratios of transfused blood products.

III. ADVANCED TRAUMA LIFE SUPPORT AND INITIAL APPROACH TO THE TRAUMA PATIENT

- **A.** Advanced Trauma Life Support (ATLS) is a course developed by the American College of Surgeons (ACS) and teaches one, safe way to provide the first hour of hospital care for the injured patient.
- **B.** The A, B, C, D, Es of trauma care are (in order of priority): Airway (assess adequacy and consider need for a definitive airway = cuffed tube in the trachea), Breathing (insure adequate ventilation), Circulation (resuscitate with volume infusion and stop the bleeding), Disability (neurologic examination), Exposure (disrobe patient)/Environment (keep the patient warm).
- **C.** The ATLS primary survey consists of rapid assessment of the airway, breathing, and circulation.
- **D.** Adjuncts to the primary survey include pulse oximetry, cardiac monitoring, urinary catheter, anteroposterior (AP) chest and pelvic x-rays, and sonography.
- **E.** An AMPLE history should be obtained: **A**llergies, **M**edications, **P**ast Illnesses/**P**regnancy, **L**ast meal, **E**vents/**E**nvironment related to the injury.

F. The ATLS secondary survey is the complete head-to-toe history and physical.
G. Adjuncts to the secondary survey include specialized diagnostic tests.
H. An ATLS caveat is that a definitive diagnosis is not required before appropriate rapid treatment of life-threatening problems, such as needle decompression of tension pneumothorax without waiting for x-ray proof of the clinical diagnosis.

IV. MEASURING INJURY SEVERITY/PERFORMANCE IMPROVEMENT/TRAUMA REGISTRIES

A. The Injury Severity Score (ISS) is an anatomic measure of injury severity. ISS ranges from zero in patents with no injury, to 75 for injuries considered incompatible with survival. Trauma patients with ISS > 15 are severely injured.
B. The Glasgow Coma Scale (GCS) score is a clinical measure of severity of brain injury based on eye opening (1 to 4), verbal response (1 to 5), and best motor response (1 to 6). The score range is 3 to 15. The GCS should be scored and recorded at the scene of the injury, at patient arrival in the emergency department, and serially thereafter.
C. The Revised Trauma Score (RTS) is a physiologic measure of injury severity based on three factors: GCS, systolic blood pressure, and respiratory rate. RTS ranges from zero to 12, with any score <12 used as an indication for trauma center level care in some locales.
D. ISS and RTS may be mathematically weighted and combined to estimate the probability of survival (P_s) for an individual trauma patient. These probabilities are frequently used for quality improvement efforts.
E. Quality improvement/performance improvement processes are an integral part of trauma center and trauma system programs.
F. Trauma registries are routinely in place now in all trauma centers and the data is frequently aggregated at a state level. The National Trauma Data Bank contains >1 million individual trauma patient records.

V. TRAUMA CENTERS AND TRAUMA SYSTEMS

A. Cook County Hospital in Chicago, IL is recognized as the first trauma center in the United States (opened in 1966).
B. In 1969, Maryland developed the first statewide trauma system.
C. The concept of the "preventable trauma death" was instrumental in advent of trauma systems across the United States, typically organized at the state level.
D. Statewide trauma systems must consider the following components: legislation; funding; injury prevention; notification (identification of incident); communication; prehospital emergency medical services including scene care, triage, and transport; trauma center/acute care hospital services, including emergency department (ED), operating room (OR), intensive care unit (ICU), and ward care; rehabilitation; disaster/mass casualties.
E. Triage guidelines are developed and adopted at a local or a state level. These are linked with destination protocols in an effort to get the right trauma patient to the right facility in the right amount of time using appropriate transportation modalities based on patient need.
F. Trauma, perhaps more than any other disease, is time sensitive and requires a team approach. Each multidisciplinary trauma team needs a team leader, typically a surgeon in US trauma centers.
G. Many states designate trauma centers as levels I, II, and III, while others also include level IV and even level V in an effort to be inclusive of all facilities.
H. Level I and level II trauma centers are able to provide full-spectrum care for the injured patient, including 24/7 neurosurgical and orthopaedic specialty care. Although many states use the ACS trauma center verification standards, many others use state-specific criteria. The ACS standards can be found in "Resources for Optimal Care of the Injured Patient 2006."

I. Rehabilitation is critical to successful outcomes for patients who have suffered multiple injuries, although rehabilitation resources are all too frequently limited.

J. Statewide trauma systems are uniquely suited to act as the framework for mass casualty and disaster planning at the local, state, and national level.

Suggested Reading

Committee on Trauma, American College of Surgeons. *Advanced trauma life support for doctors*, 7th ed. Chicago: American College of Surgeons, 2004.
The eighth edition is due in October 2008.

Committee on Trauma, American College of Surgeons. *Resources for optimal care of the injured patient*. Chicago: American College of Surgeons, 2006.
The ultimate resource for trauma center design.

MacKenzie EJ, Fowler CJ. Epidemiology. In: Feliciano DV, Mattox KL, Moore EE, eds. *Trauma*, 6th ed. New York: McGraw-Hill, 2008.
A must-read description of the injury problem in the United States as a chapter in the definitive trauma textbook.

TRANSPORTING THE CRITICAL PATIENT

Gina R. Dorlac and Jay A. Johannigman

116

I. GENERAL PRINCIPLES

A. Transport of critical patients occurs any time a patient is moved from one physical location to another. This may be intra- or interfacility, by any means of transportation (stretcher, ground-based ambulance, rotary wing aircraft, fixed wing aircraft).

1. Essentials:

a. Pretransport evaluation (whether the transport takes minutes or hours!)

i. What are risks versus benefits?

ii. All patient movement has inherent risks, and should only be done if the benefits of transport are significant and outweigh the risks.

iii. Risks of patient movement increase with severity of illness and duration of transport time.

iv. Best managed with a thorough checklist and a systematic approach.

v. There are no absolute contraindications to transporting the critical patient.

vi. There are many factors which may make patient movement high risk.

vii. The level of patient care provided must not degrade during the period of transport.

b. Monitoring

i. Patients who require monitoring before transport also require monitoring during transport.

ii. Requires care provider who:

(a) Can monitor the information

(b) Respond appropriately to changes in status

(c) The level of criticality dictates the level of expertise of the care provider

2. Care provided:

a. For longer transport distances and longer time periods:

i. Same monitoring and care must be provided as in the intensive care unit (ICU) (dosing of routine medications, deep vein thrombosis [DVT] prophylaxis, nutrition, decubitus ulcer prevention, etc.).

b. Short intrafacility transports:

i. Do not require this provision of care.

ii. Bare minimum requirements for intrafacility transports are ability to provide advanced cardiac life support (ACLS) response and emergency airway management.

3. Caution: Many recommendations for care of the critical patient during transport are anecdotal rather than evidence based.

II. INDICATIONS

A. To obtain necessary procedures or diagnostic tests (radiographic studies, operating room, angiography suite) which cannot be performed at bedside or for which better quality will result if done in designated area rather than at bedside

B. To transfer patient to a facility that provides a higher level of care

C. To remove patient from a high-risk area (combat zone, disaster area)

III. PROCEDURE

A. Patient evaluation

1. Airway
   - **a.** Secure endotracheal tube and ensure that the tube will not be obstructed by patient activity or motion (bite block).
   - **b.** Consider delaying transport until 24 hours post tracheostomy.
   - **c.** Consider prophylactic intubation for even minimal respiratory instability.
2. Ventilation
   - **a.** Familiarity with available transport ventilators is essential. Support from an experienced respiratory therapist is recommended. Transport ventilators exist which can match some but not all ICU ventilator modes.
   - **b.** Allow room for deterioration in pulmonary physiology, especially for longer duration transports. Patients already on high F_{IO_2}/high positive end-expiratory pressure (PEEP) have little margin for worsening.
   - **c.** Consider intrafacility transport on ICU ventilator for patients with severe pulmonary impairment.
   - **d.** Aggressively maintain pulmonary recruitment and PEEP.
   - **e.** Always have a "rescue" mode of providing ventilation and oxygenation (such as an AMBU bag and oxygen tank).
3. Cardiac
   - **a.** ACLS response must be immediately available.
   - **b.** Consider placing defibrillator pads for those patients at highest risk of dysrhythmia (acute inferior wall myocardial infarction [MI] post thrombolytic therapy have 10% risk, new intraventricular conduction delay post MI have 30%).
   - **c.** Consider elective intubation for marginal patients: can decrease myocardial oxygen demand, unload heart failure.
4. Metabolic
   - **a.** Electrolytes and acid base status should be normal or normalizing.
   - **b.** Patients on insulin infusion will require continued monitoring of blood glucose; diabetic ketoacidosis will require continued electrolyte monitoring.
5. Infectious disease
   - **a.** Appropriate isolation for patients with communicable disease.
   - **b.** For known infection, consider possibility of sepsis progressing. Anticipate potential for need to broaden antibiotic coverage or start vasopressor agents.
6. Orthopaedic
   - **a.** Fractures must be stabilized pretransport, consider external fixation. Traction is unlikely to be able to be maintained during transport.
   - **b.** Evaluate for extremity compartment syndrome before transport; may develop during prolonged transport especially in air transports.
7. Neurologic
   - **a.** Many patients will require deeper level of sedation to facilitate safe transport; avoid inadvertent removal of therapeutic devices. Consider neuromuscular blockade if appropriate. During short transports, sedation may be managed by intermittent bolus therapy; for longer transports, continuous infusions should be used.
   - **b.** Consider intracranial pressure (ICP) monitoring in critical brain injured patients in whom a consistent neurologic examination is not available. ICP monitoring must be continuous. Elevate head of bed if possible.
   - **c.** Anticipate worsening intracranial hypertension and be prepared to treat (hypertonic saline, mannitol, acute mild hyperventilation).
   - **d.** Seizure prophylaxis and acute treatment available.

e. Anticipate potential for diabetes insipidus and consider bringing desmopressin (DDAVP).

8. Burns
   a. Thermoregulation can be difficult in transport environment. Aggressively maintain normothermia using any means available: ambient temperature control, blankets, and head covering.
   b. Avoid burn wound manipulation in transport: wounds should remain dressed and moist.

B. Equipment considerations

1. Ventilator, infusion pump, monitor, suction, and defibrillator must all be approved for use in transport vehicle; have adequate battery power for transport and/or ability to be plugged into transport vehicle.
2. If in-transport laboratory testing is required, point of care testing device and supplies must be available and calibrated before transport.
3. Supplies to include medications, intravenous fluids, and batteries, and oxygen must be sufficient for entire transport time. Anticipate unexpected delays.

C. Team composition

1. Varies depending on patient numbers and acuity of patients. Highest demand in flight is typically on nursing duties. Requirement for a physician in attendance will depend on patient acuity and availability of the physician to join team in case of deterioration.

D. Transport physiology

1. Patients transported at altitude have additional physiologic stresses that must be considered. Anticipate gas expansion in hypobaric environment, decreased ambient partial pressure of oxygen, low humidity, and less well-regulated temperature.

IV. POSTPROCEDURE CONSIDERATIONS

A. Care of the patient is the responsibility of the transporting team until appropriate assessment and hand-off are made at the receiving facility.

Suggested Reading

Austin PN, Johannigman JA (eds). Transport of the mechanically ventilated patient. *Resp Care Clin North Am* 2002;8(1):1–66.
An in depth review of mechanical ventilation in transport, both intra- and inter-facility, to include aspects of ventilator mechanics and team training.

Holleran RS, ed. *Air and surface patient transports: principles and practice*, 3rd ed. New York: Mosby, 2002.
An official publication of the Air and Surface Transport Nurses Association, a comprehensive reference covering pathophysiology and transport related management; case studies are included.

117 HEAD TRAUMA

Joshua J. Wind, Joshua M. Ammerman, and James M. Ecklund

I. GENERAL PRINCIPLES

A. Traumatic brain injury (TBI) is a leading cause of death and long-term disability, and results in an enormous economic cost to society. More than 1.5 million head injuries occur each year, accounting for 250,000 hospitalizations, 60,000 deaths, and 80,000 patients left with permanent neurologic disability. Outcomes from TBI have improved with improved critical care and multidisciplinary management teams made up of trauma surgeons, intensivists, neurosurgeons, and others. The use of advanced monitoring techniques and evidence-based approaches to TBI management have also contributed to these improved outcomes.

II. ETIOLOGY

A. Head trauma can be categorized as closed or penetrating. The most frequent causes for closed TBI are motor vehicle accidents, falls, and assaults. Frequent causes of penetrating TBI are gunshot wounds or fragmentation injuries in the military population.

III. PATHOPHYSIOLOGY

A. *Primary brain injury*—occurs at time of injury as a result of direct trauma to brain tissue.

B. *Secondary brain injury*—occurs after initial injury, causing additional insults to the brain. This is usually secondary to hypoxia, hypotension, intracranial hypertension, and/or complex inflammatory cascade.

C. Increased intracranial pressure (ICP) may be a result of mass effect imparted during the primary injury such as a hematoma, or as a result of edema from secondary processes. Much of the management of TBI is aimed at preventing or treating elevated ICPs.

1. Monro-Kellie doctrine → the skull is a rigid compartment containing brain tissue, cerebrospinal fluid (CSF), and intravascular blood. Because this space is unable to expand, any change in its contents (intracranial mass lesion or diffuse edema) must be followed by a subsequent reduction in other components in order to compensate. This eventually leads to a decrease in cerebral blood flow and brain perfusion.
2. Herniation occurs when ICP rises to the point where brain contents herniate through a skull compartment opening (either through the tentorial incisura, below the falx cerebri, through the foramen magnum).
3. Brain death occurs when cerebral edema and herniation eliminates adequate blood flow to the brain, resulting in widespread infarction. Brain death is defined as the irreversible cessation of all brain and brainstem functions.

IV. DIAGNOSIS

A. History of traumatic event and neurologic status at the scene

B. Neurologic examination

1. Examination for scalp lesions, skull fractures (open or closed), and CSF leak

2. Pupil size and reactivity
3. Motor and sensory examination
   a. Uncal herniation syndrome includes ipsilateral fixed, nonreactive pupil, and contralateral hemiparesis (rarely ipsilateral-"Kernohan's notch phenomenon")
   b. Peripheral and central reflex examination
   c. Glasgow Coma Scale (GCS) (Table 117-1)

C. Radiographic studies
1. Noncontrast computed tomography (CT) scan of the head is often used as a primary radiographic study for evaluation of a patient with a head injury. It is an adequate modality for evaluating most skull fractures, mass lesions including hematomas and contusions, and other processes including hydrocephalus or cerebral edema.
2. Vascular studies in patients with suspected cervical or intracranial vascular injury, including CT angiography, magnetic resonance (MR) angiography, or conventional cerebral angiography. Adjunct modalities also include magnetic resonance imaging (MRI) and transcranial Doppler ultrasound (TCD). More recently, CT or MR perfusion studies have been used selectively to optimize treatment and diffusion tensor imaging is being investigated as an adjunct for prognosis.

V. TREATMENT

A. Ensure adequate airway, breathing, and circulation (systolic blood pressure [SBP] >90, SpO_2 >90). Both hypotension and hypoxia are associated with significantly increased mortality and morbidity.

B. Diagnose and obtain surgical consultation for significant mass lesions such as epidural hematomas (EDH), subdural hematomas (SDH), depressed skull fractures, contusions, or intraparenchymal hematomas. Guidelines for surgical management of these lesions are included in the suggested reading.

C. ICP monitoring is indicated in all patients with GCS 3 to 8 who have a CT revealing lesions or edema or patients with normal CT when two or more of the following are present: age older than 40, motor posturing, and SBP <90 mm Hg. Ventriculosomy is desirable when feasible, as it is more cost effective, accurate, and allows CSF drainage to aid in the treatment of elevated ICP. Other types of ICP monitors (intraparenchymal fiberoptic monitors, for example) are acceptable but have the added complexity of signal drift and the inability to recalibrate once placed.

D. Once ICP monitoring has been initiated, the goal is to maintain ICP <20 mm Hg, and to preserve cerebral perfusion pressure (CPP) ideally above 60 (CPP = mean arterial pressure − ICP). CPP <50 should be avoided;

TABLE 117-1 Glasgow Coma Score

Eye	Motor	Verbal
1. No opening	1. No motor response	1. No verbal response
2. Open to pain	2. Decerebrate posturing	2. Incomprehensible sounds
3. Open to voice	3. Decorticate posturing	3. Inappropriate words
4. Open spontaneously	4. Withdraws to pain	4. Confused response
	5. Localizes to pain	5. Oriented response
	6. Follows commands	

The components are added together for a cumulative Glasgow Coma Score. If the patient is intubated, a score of 1 T is used for the verbal component.

however, aggressive attempts to maintain elevated CPP (i.e., >70) may result in pulmonary complications such as acute respiratory distress syndrome (ARDS).

E. A three-tiered management algorithm for TBI and elevated ICP is presented below:

1. First tier measures:
- **a.** Elevate head of bed to 30 to 45 degrees.
- **b.** Keep neck straight to avoid jugular outflow obstruction.
- **c.** Avoid hypotension and hypoxia.
- **d.** Ventilate to normocarbia ($PaCO_2$ 35 to 40).
- **e.** Light sedation.

2. Second tier measures:
- **a.** Heavy sedation
- **b.** Use of paralytics
- **c.** CSF drainage with ventriculostomy
- **d.** Mannitol or hypertonic saline
- **e.** Mild hyperventilation ($PaCO_2$ 30 to 35)

3. Third tier measures:
- **a.** Decompressive craniectomy
- **b.** Barbiturate coma
- **c.** Hyperventilation ($PaCO_2$ 26 to 30)
- **d.** Hypothermia (unclear data)
  - **i.** Early hyperventilation and mannitol before ICP monitoring should be limited to patients with evidence of herniation as a temporizing measure.

F. Multiple other monitoring tools can provide additional input to guide therapy, including brain tissue oxygenation ($PbtO_2$), jugular venous O_2 saturation ($SjvO_2$), cerebral blood flow, and continuous electroencephalogram (EEG).

VI. COMPLICATIONS

A. The primary complication of TBI is secondary brain injury which can compound the neurologic morbidity and mortality. The most severe result is progression to herniation and brain death.

B. Systemic complications of TBI:

1. Diabetes insipidus—hypothalamic nuclei produce arginine vasopressin which functions at the collecting duct of the kidney to reabsorb free water. Injury to these nuclei, most commonly seen in very severe head injuries, results in the inability to concentrate urine and subsequent elevation of serum osmolality.

2. Syndrome of inappropriate antidiuretic hormone (SIADH)—excessive release of arginine vasopressin, resulting in excessive concentration of urine and dilution of serum electrolytes such as sodium.

3. Cerebral salt wasting—poorly understood condition where volume *and* sodium are excreted in the urine, resulting in hypovolemia and hyponatremia.

4. Seizures—can occur early (first 7 days), or late. Prophylactic anticonvulsants recommended for the first 7 days. Phenytoin is best studied, and therefore currently recommended; but trials are ongoing for other agents.

5. Coagulopathy—release of tissue factors may result in increased fibrinolysis and hypocoagulable state. This may progress to disseminated intravascular coagulation (DIC).

6. Cardiopulmonary complications—myocardial infarction, acute respiratory distress syndrome, heart failure.

7. Deep venous thrombosis and pulmonary embolus—pneumatic compression devices are recommended initially; prophylactic doses of anticoagulation can be started after 2 to 3 days with very small risk of bleeding.
8. Infection—patients with head injuries are at risk for ventilator-related pneumonia, line sepsis, and other infections. CSF leaks increase risk for meningitis. Antibiotic use during ventriculostomy placement is indicated, but there is no clear indication for continuous antibiotics while ventriculostomy is in place.
9. Nutrition—patients should attain 100% to 140% of caloric demands by 1 week after injury.

Suggested Reading

Aarabi B, Alden T, Chestnut R, et al. Management and prognosis of penetrating brain injury. *J Trauma (Supplement)* 2001;51(2):S1–S86.
Published evidence-based guidelines from an expert panel.

Bullock MR, Polishock JT (eds). Guidelines for the management of severe traumatic brain injury (3rd edition). *J Neurotrauma* 2007;24(Suppl 1):S1–S106.
Published evidence-based guidelines from an expert panel

Bullock MR, Chestnut R, Ghajar J. Guidelines for the surgical management of traumatic brain injury. *Neurosurgery (Supplement)* 2006;58(3):S1–S62.
Published evidence-based guidelines from an expert panel.

Manley G, Knudson M, Morabito D, et al. Hypotension, hypoxia, and head injury: frequency, duration, and consequences. *Ach Surg* 2001;136:1118–1123.
Good discussion of secondary injury.

Marik P, Varon J, Trask T. Management of head trauma. *Chest* 2002;122:699–711.
Good overview.

Narayan RK, Wilberger JE, Povlishock JT, eds. *Neurotrauma.* New York: McGraw-Hill, 1996.
Excellent comprehensive textbook on neurotrauma.

Valadka AB, Andrews BT, eds. *Neurotrauma: evidence based answers to common questions.* New York: Thieme Medical Publishers, 2005.
Evidence-based approach to common management issues.

118 SPINAL CORD TRAUMA

Howard B. Levene, Michael Y. Wang, and Barth A. Green

I. EPIDEMIOLOGY AND CLINICAL SIGNIFICANCE

- **A.** Affects approximately 11,000 Americans per year
- **B.** A total of 200,000 patients living with spinal cord injury (SCI)
- **C.** Typically affects young males (15 to 29 years), but a growing trend of middle-aged and elderly patients due to lifestyle habits and improved survivability of injuries
- **D.** Etiology
  - **1.** Motor vehicle accident 47%
  - **2.** Falls 23%
  - **3.** Violence 14%
  - **4.** Sports/recreation 9%
  - **5.** Other 7%

II. NEUROLOGIC INJURY

- **A.** SCI can be classified by:
  - **1.** Mechanism (penetrating vs. blunt trauma)
  - **2.** Level (cervical, thoracic, or lumbar)
    - **a.** Designated as the lowest spinal segment with completely normal function
  - **3.** Neurologic injury (degree of impairment), frequently designated by the American Spinal Injury Association (ASIA) Grade (Table 118-1)
    - **a.** Grade A Complete: no sensory or motor function preserved in sacral segments S4-5
    - **b.** Grade B Incomplete: sensory, but not motor, function preserved below neurologic level and extends through sacral segments S4-5
    - **c.** Grade C Incomplete: motor function preserved below neurologic level with muscle grade less than antigravity strength
    - **d.** Grade D Incomplete: motor function preserved below neurologic level with muscle grade greater than or equal antigravity strength
    - **e.** Grade E Normal: sensory and motor functions normal
- **B.** Complete SCI
  - **1.** No preservation of motor function and/or sensation three spinal segments below level of injury
  - **2.** Complete injuries above T6 usually associated with spinal shock
    - **a.** Hypotension from interruption of sympathetics
    - **b.** Bradycardia from unopposed vagal (parasympathetic) output
    - **c.** Hypothermia
    - **d.** Transient loss of all neurologic function resulting in a flaccid paralysis and areflexia
- **C.** Incomplete SCI
  - **1.** Any preservation of motor and/or sensory function three spinal segments below level of injury, including sphincter tone or sacral sensation
- **D.** Specific incomplete SCI syndromes
  - **1.** Central cord syndrome
    - **a.** Occurs in two patient populations: young athletes with congenital cervical stenosis and the elderly with acquired cervical stenosis from spondylosis

TABLE 118-1 American Spinal Injury Association Grading Scale for Spinal Cord Injury

Clinical grade	Neurologic examination
A	No motor or sensory function preserved
B	Sensory but no motor function preserved
C	Nonuseful motor function preserved (less than antigravity strength)
D	Motor function preserved but weak
E	Normal motor and sensory function

- **b.** Hyperextension injury
- **c.** Upper extremity weakness out of proportion to lower extremity weakness
- **d.** No evidence of cervical spine fracture

2. Brown-Sequard syndrome
- **a.** Spinal cord hemisection
- **b.** Loss of contralateral pain and temperature sensation, ipsilateral proprioception and vibratory sensation, and ipsilateral motor function

3. Anterior cord syndrome
- **a.** Spinal cord infarction in distribution of anterior spinal artery (anterior two thirds of cord)
- **b.** Complete loss of motor function and loss of pain and temperature sensation but preserved posterior column function (proprioception and vibratory sensation)

4. Conus medullaris syndrome
- **a.** Associated with thoracolumbar junction fracture
- **b.** Early loss of sexual and sphincter function
- **c.** Symmetric "saddle" loss of motor and/or sensory function in lower extremities

III. PATHOPHYSIOLOGY

A. Primary injury mechanisms

1. Kinetic energy transferred to neural elements during trauma

2. Compression from bone, cartilage, hematoma, or foreign bodies

3. Results from
- **a.** Movement and stressing of the spine beyond its physiologic limits in hyperflexion or hyperextension
- **b.** Retropulsion of bone or disc into the spinal canal
- **c.** Dislocation of the spinal column
- **d.** Direct laceration or transection of the cord

B. Secondary injury mechanisms

1. Systemic hypoxia and hypotension from neurogenic shock, hypoperfusion, hypoxia, other systemic injuries

2. Local vascular insufficiency of the cord from trauma

3. Ongoing spinal compression

4. Biochemical changes
- **a.** Excitotoxicity
- **b.** Neurotransmitter accumulation
- **c.** Arachidonic acid release
- **d.** Free radical production
- **e.** Eicosanoid production
- **f.** Lipid peroxidation

g. Endogenous opioids
h. Cytokines
5. Electrolyte shifts
a. Increased intracellular calcium
b. Increased extracellular potassium
c. Increased intracellular sodium
6. Edema
7. Loss of energy metabolism with decreased adenosine triphosphate (ATP) production

IV. INITIAL ASSESSMENT AND STABILIZATION

A. Primary trauma survey (**a**irway, **b**reathing, **c**irculation, **d**isability, **e**xposure [ABCDE])
1. Special attention to hemodynamic stability to maintain cord perfusion and management of neurogenic shock
2. Maintenance of spinal alignment and immobilization
B. Neurologic examination (completeness and level of injury)
C. Radiographic assessment
1. Mechanism and degree of spinal column injury
2. Degree of persistent neural compression
3. Detection of second-site spinal injuries (occur in 15%) of SCI patients
D. Early intervention to prevent the onset of delayed sequelae (respiratory, cutaneous, gastrointestinal, thromboembolism)

V. ASSESSMENT OF SPINAL COLUMN STABILITY

A. Definition
1. Clinical instability: potential for further neurologic injury if allowed to bear normal physiologic loads
2. Radiographic instability
a. Abnormal motion on dynamic x-rays (e.g., >3.5 mm subluxation or >11 degrees of angulation in the cervical spine)
b. Fracture or alignment pattern consistent with severe instability (e.g., spondyloptosis with a fracture dislocation or Chance fracture) (Fig. 118-1)
c. Substantial destruction of the bony/ligamentous elements on imaging (e.g., two of three columns being injured) (Fig. 118-2)
3. Predictors of delayed instability
a. Fracture patterns that would be predicted, if left untreated, to result in late neural compression, deformity, or pseudarthrosis
B. Instability of the spinal column militates for maintenance of spinal precautions and bracing. In many instances surgical realignment, fixation, and fusion will be necessary.
C. Missile injuries rarely destabilize the spine

VI. TREATMENT

A. Management in the field
1. Airway management, maintenance of adequate blood pressure (BP) (i.e. SBP >120, MAP >90)
2. Major blunt trauma victims whether conscious or unconscious should be deemed to have SCI until proved otherwise
3. Cervical collar in combination with rigid backboard should be used to immobilize spine
B. Acute hospital management
1. Degree of stability
a. Rigid immobilization with cervical traction and kinetic treatment table or halo-vest orthosis for unstable fractures

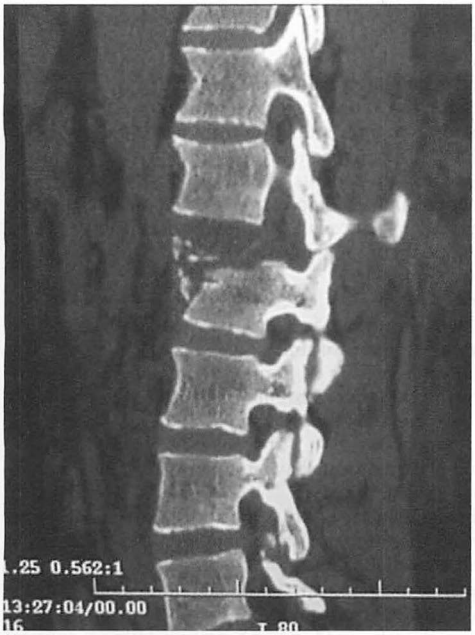

Figure 118-1. Chance fracture.

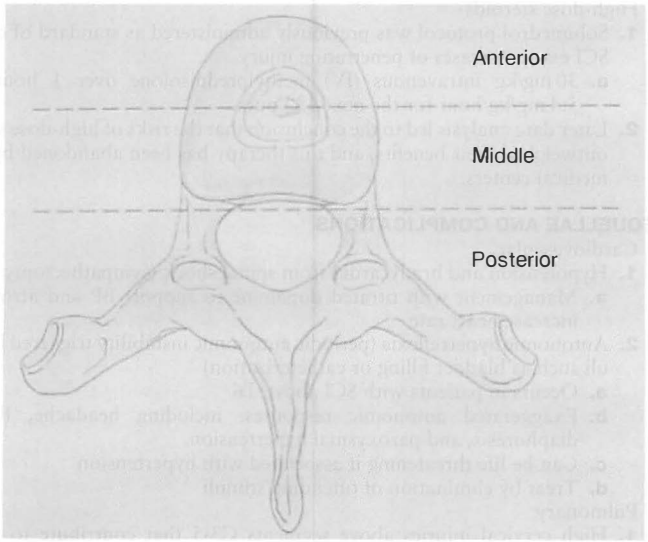

Figure 118-2. Three-column injury model.

- **b.** Nonrigid immobilization with cervical collar or thoracolumbosacral orthosis for stable fractures
- **2.** Need for neurologic decompression
  - **a.** Closed reduction and traction for dislocation or subluxation with cord and/or root compression to restore normal alignment
    - **i.** Neurologic deterioration after reduction from herniated disc
    - **ii.** Recommend magnetic resonance imaging (MRI) before reduction in obtunded or incomplete patients
  - **b.** Open surgical reduction and decompression for irreducible dislocation, bone/disc fragments in the canal, or epidural hematoma causing persistent cord and/or root compression
- **3.** Timing of decompressive surgery
  - **a.** Experimental evidence
    - **i.** Threshold SCI was produced in dogs with inflatable epidural balloons for varying amounts of time.
    - **ii.** Earlier decompression (within 8 hours) resulted in better neurologic recovery for the animal by minimizing secondary injury mechanisms of cord compression.
  - **b.** Clinical evidence
    - **i.** Results from animal experiments have not met with same straightforward results in clinical practice.
    - **ii.** Most SCIs suffered in humans are suprathreshold injuries with irreversible primary disruption of ascending and descending white matter tracts and neuronal death at the time of injury.
    - **iii.** Early decompression may mitigate secondary injury mechanisms but will not affect irreversible primary injury mechanisms.
    - **iv.** Controversy in early (i.e. <24 hours) versus delayed surgical decompression based on inability to differentiate threshold versus suprathreshold injuries on clinical or radiographic grounds.

C. High-dose steroids

- **1.** Solumedrol protocol was previously administered as standard of care for SCI except in cases of penetrating injury.
  - **a.** 30 mg/kg intravenous (IV) methylprednisolone over 1 hour; then 5.4 mg/kg/hour for the next 23 hours.
- **2.** Later data analysis led to the conclusion that the risks of high-dose steroids outweighed their benefits, and this therapy has been abandoned by many medical centers.

VII. SEQUELLAE AND COMPLICATIONS

A. Cardiovascular

- **1.** Hypotension and bradycardia from spinal shock (sympathectomy effect)
  - **a.** Management with titrated dopamine to support BP and atropine to increase heart rate
- **2.** Autonomic hyperreflexia (periodic autonomic instability triggered by stimuli such as bladder filling or catheterization)
  - **a.** Occurs in patients with SCI above T6
  - **b.** Exaggerated autonomic responses, including headache, flushing, diaphoresis, and paroxysmal hypertension
  - **c.** Can be life threatening if associated with hypertension
  - **d.** Treat by elimination of offending stimuli

B. Pulmonary

- **1.** High cervical injuries above segments C3-5 that contribute to phrenic nerve may leave patient ventilator dependent or with weak cough mechanism to clear airway secretions or obstructions.
- **2.** All injuries above T5 will have significant loss of inspiratory/expiratory force and volume given intercostal denervation.

3. Aggressive pulmonary toilet is required to prevent atelectasis and pneumonia.
4. Placement of an abdominal binder can minimize paradoxical respiratory effort and increase respiration.
5. Immobilization makes patient vulnerable to deep vein thromobosis (DVT) and pulmonary embolism (PE).
6. DVT prophylaxis should be undertaken with subcutaneous (SQ) heparin (or related drugs) combined with sequential compression devices for lower extremities.

C. Gastrointestinal
1. Most patients with acute SCI present with partial ileus.
2. Nasogastric or orogastric tube should be placed to prevent gastric distension and perforation.
3. H_2-receptor antagonist or proton pump inhibitor should be used to prevent ulcers from stress of trauma and/or use of high-dose steroids.
4. Not all cardinal signs of acute abdomen are present in spinal cord injured patients.

D. Genitourinary
1. Most spinal cord injured patients cannot void spontaneously
2. Indwelling Foley catheter used until patient hemodynamically and neurologically stable
3. Intermittent straight catheterization used after Foley removed to decrease incidence of urinary tract infections

E. Infectious disease/fever workup
1. White blood cell count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) as markers of infection; chest x-ray (CXR) for atelectasis or pneumonia
2. Urine analysis and urine cultures for urinary tract infection
3. Duplex ultrasound of lower extremities for DVT
4. Liver function tests (LFTs), total and direct bilirubin, and amylase and lipase, for hepatitis, acalculous cholecystitis, or pancreatitis
5. Blood cultures for sepsis
6. Inspection of skin/wound for infection
7. Bone scan and plain x-rays for heterotopic bone formation

F. Cutaneous
1. Decubitus ulcers from prolonged positioning on pressure points
2. Prevention with frequent turning protocol, daily bathing and lotion application, and careful skin inspection
3. Early use of rotating beds and alternating inflated air mattresses
4. Superficial wounds treated with daily sterile occlusive dressings
5. Deep, infected, or devascularized wounds treated with debridement and/or grafting

G. Musculoskeletal
1. Development of contractures and spasticity may be slowed by aggressive range-of-motion exercises.
2. Heterotopic bone formation may be halted with etidronate sodium.

VIII. FUTURE DIRECTIONS

A. Because of the disproportionate socioeconomic effects of SCI, substantial efforts have been undertaken to minimize neurologic impairments and to improve adaptations to normal life.

B. Neuroprotective agents under investigation
1. Hypothermia
   a. Experimental evidence has shown that cooling protects neural tissues by decreasing its metabolic requirements and increasing its tolerance for decreased blood flow.

   b. Efficacy and safety of moderate hypothermia (32° C to 34° C) in clinical setting currently under investigation.
2. Minocycline
   a. Reduces oligodendrocyte and microglial apoptosis
   b. Clinical trial under way in Canada.
3. Activated macrophage injections into the spinal cord.
4. Riluzone, a sodium channel inhibitor, is in multicenter trials.
5. Early versus late surgery is currently being studied in a noncontrolled manner (STASCIS trial).

C. Restorative/regenerative strategies
1. Oscillating field stimulation to promote axonal regrowth along the cranial/caudal plane (as opposed to random orientations) is being studied in a noncontrolled manner.
2. Rho inhibitors
   a. Nogo, a critical inhibitor of neural regeneration acts through the guanosine triphosphatase (GTPase), Rho.
   b. Local injection of anti-Rho antibodies is in a phase II study.
3. Allogeneic oligodendrocyte precursor transplants are beginning clinical trials in 2009.
4. A number of investigations into the use of human mesenchymal or embryonic stem cells have been initiated internationally. No trial data has been published to date.

D. Adaptive strategies
1. Intensive therapy with functional electrical stimulation (FES)
2. Robotics and brain machine interfaces
3. Psychosocial considerations
4. Reintegration
   a. Fertility programs
   b. Occupation considerations

Suggested Reading

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Denis F. The three column spine and its significance in the classification of acute thoracolumbar spinal injuries. *Spine* 1983;8:817.
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Gore R, Mintzer R, Galenoff L. Gastrointestinal complications of SCI. *Spine* 1981; 6:538.
Descriptive review of GI ailments specific to spinal cord injured patients.
Hurlbert RJ. The role of steroids in acute SCI: an evidence-based analysis. *Spine* 2001;26:S39–S46.
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Inamasu J, Nakamura Y, Ichikizaki K. Induced hypothermia in experimental traumatic SCI: an update. *J Neurol Sci* 2003;209:55–60.
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Reyes O, Sosa I, Kuffler DP. Neuroprotection of spinal neurons against blunt trauma and ischemia. *PR Health Sci J* 2003;22:277–286.
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One of few studies attempting to address question of early versus delayed surgery in clinical practice.
Robertson PA, Ryan MD. Neurologic deterioration after reduction of cervical subluxation: mechanical compression by disc material. *J Bone Joint Surg* 1992;72B: 224–227.
Paper describing significant complication of intervertebral disc rupture after closed reduction and traction.
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Important paper defining radiographic criteria for spine stability.

ABDOMINAL TRAUMA

Louis C. Lee, Reza Askari, and Christopher P. Michetti

119

I. OVERVIEW

A. Background

1. The abdomen is frequently injured after both blunt and penetrating trauma.
2. Abdominal trauma occurs in 20% of civilian injuries requiring surgery.
3. Half of all preventable deaths are related to suboptimal management of abdominal trauma.
4. Physical examination is often inadequate to identify or exclude intra-abdominal injuries (especially blunt trauma).
5. Multiple factors including mechanism of injury, body region injured, hemodynamic and neurologic status, and associated injuries influence the diagnostic approaches used and outcome of abdominal injuries.

B. Etiology

1. Blunt trauma (most common etiology) is caused by motor vehicle crashes (MVCs), motorcycle crashes, falls, assaults, and to pedestrians struck by vehicles.
2. Penetrating abdominal trauma is usually caused by gunshot or stab wounds.
3. Almost all causes are preventable.

C. Diagnosis

1. History and physical examination
   a. Trauma history: **A**llergies, **M**edications, **P**ast medical/surgical history, **L**ast meal, **E**vents surrounding the injury (AMPLE).
   b. History of traumatic event is important in determining the likelihood of intra-abdominal injury.
   c. Suggestive clinical findings include abdominal wall contusions (seatbelt sign), pain, tenderness, or unexplained hypotension.
   d. Peritoneal signs are absent in 40% of patients with significant abdominal injuries.
   e. Rectal examination for gross blood, bony fractures, tone, or urethral injury.
   f. Foley catheterization is appropriate when no urethral injury is suspected: hematuria indicates injury to bladder, ureters, or kidneys.
   g. Physical findings are unreliable for patients with an abnormal sensorium secondary to head trauma, spinal cord injury, intoxication, or distracting pain from another source.
2. Plain radiographs
   a. Chest x-ray may reveal pneumoperitoneum; a gastric bubble or bowel in the chest is consistent with a ruptured diaphragm, and lower rib fractures suggest underlying liver or spleen injury.
   b. Abdominal x-ray has no role in the assessment of abdominal trauma.
3. Diagnostic peritoneal lavage (DPL)
   a. Used to evaluate hemodynamically unstable patients with blunt trauma to detect gross hemoperitoneum; also used for stable patients with anterior stab wounds to determine peritoneal penetration.
   b. Refer to Chapter 13 for details.

4. Computed tomography (CT)
   a. Abdomen and pelvic CT is the mainstay of diagnosis for abdominal and retroperitoneal injury in the hemodynamically stable patient.
   b. With intravenous contrast material, CT can detect arterial contrast extravasation.
   c. Oral contrast is not necessary for trauma CT, does not increase sensitivity.
   d. Sensitivity rates are between 92% and 97.6% and specificity rates as high as 98.7%. Negative predictive value up to 99%.
   e. Unreliable in identifying hollow visceral injuries.
   f. Contraindicated in hemodynamically unstable patients (who would benefit from intervention, rather than diagnostic testing).
5. Focused assessment with sonography for trauma (FAST)
   a. Includes four areas of examination:
      i. Right upper quadrant: Morrison's pouch between the right kidney and liver
      ii. Left upper quadrant: between the left kidney and spleen
      iii. Subxyphoid: pericardium (alternatively transsternal)
      iv. Suprapubic: perivesicular spaces
6. FAST has mostly replaced DPL and gained acceptance in the evaluation of abdominal trauma, especially in the hemodynamically unstable patient; primarily used to examine the peritoneal cavity for blood.
   a. Accurate in detecting intra-abdominal blood (94% to 96%) in experienced hands.
   b. Accuracy increases by repeating FAST over the course of resuscitation.
   c. Advantages include being rapid, portable and noninvasive; disadvantages include low specificity for source of hemorrhage and high operator dependence.
   d. A normal FAST does not exclude injury: hollow viscus and retroperitoneal injuries are not detected reliably by FAST.
   e. With appropriate training, FAST can be effectively performed by nonradiologists.
   f. The FAST examination should not be limited to the trauma bay: portable ultrasound machines can be easily used at the bedside at any time after the initial trauma.
7. Laparoscopy:
   a. Use of diagnostic laparoscopy in blunt abdominal trauma is a developing field
   b. Difficult to adequately examine small bowel and retroperitoneum
   c. Accurate in determining peritoneal or diaphragmatic penetration from stab wounds or tangential gunshot wounds
8. Nonoperative management (NOM) and serial examinations:
   a. Can be used for some blunt trauma and superficial stab wound patients with normal mental status

D. Treatment

1. For blunt abdominal trauma, treatment is dictated by the specific injuries present.
2. Operative exploration is required in all patients with anterior abdominal gunshot wounds because visceral injury is present in >90% of cases.
3. For stab wounds, exploration is necessary in the presence of peritoneal signs, hemodynamic instability, evisceration of abdominal contents, or confirmed peritoneal penetration.
4. Unexplained hypotension with physical signs of abdominal trauma may warrant exploration.

II. SPECIFIC INJURIES

A. Liver and porta hepatis

1. Background

- **a.** The liver is the most commonly injured organ in blunt abdominal trauma.
- **b.** Spontaneous hemostasis is observed in >50% of small hepatic lacerations at the time of laparotomy.
- **c.** Most liver injuries heal without intervention.
- **d.** Overall mortality rate ranges from 8% to 10% depending on number of associated injuries and injury severity.
- **e.** Injuries are graded from I (minor) to V (severe), ranging from minor tears to major lobar disruptions and avulsion from the inferior vena cava.
- **f.** Hemobilia results from erosion of an injured blood vessel into a biliary duct.
- **g.** Traumatic injuries to the porta hepatis are uncommon. It is more common with penetrating trauma and has a 50% mortality rate from hemorrhage.

2. Diagnosis

- **a.** Abdominal CT is the most sensitive and specific study in identifying and assessing the severity of injury.
- **b.** FAST or DPL is used in hemodynamically unstable patients.
- **c.** Triad of right upper quadrant abdominal pain, jaundice, and gastrointestinal hemorrhage occur in approximately one third of patients with hemobilia.

3. Treatment

- **a.** NOM is the treatment of choice in hemodynamically stable patients.
- **b.** Angiography with embolization can be used to stop arterial hemorrhage when contrast extravasation is seen on CT.
- **c.** Surgery is indicated for patients who are hemodynamically unstable, develop peritonitis, or require continuous blood transfusions.
  - **i.** Key principles in operative trauma are exposure and hemostasis.
  - **ii.** Simple lacerations are managed by direct pressure, suture repair, electrocautery, argon beam coagulation, and topical hemostatic agents.
  - **iii.** Hepatic packing is the preferred initial technique for significant injuries with hemorrhage.
  - **iv.** Compression of the portal triad (Pringle maneuver) is effective if the aforementioned techniques fail.
  - **v.** In cases of hepatic venous or retrohepatic inferior vena caval injuries, total hepatic exclusion or atriocaval shunts are options. Damage control techniques (abdominal packing and temporary abdominal closure) should receive strong consideration in the face of such injuries.
- **d.** Gallbladder injuries are treated with cholecystectomy.
- **e.** Injuries to extrahepatic bile ducts require primary repair or anastomosis to bowel.
- **f.** Bile leaks are treated with closed drainage either at surgery or percutaneously with the aid of CT or ultrasound.

4. Complications

- **a.** Bleeding, hemobilia, bile leak, and intra-abdominal abscess.
- **b.** Bile leak occurs in 25% of patients with major hepatic injuries.
- **c.** Abscesses occur in 10% of patients with liver injuries; likelihood of infection increases with grade of injury, number of transfusions, use of sump drains, concomitant bowel injury, and perihepatic packing.

B. Spleen

1. Background

- **a.** Commonly injured in both blunt and penetrating trauma
- **b.** May result from a blow, fall, or sports injury involving the left chest, flank, or upper abdomen; side impact MVCs a common cause
- **c.** Injuries graded from I (minimal) to V (most severe)

2. Diagnosis
- **a.** FAST or DPL is used in hemodynamically unstable patients.
- **b.** CT with intravenous contrast (oral contrast is unnecessary) is the most sensitive and specific study for identifying and grading splenic injuries.

3. Treatment
- **a.** NOM of blunt splenic injuries is the treatment of choice in hemodynamically stable patients.
- **b.** Surgery is indicated for hemodynamically unstable patients.
- **c.** NOM of high grade injuries is preferably done at level I trauma centers with the experience and intensive resources required.
- **d.** Patients undergoing NOM should be closely monitored, usually in an intensive care unit, for 48 to 72 hours with attention to vital signs, serial hematocrits, and serial abdominal examinations.
- **e.** Surgery or angiography with embolization can be considered for stable patients with extravasation of intravenous contrast on CT.
- **f.** The success rate of NOM is approximately 90% but varies with the grade of injury.
- **g.** Surgical treatment varies depending on the severity of injury, presence of shock, and associated injuries.

4. Complications
- **a.** Recurrent or delayed bleeding
- **b.** Subphrenic abscess
- **c.** Left pleural effusion secondary to sympathetic response
- **d.** Overwhelming postsplenectomy infection (OPSI)
  - **i.** Asplenic patients are at increased risk for sudden and often lethal systemic bacterial infection.
  - **ii.** OPSI is usually caused by encapsulated organisms (*Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis).*
  - **iii.** The incidence of OPSI is 0.6% in children and 0.3% or less in adults after splenectomy for trauma; there is a higher incidence after splenectomy for hematologic disease.
  - **iv.** After splenectomy, vaccination against the above three organisms is given before discharge or 2 weeks postoperatively.
  - **v.** Use of prophylactic antibiotics in asplenic patients is controversial, but is often used in young children.

C. Kidneys

1. Background
- **a.** Approximately 10% of all abdominal trauma involves the kidneys
- **b.** Graded from I (minimal) to V (most severe)
- **c.** Retroperitoneal, so may not be identified with physical examination, DPL, or FAST
- **d.** Gerota's fascia encapsulates the kidney and will often tamponade a hematoma

2. Diagnosis
- **a.** CT with intravenous contrast is the study of choice.
- **b.** High grade renal injuries may be seen on FAST examination.
- **c.** Intravenous pyelogram (IVP) has no indication in trauma outside of the operating room; replaced by CT.

3. Treatment
- **a.** NOM is the treatment of choice for hemodynamically stable patients.
- **b.** A completely devascularized, nonfunctioning kidney should be managed nonoperatively initially.
- **c.** Absolute indications for operative repair or nephrectomy include exsanguination, expanding or pulsatile retroperitoneal hematoma, or continued instability.

4. **Complications**
   a. Urinoma
   b. Acute renal insufficiency (unlikely with one kidney injury)
   c. Urinary tract infection or infected urinoma
   d. Perinephric abscess
   e. Hypertension (late complication in some severe injuries)

D. Diaphragm

1. **Background**
   a. Often caused by penetrating injuries.
   b. Patients sustaining penetrating injuries between the nipple and the costal margin should be investigated to rule out diaphragmatic injury.
   c. Following penetrating trauma, injury to the diaphragm involves both sides equally; in blunt trauma the left side is more frequently injured.
2. **Diagnosis**
   a. Requires a high index of suspicion; often clinically occult.
   b. Radiologic modalities, including CT, are usually insufficient to exclude this injury.
   c. Chest radiography is abnormal in 85% of cases, yet diagnostic in only 27% of cases.
   d. If the diagnosis is uncertain, further evaluation is warranted with laparoscopy, thoracoscopy, or exploratory laparotomy.
3. **Treatment**
   a. Almost all diaphragm injuries require repair due to risk of enlargement over time with continuous movement of the diaphragm.
   b. Suture repair to create watertight closure.
   c. Larger defects may require use of prosthetic material.
4. **Complications**
   a. Delayed or missed diagnosis
      i. Early recognition is critical, since mortality of an untreated injury and subsequent bowel strangulation is approximately 30%.

E. Small intestine

1. **Background**
   a. Most commonly injured organ in penetrating abdominal trauma.
   b. Blunt small bowel injury (SBI) is extremely rare, with an incidence of 1.2% of all trauma admissions; one fourth of all SBI are perforated.
2. **Diagnosis**
   a. Difficult in cases of blunt trauma.
   b. Physical findings may be delayed until the patient is septic or has peritonitis.
   c. Presence of abdominal wall bruising, especially from a seat belt, should raise suspicion of SBI.
   d. Lumbar Chance fractures are associated with SBI (as well as pancreatic and duodenal injuries).
   e. Findings of SBI on CT may include free air, free fluid without solid organ injury, thickened bowel wall, and mesenteric hematoma. Aside from free air, all other CT findings are insensitive and nonspecific for SBI.
      i. Fourteen percent of patients with perforated SBI have a "negative" CT.
      ii. Oral contrast leak is seen on CT in only 2.9% of perforated SBI.
   f. Peritonitis or increasing abdominal tenderness mandate exploration.
3. **Treatment**
   a. Operative technique depends on the severity of injury and can range from simple repair to resection with anastomosis.
   b. If there is concern for vascular sufficiency, return to the operating room after 24 to 48 hours to reevaluate bowel viability.

4. **Complications**
   a. Intra-abdominal abscess
   b. Sepsis, especially if treatment is delayed
   c. Anastomotic leak
   d. Bowel ischemia/necrosis

Suggested Reading

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The national standard of trauma care. The ATLS course is available to physicians worldwide through the American College of Surgeons.

Fakhry SM, Watts DD, Luchette FA. Current diagnostic approaches lack sensitivity in the diagnosis of perforated blunt small bowel injury: analysis from 275,557 trauma admissions from the EAST multi-institutional HVI trial. *J Trauma* 2003;54:295–306.

The definitive study on small bowel injury; discusses prevalence, morbidity, mortality, and diagnostic modalities.

Jansen JO, Yule SR, Loudon MA. Investigation of blunt abdominal trauma. *Br Med J* 2008;336:938–942.

A concise and updated clinical review on the diagnostic workup of blunt abdominal trauma, including an algorithm for its investigation and management.

Peitzman AB, Heil B, Rivera L, et al. Blunt splenic injury in adults: multi-institutional study of the Eastern Association for the surgery of trauma. *J Trauma* 2000;49: 177–187.

A large multicenter study of nonoperative management of splenic injury, including factors contributing to success or failure, and failure rates by grade of injury.

Santucci RA, McAninch JW, Safir M, et al. Validation of the American Association for the surgery of trauma organ injury severity scale for the kidney. *J Trauma* 2001;50:195–200.

In a retrospective review of more than 2,500 patients, the authors validate the AAST kidney injury scale. This study confirms the correlation between grade of injury and the need for surgical repair or nephrectomy.

Trunkey DD. Hepatic trauma: contemporary management. *Surg Clin N Am* 2004;84: 437–450.

A thorough presentation of the historical and modern treatment of liver injuries, including nonoperative and operative management.

BURNS

Philip Fidler and James C. Jeng

120

I. GENERAL PRINCIPLES

A. Definition. A burn is a tissue injury resulting from excessive exposure to thermal, chemical, electrical, or radioactive agents. The transfer of thermal energy over time is proportional to dermal damage.

1. Epidermis: invaluable for its barrier and immunologic functions, prevents evaporative losses and bacterial invasion.
2. Dermis: provides the overall structural integrity of the skin.
3. The epidermis will recover so long as viable dermis is present; therefore, the essence of burn wound care is to maintain dermal viability.

II. CLASSIFICATION

A. It is essential to distinguish between partial thickness (second degree) and full thickness (third degree) injuries of the dermis, as the latter require operative intervention.

1. Full thickness injury—pale, leathery, and insensate skin.
2. Partial thickness injury—blistering, weeping, pink, and painful skin.
3. No technology supercedes clinical experience in making this distinction, laser Doppler gaining.
4. The injury is dynamic and partial thickness injuries can worsen ("convert") to full thickness injuries for various reasons.

III. EPIDEMIOLOGY

A. In the United States, 60,000 to 80,000 people are hospitalized annually for burn care, but only 1,500 to 2,000 people sustain >40% total body surface area (TBSA) burns.

B. Risk factors

1. Infants and elderly
2. Cognitive impairment
   a. Behavioral disorders
   b. Alcohol/drug impairment

C. Prognosis markedly improved in the last 25 years

1. Lethal dose 50 (LD50) for young adults with 90% TBSA and an LD50 for elderly with 40% TBSA.
2. Paradigm shift toward, "early" (within 5 days), operative excision as it was realized that burned tissue drives burn shock.
3. Diminution of burn wound sepsis and advances in critical care borrowed from all disciplines have contributed to improved outcomes for young patients and in the elderly.
4. Clinical data points predicting mortality (mortality rates of 90% when all three are present and 33% when two factors are present).
   a. Age older than 60 years
   b. TBSA burned ≥40%
   c. Inhalation injury

IV. PATHOPHYSIOLOGY

- **A.** Burn shock
  - **1.** Vasodilatory shock and has an astounding volume requirement
  - **2.** Occurs in ≥20% TBSA burns
    - **a.** Begins with intravascular volume depletion from interstitial edema in both burned and unburned tissue
    - **b.** Forces central shunting of blood to improve core perfusion but deprives the burn wound
    - **c.** Great insensible evaporative water losses until wounds are closed
  - **3.** Similar to sepsis and systemic inflammatory response syndrome (SIRS)
- **B.** Massive edema
  - **1.** Burn wound
  - **2.** Nonburned tissues
    - **a.** Results from increased vascular permeability driven by vasoactive mediators including kinins, serotonin, histamine, prostaglandins, and oxygen radicals
    - **b.** Decreased oncotic pressure
- **C.** Cardiovascular response
  - **1.** Decreasing preload
  - **2.** First 48 hours decreasing cardiac output (myocardial depressant factors likely gut derived)
    - **a.** Decreasing compliance and contractility
      - **i.** Worse in inhalation injury
    - **b.** Elevated creatinine kinase-myocardial band (CK-MB), troponin-I global cardiac injury not coronary thrombosis
  - **3.** After first 48 hours develop hyperdynamic cardiac state that may last for weeks
- **D.** Infection—increased susceptibility
  - **1.** Lungs
    - **a.** Pneumonia
    - **b.** Tracheobronchitis
  - **2.** Wound beds—devitalized full thickness eschar
    - **a.** First 10 days are typically gram-positive organisms
    - **b.** Next *Pseudomonas* is a common and a potentially lethal organism
    - **c.** Next fungal infections
  - **3.** Central line sites
  - **4.** Urinary tract
  - **5.** Gut
    - **a.** If not fed, may be source of translocation of bacteria and source of sepsis.
    - **b.** Enteral feedings can prevent gut atrophy and immunoenhancing nutritional regimens, especially those with glutamine further resist atrophy and may afford better outcomes.

V. DIAGNOSIS

- **A.** History
  - **1.** The heat source and circumstances of the injury
  - **2.** When the burn injury occurs coincidentally with blunt trauma
    - **a.** Life threatening injuries take precedence in early management.
    - **b.** Burn skin management is secondary.
  - **3.** If burn occurs in closed space—expect inhalation injury
- **B.** Scalds
  - **1.** Energy transfer of hot liquid is underappreciated and may be lethal.
  - **2.** May involve large body surface areas, particularly while bathing.
  - **3.** More serious in children 4 years or younger or elderly who often have other comorbid conditions

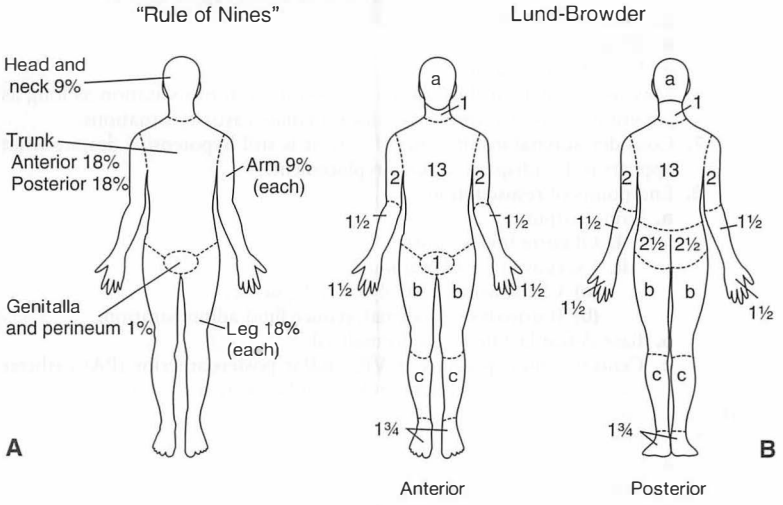
C. Electrical injuries
  1. High voltage
    a. May present with little injury to the skin, but significant injuries to the muscle, vasculature, and bone underneath
    b. Cardiac standstill
  2. Low voltage
    a. Present as thermal burns, with injuries to the tissue from the outside in
    b. Ventricular fibrillation

VI. PHYSICAL EXAMINATION

A. Multiples of the number 9 ("the rule of nines")
B. Lund-Browder scale (Fig. 120-1)
C. For noncontiguous injuries, the palmer surface of the patient's hand can be used to estimate 1% TBSA

VII. TREATMENT

A. Burn shock
  1. Ideal resuscitation meets the perfusion needs of the partial thickness injury, preventing conversion to a full thickness injury and optimizing organ function.
  2. Underperfusion deprives the wound of nutrient delivery and gas exchange leading to full thickness conversion.
  3. Excessive resuscitation adds to tissue edema, other complications, and conversion.



Relative percentage of body surface areas (% BSA) affected by growth

	0 yr	1 yr	5 yr	10 yr	15 yr
a— ½ of head	9½	8½	6½	5½	4½
b— ½ of 1 thigh	2¾	3¾	4	4¼	4½
c— ½ of 1 lower leg	2½	2½	2¾	3	3¼

Figure 120-1. A: Rule of Nines. **B:** Lund-Browder scale.

TABLE 120-1 Parkland and Modified Brook Formulas

Parkland formula	Total fluids for 24 h =	
	Ringer's lactate	4 mL × kg × %BSA
Modified Brooke formula	Total fluids for 24 h =	
	Ringer's lactate	1.5 mL × kg × %BSA
	Plasma	0.5 mL × kg × %BSA
	D5W	2,000 mL

Example: A 70-kg man with a 50% TBSA burn would therefore have a total deficit of 14 L (4 mL × 70 kg × 50% BSA = 14,000) in 24 hour. Half the 24-hour deficit should be repleted in the first 8 hours, due to the high risk of hypovolemic shock early in the course. In this example, that is 7 L within the first 8 hours or a rate of 875 mL/hour for the first 8 hours. It is important to note that this recommendation starts at the estimated time of injury, not simply the time care is rendered. The rate would subsequently be decreased to **438 mL/hour** for the next 16 hours.
BSA, body surface area; D5W, dextrose 5% in water.

4. Central venous access is generally necessary and ideally, but not essentially, placed through nonburned tissue.
5. Resuscitative regimens
   a. TBSA burned and weight guide fluid management
   b. No evidence-based level one data for resuscitative fluids use
      i. Isotonic electrolyte solutions such as normal saline or lactated Ringers' solutions during at least the first 12 hours of resuscitation and in most instances the first 24 hours (Table 120-1)
   c. Colloids use remains controversial
   d. Albumen
   e. Fresh frozen plasma
6. May use the gut for fluid administration in burn resuscitation as long as patient is not on vasopressors—ideal in mass casualty situations.
7. Consider adrenal insufficiency if patient is still hypotensive despite what appears to be adequate volume replacement.
8. End points of resuscitation
   a. Urine output
      i. Oliguria bodes poorly
      ii. Excessive (≥1 mL/kg/hour)
         (a) Check urine electrolytes and glucose.
         (b) If urinalysis is normal, reduce fluid administration.
   b. Base deficit/lactate levels normalized
   c. Central venous pressure (CVP) and/or posteroanterior (PA) catheter numbers suggest adequate preload and cardiac function

B. Metabolism and nutrition
1. Metabolism
   a. Insensible fluid and protein losses from burn wounds are extreme and may result in hyperthermia initially.
   b. Then, as vasomotor autoregulation diminishes significant evaporative heat loss occurs.
   c. Keep the patients' room temperature >90°F.
   d. Increased muscle proteolysis, lipolysis, and gluconeogenesis occurs.
   e. Hyperglycemia is common and may exacerbate muscle wasting.
   f. Glucose control is essential with insulin drip.
   g. Hypermetabolic response that occurs after a thermal injury is greater than that observed after any other form of trauma or sepsis.

h. Protein catabolism is compounded by insensible losses through the wound bed and leaking into the interstitium, resulting in severe hypoproteinemia.

2. Nutrition
   a. Ideally, enteral nutrition should be started the day of the injury and can serve to provide volume and calories.
   b. Caloric needs = 2 to 3 times normal basal energy expenditure and require at least 2 g/kg protein with a calorie to nitrogen ratio approaching 100:1.
   c. Total parenteral nutrition (TPN) only for patients not tolerating enteral feedings.
   d. Anabolic enhancement
      i. Recombinant human growth hormone
         (a) Caution; may cause hyperglycemia
      ii. Oxandrolone; given enterally 10 mg bid

C. Infection
   1. Multiple defects in burn patients' immune system predisposes them to an increased risk of infection
   2. Burn wound sepsis
      a. Prevention of
         i. Topical antimicrobials (e.g., silver sulfadiazine or mafenide acetate)
            (a) Mafenide acetate penetrates eschar and is most effective against gram-negative organisms but is known to cause metabolic acidosis as a carbonic anhydrase inhibitor.
         ii. Local wound care
      b. **Treatment**
         i. Urgent surgical excision and tissue coverage with autograft, skin substitute, or topical antibiotics if suspect burn wound sepsis

D. Inhalation/respiratory injury
   1. Restrictive respiratory failure secondary to burn eschar involving the torso requires urgent escharotomy
   2. Inhalation injury
      a. Airway management as always is paramount.
         i. Observe for signs of upper airway obstruction, secondary to edema, which develops hours after the initial injury.
         ii. Stridorous patients should be intubated urgently with an adequate endotracheal (ET) tube to allow for bronchoscopy as needed.
         iii. Immediate life threats
            (a) Carbon monoxide
               (1) Lethal level >60% COHgb
               (2) F_{IO_2} 100% until normal level
            (b) Hydrogen cyanide (CN^-)
               (1) Lethal level in serum ≥ 1 μg/mL
               (2) Inhibits cytochrome oxidase
               (3) Increases dead space
               (4) Consider sodium thiosulphate
      b. Toxic combustants inhaled cause a severe inflammatory response in the bronchial pulmonary tree and systemically.
         i. Endobronchial and interstitial edema
         ii. Mucociliary dysfunction
         iii. Alveolar disruption
         iv. Functional pulmonary shunting
         v. Decreased lung compliance

vi. Endobronchial slough
(a) Combines with exudates + fibrin = casts with increased bacterial growth and obstruction of airways
vii. Neutrophils invade in alveolar spaces through the pulmonary vasculature and likely contribute to O_2-free radical production, promoting the inflammatory cascade and local injury
viii. Mortality is greatly increased when matched to burn injuries of like size without inhalation injury
ix. Currently, no objective scale of severity for inhalation injury
x. Upper airway assessment should be carried out before extubation by deflating cuff and noting an air leak. It may not be safe to extubate if no air leak!

c. Shock state is intensified with added inhalation injury often requiring up to 50% more fluid for adequate resuscitation

E. Chemical injury
1. Acids
a. Burn by coagulation necrosis creating an eschar that limits deeper penetration.
b. Hydrofluoric acid burns carry the unique concern of calcium and magnesium chelation and risk cardiac arrest secondary to severe hypocalcemia and hypomagnesimia.
i. Intra-arterial infusion of calcium gluconate has been met with some success and may limit digital ischemia.
ii. Calcium gluconate slurry may be massaged into the exposed area to potentiate systemic absorption.
iii. Carefull y monitor electrocardiogram (ECG).
2. Alkali
a. Burn by causing liquefaction necrosis in the subcutaneous fat, creating vascular thrombosis and subsequent dermal ischemia

F. Electrical injury
1. Life-threatening problems are dysrhythmias
2. Spinal cord injury
a. Direct nerve/cord damage
b. Tetany resulting in spinal column fracture and cord injury
c. May result in respiratory problems depending on the level of injury
3. Cutaneous lesions
a. May be subtle and efforts should be made to find entrance and exit lesions, as these will direct the practitioner to focus on the intervening tissues
4. Compartment syndromes
a. Myonecrosis is common, particularly in the upper extremities.
b. Myonecrosis puts the kidneys at risk for myoglobinuric renal failure.
i. Elevations of creatinine phosphokinase (CPK) into the tens of thousands are often present and maintaining a high urine output of 100 mL/hour reduces the risk of renal failure.
ii. Mannitol may be added once resuscitation is well under way.
iii. Alkalinizing the urine is advocated by some.
iv. Maintain urine output at 100 mL/hour.
v. Consider monitoring the CPK for several days to assess the amount of muscle damage and recovery; with continued elevations suggesting need for further debridement.
c. Fasciotomy for elevated compartment pressures.
d. Debridement of nonviable or necrotic muscle and/or other tissue.
5. Fluid resuscitation must be initiated quickly, with higher volumes than anticipated due to underlying tissue injury

G. Pain
- **1.** Rationale
  - **a.** On a scale of 1:10; burns rate a 10
  - **b.** Pain control leads to
    - **i.** Patient comfort
    - **ii.** Decreased catabolism, cardiovascular stress
    - **iii.** Reduced risk of posttraumatic stress disorder
- **2.** Management
  - **a.** Simultaneous drips of narcotic and benzodiazepines.
  - **b.** Anticipate higher than usual doses.
  - **c.** It is not prudent to reduce these medications for frequent neurologic assessment.
  - **d.** Once the patient's burn wounds have been managed adequately, a stepwise weaning of these agents is done to permit ventilator weaning and to avoid withdrawal.

VIII. COMPLICATIONS

A. Eschar formation
- **1.** Escharotomy
  - **a.** *Particularly* for circumferential chest eschar to optimize oxygenation/ventilation
  - **b.** For limbs to prevent compartment syndromes
- **2.** Burn wound sepsis
  - **a.** Early excision
    - **i.** Has lessened this complication
    - **ii.** Nonetheless, loss of skin barrier and immune suppression may still not totally prevent burn wound sepsis
  - **b.** Signs
    - **i.** Diffuse or focal discoloration of the burn
    - **ii.** Purulent fluid from the wound
    - **iii.** Early eschar separation
    - **iv.** Confirm by biopsy of wound
  - **c.** Treatment
    - **i.** Immediate treatment or *systemic sepsis will occur*
    - **ii.** Total excision of the infected wound
    - **iii.** Systemic antibiotics covering the infective microbes
- **3.** Abdominal compartment syndrome
  - **a.** If allowed to occur, promotes renal failure, respiratory failure, and bowel ischemia
  - **b.** Urinary bladder pressure measurement with transducer
  - **c.** Gives indirect measure of abdominal pressure
  - **d.** $\geq$20 cm H_2O pressure suggests abdominal hypertension and $\geq$30 cm H_2O is generally accepted as requiring operative intervention, celiotomy and leaving the abdominal compartment open
- **4.** Pneumonia
  - **a.** Increased risk because of immune compromise, immobility, and problems clearing secretions
  - **b.** Worse with inhalation injury (see VII.D.2.)
  - **c.** Incidence increases with the larger burns
  - **d.** Prevention
    - **i.** Good pulmonary toilet
    - **ii.** Limit aspiration by keeping head of bed at 30 degrees
    - **iii.** If on ventilator; lung protective ventilator management
    - **iv.** Frequent surveillance
    - **v.** Prophylactic antibiotics are not recommended

- **e.** Treatment
  - **i.** Culture-directed therapy reflecting local biograms

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THORACIC TRAUMA

Hani Seoudi

121

I. GENERAL PRINCIPLES. Chest injuries cause one of every four trauma deaths in North America. Multiple life-threatening conditions can result from thoracic trauma and should, therefore, be looked for in the primary survey of the trauma patient.

II. ETIOLOGY. Motor vehicle crashes, falls, and penetrating wounds are the principal causes.

III. DIAGNOSIS

A. Tension pneumothorax. Air enters the pleural space but does not leave because of a flap valve effect in the injured lung or from an open (sucking) chest wound. As a result, the ipsilateral lung collapses and the mediastinum is pushed toward the contralateral lung. This results in hypotension and tachycardia due to impaired venous return. These effects are particularly pronounced in children and in hypovolemic patients.

B. Massive hemothorax. This represents rapid accumulation of >1,500 mL of blood within the pleural space.

C. Flail chest. This indicates that a segment of chest wall has lost bony continuity with the remainder of the chest due to fracture of more than one rib in more than one location unilaterally or bilaterally, resulting in paradoxical movement of the flail segment during respiration. The morbidity of this condition is primarily due to the associated severe pulmonary contusion.

D. Cardiac tamponade. This may result from either blunt or penetrating trauma. Acute accumulation of relatively small amounts of blood can result in tamponade pathophysiology. Clinical findings include hypotension, tachycardia, muffled heart sounds, distended neck veins, and pulsus paradoxus.

E. Major airway injury. This injury is characterized by stridor and subcutaneous emphysema. Endotracheal intubation can be very difficult and a failed attempt at intubation can actually compromise the airway further. It is recommended that an emergency tracheostomy/cricothyroidotomy be performed. Urgent operative repair is needed.

F. Penetrating chest injury. Penetrating injuries in addition to the stated problems may also result in bronchovenous fistula, whereby air flows from the injured bronchus into one of the pulmonary veins resulting in massive air embolism. This condition can have a delayed presentation and appear when positive pressure ventilation is initiated. The condition is rapidly fatal and requires immediate thoracotomy.

IV. IMMEDIATE LIFESAVING INTERVENTIONS

A. Endotracheal intubation: Intubation is indicated when the airway is compromised by direct trauma, aspiration of blood/gastric contents, or a depressed level of consciousness. Oral intubation is the preferred method.

B. Cricothyroidotomy: Dividing the cricothyroid membrane provides a much quicker surgical access to the airway compared to tracheostomy. Tracheostomy is usually not performed in a lifesaving situation.

C. Needle decompression or tube thoracostomy. Immediately on identification of a tension pneumothorax, a needle thoracostomy should be performed. This should be followed by a tube thoracostomy as quickly as possible.

D. Thoracotomy. It is recommended that a thoracotomy be performed if the initial drainage from the tube thoracostomy is 1,500 mL or greater or when the hourly output is >250 mL for several hours. Resuscitative thoracotomy, also known as *emergency department thoracotomy*, is performed on pulseless trauma patients who have other signs of life. Generally a resuscitative thoracotomy is not performed on blunt trauma victims who are without vital signs (unless the patient loses vital signs while being examined by the resuscitating surgeon). The procedure is more likely to be successful with penetrating injury as it can provide access to localized points of hemorrhage from the heart, descending aorta, and lung. The overall success rate of this procedure is dismal.

V. DIAGNOSTIC STUDIES

A. Chest radiograph.

B. Computed tomography (CT). High-speed helical CT scanners permit rapid evaluation of chest injuries and are accurate for diagnosing lung contusions and occult hemopneumothorax. Modern CT scanners are highly accurate in diagnosing blunt aortic injury. Dynamic CT with contrast: this technique is now recommended for visualizing major pulmonary emboli.

C. Angiography. Aortography remains the gold standard for making the diagnosis of blunt aortic injury. Pulmonary angiography remains important for the diagnosis of pulmonary emboli.

D. Echocardiography. Echocardiography is used to evaluate unstable patients for possible cardiac injury or to detect fluid or blood in the pericardium, to evaluate heart valves, and to assess ventricular function. Transesophageal echocardiography (TEE) is more precise than the transthoracic echo but requires special expertise and may not always be possible in the trauma patient.

VI. TREATMENT

A. Chest wall and pleural cavity injury

1. Rib fractures: Rib fractures need only be treated symptomatically. Pain control can be challenging depending on the number of rib fractures. A thoracic epidural catheter may be needed if the patient is requiring large doses of narcotics for pain control.
2. Flail chest: This injury is particularly challenging because patients frequently go into respiratory failure due to the severe pain, and hypoxia due to the underlying pulmonary contusion. Mechanical ventilation is usually necessary.
3. Sternal fracture. Symptomatic treatment for this injury is appropriate.
4. Pneumothorax
   a. Pneumothorax is generally treated with tube thoracostomy. A very small pneumothorax may be observed if the patient is not symptomatic. Open pneumothorax: the initial management includes immediately applying an occlusive dressing over the wound and insertion of a chest tube; operative intervention is urgently needed when the assessment for other life-threatening injuries has been completed.

B. Lung

1. Pulmonary contusion. Treatment is supportive with supplemental oxygen. Mechanical ventilation is necessary if there is severe hypoxia.
2. Acute respiratory distress syndrome (ARDS). ARDS is a syndrome of diffuse inflammatory reaction in the lung as part of a systemic inflammatory

response. It may occur following multiple trauma, sepsis, massive blood transfusions, and many other causes. See Chapter 43 for more details.

C. Trachea and major bronchial injuries. After securing an airway, these injuries require immediate operative intervention.

D. Heart and great vessels (see Chapter 33).

1. Blunt cardiac injury. This term encompasses a variety of injuries including myocardial contusion, rupture of a cardiac chamber or septum, and valve disruption.

a. Treatment for myocardial contusion requires cardiac monitoring and supportive care.

b. Treatment of chamber, septal, or valve injury requires urgent surgical repair.

2. Blunt aortic injury. Most patients with this injury die before reaching the hospital. Approximately half of those who reach the hospital will have a free rupture within the first 24 hours. Therefore, urgent surgical repair is indicated. Nonoperative management: treatment principles are similar to nonoperative management of aortic dissection, that is, β-blockade and antihypertensives; endovascular stent grafts are now being used much more frequently particularly for the poor-risk or elderly patient.

E. Traumatic asphyxia. When a trauma patient is diagnosed with this problem, treatment is supportive after establishing an airway and ventilation.

F. Esophageal rupture. Surgical treatment is indicated.

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COMPARTMENT SYNDROMES

Christoph R. Kaufmann

122

I. COMPARTMENT SYNDROMES OF THE EXTREMITIES

A. GENERAL PRINCIPLES

1. Any anatomic structure or external device that limits the ability of tissues to swell, can cause compartment syndrome.
2. Compartment syndromes are typically described in three areas: extremities, abdomen, chest.
3. Anatomically, extremity compartments are formed by fascial layers surrounding muscle groups.
4. As compartment pressure increases, nerves, followed by muscles, lose function (if treatment is delayed).
5. Extremity compartment syndrome can occur in the calf, thigh, buttock, forearm, arm, hand, or foot. The most frequent compartment affected is the anterior compartment of the calf.
6. Two different types of extremity compartment syndromes are described. Only their etiology is different:
   a. Extremity compartment syndrome
   b. Secondary extremity compartment syndrome

B. ETIOLOGY

1. Extremity compartment syndrome: crush, ischemia, arterial injury, vascular ligation (including vena cava, common iliac, common femoral, or popliteal veins), fracture (open or closed), direct blunt trauma (with hematoma or edema), prolonged external pressure, electrical injury.
2. Secondary extremity compartment syndrome: hypotension and/or massive volume resuscitation lead to whole body tissue edema, including the muscles of the various compartments. This may be the result of massive burns or other large physiologic insults and is part of the postresuscitation systemic inflammatory response syndrome (SIRS).

C. PATHOPHYSIOLOGY

1. Injury and/or resuscitation cause a hematoma and/or edema of the muscles.
2. In the face of a fixed compartment volume, pressure increase follows muscle edema.
3. At some point, pressure in the compartment exceeds capillary perfusion pressure (approximately 30 mm Hg) and the capillaries collapse.
4. Tissue ischemia results in nerve and muscle damage.

D. DIAGNOSIS

1. High index of suspicion is the key, especially in the neurologically compromised patient.
2. Clinical examination:
   a. Tense or tight compartments to touch
   b. Pain disproportionate to associated injury
      i. Critical mistake is to treat with more pain medication.
   c. Increased pain with passive muscle stretch (classically for anterior calf compartment: dorsiflexion of the great toe).
   d. Hypesthesia and/or muscle weakness.

e. Distal pulses remain intact unless a proximal arterial injury is the reason for the compartment syndrome.
   i. Critical mistake is to think that diagnosis of compartment syndrome is dependent on pulse loss.

3. Direct measurement
   a. 16-GA needle and arterial line setup
   b. Commercial device with direct readout
   c. Less than 20 mm Hg is usually not problematic, 20 to 30 requires expert interpretation of the clinical picture, >30 is clearly abnormal and requires fasciotomy

E. TREATMENT

1. First step is always to remove constricting wraps or dressings and to remove or bivalve any cast as these devices may cause or hide compartment syndrome
2. Fasciotomy
   a. Prophylactic, if high enough index of suspicion or with prolonged ischemia or ligated major vein, especially in the face of a proximal arterial injury
   b. Mandatory for high compartment pressure with possible viability
   c. Classically, for the calf: a four-compartment fasciotomy through two incisions, one lateral, one medial (with large fascial incisions, approximately 25 cm long in each compartment)
   d. Skin left open
   e. Often requires a late skin graft to cover resulting defect

F. COMPLICATIONS

1. Rhabdomyolysis
2. Ischemic neuropathy
3. Myonecrosis and fibrosis
4. Renal failure from myoglobinemia
5. Reperfusion syndrome
6. Limb loss

II. ABDOMINAL COMPARTMENT SYNDROME (ACS)

A. GENERAL PRINCIPLES

1. Abnormally high pressure in the abdomen = intra-abdominal hypertension that causes physiologic consequences.
2. Renal function, ventilatory dynamics, and cardiovascular performance may all suffer.
3. Opening the abdomen usually relieves the signs and symptoms.
4. Will need to leave abdomen open and close in several days when swelling resolves.
5. May be divided into primary ACS and secondary ACS based on etiology, although diagnosis and treatment are the same.
6. See Chapter 108 for further discussion.

B. ETIOLOGY

1. Primary ACS
   a. Abdominal injury or disease
   b. Postoperative abdominal surgery
   c. Ascites in critically ill cirrhotic patients
2. Secondary ACS
   a. Massive volume resuscitation, typically after trauma or burns
   b. Medical problems, such as sepsis and multiple organ failure
3. Both
   a. Space-occupying fluid in the abdomen (blood, ascites)
   b. Edematous tissue in the abdomen (bowel, retroperitoneum)
   c. Space-occupying hematomas in the retroperitoneum (including those associated with pelvic fractures)

C. PATHOPHYSIOLOGY
1. Decreased venous return
   a. Causes renal dysfunction
   b. May cause elevation in intracranial pressure (ICP)
2. Abdominal contents exert pressure through the diaphragm
   a. Respiratory dysfunction
   b. Cardiovascular dysfunction

D. DIAGNOSIS
1. Hallmarks are tensely distended abdomen (but can occur with a normal abdominal examination) and oliguria.
2. May also have decreased cardiac output, decreased pulmonary function, and/or increased ICP.
3. Intra-abdominal pressure measurement is helpful if no response to volume resuscitation.
4. Methods of measurement
   a. Bladder pressure
      i. Method: clamp Foley, instill 50 to 100 mL normal saline (NS), measure pressure at level of symphysis
      ii. Results: >12 mm Hg is abnormal, 25 to 35 mm Hg is the range that various authors use to determine need for operative decompression in the operating room (OR)
   b. Measure pressure in inferior vena cava
5. Elevated intra-abdominal pressure alone is not an indication for operative decompression. The patient must also demonstrate evidence of organ dysfunction.

E. TREATMENT
1. Standard
   a. Laparotomy to decompress in OR—beware of reperfusion syndrome
   b. Temporary abdominal closure
      i. Intravenous (IV) bag sewn to skin
      ii. Vacuum pack
         (a) Plastic sheet over bowel, towel, two drains hooked to suction, adhesive dressing to cover
         (b) Commercial product
   c. Close abdomen
      i. Primarily after a few days delay, if possible
      ii. If not possible to close fascia after a few days:
         (a) Serially pull together fascia with repeated trips to OR (many methods exist)
         (b) Close skin and accept hernia (option to close fascia later remains)
         (c) Skin graft on bowel and accept hernia (option to close fascia later remains)
2. Other treatment options
   a. Withdraw fluid (ascites)

F. COMPLICATIONS
1. Multiple organ dysfunction/failure
   a. Renal failure
   b. Pulmonary failure
   c. Cardiovascular failure
2. Death (100% if not treated and 40% to 70% if treated)

III. THORACIC COMPARTMENT SYNDROME

A. GENERAL PRINCIPLES
1. Rare occurrence
2. Well described in cardiac literature, less so in trauma literature
3. In concept, similar to ACS, but occurs in the chest
4. Signs: elevated airway pressure, low cardiac output, worsening acidosis

5. May result in cardiopulmonary collapse
6. Treatment is opening the chest (and often the pericardium), usually through median sternotomy

Suggested Reading

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Meldrum DR, Moore FA, Moore EE, et al Prospective characterization and selective management of the abdominal compartment syndrome. *Am J Surg* 1997;174:667.
One of the first papers to address grading the severity of abdominal compartment syndrome.

Sugrue M. Abdominal compartment syndrome. *Curr Opin Crit Care* 2005;11(4):333.
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Tremblay LN, Feliciano DV, Rozycki GS. Secondary extremity compartment syndrome. *J Trauma* 2002;53:833.
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Velmahos GC, Toutouzas KG. Vascular trauma and compartment syndromes. *Surg Clin North Am* 2002;82(1):125–141.
Comprehensive review that includes diagnostic and therapeutic pitfalls.

SEPSIS

123

Antine E. Stenbit and Kenneth J. Serio

I. GENERAL PRINCIPLES

A. Definitions

1. Systemic inflammatory response syndrome (SIRS)
   - a. Definition of SIRS: Complex activation of the immune system due to a variety of etiologies, including infection, trauma, burns, or a sterile inflammatory process.
   - b. Characteristic clinical features of SIRS:
     - i. Altered body temperature (<36°C or >38°C)
     - ii. Hyperventilation (tachypnea >20 breaths per minute or $Paco_2$ <32 mm Hg)
     - iii. Altered leukocyte count (<4,000 or >12,000)
2. Sepsis
   - a. Definition of sepsis: Sepsis is defined as SIRS in conjunction with a documented infection.
3. Severe sepsis
   - a. Definition of severe sepsis: Severe sepsis is defined as sepsis with associated organ dysfunction or tissue hypoperfusion.
4. Septic shock
   - a. Definition of septic shock: Septic shock is defined as sepsis with associated hypotension, despite adequate fluid resuscitation.

B. Epidemiology

1. There are approximately 750,000 cases of sepsis per year in the United States and sepsis is the 10th most common cause of death.
2. There has been an increased incidence and number of attributable deaths due to sepsis observed between 1979 and 2000.
3. Despite novel treatments and improved intensive medical care, severe sepsis mortality is 25% to 30% and mortality due to septic shock approaches 40% to 70%.

II. PATHOPHYSIOLOGY

A. Exposure to lipopolysaccharide (LPS)

1. Systemic exposure to microbial antigens, including LPS from gram-negative bacteria, leads to the clinical manifestations of sepsis. Recent evidence suggests that host genetics may predict the nature of this response.

B. Role of toll-like receptors (TLRs)

1. The binding of LPS (and other microbial components) to TLR-2 and TLR-4 on inflammatory cells results in a coordinated immune response, involving T-cells, B-cells, macrophages, neutrophils, endothelial cells, and dendritic cells. These events lead to a subsequent alteration in expression of complement, fibrinolytic, coagulation, and inflammatory genes and their products.

C. Mediators of Sepsis

1. Mediators implicated in the pathogenesis of sepsis include cytokines (such as interleukin-1 [IL-1], interleukin-6 [IL-6], interleukin-8 [IL-8]), growth factors (such as tumor necrosis factor-α [TNF-α], high mobility group box-1

[HMGB-1]), proteases, oxidants, arachidonic acid metabolites, platelet-activating factor, bradykinin, and nitric oxide.

D. End-organ consequences

1. The end-organ effects of sepsis include enhanced microvascular thrombosis and permeability, vasodilation and maldistribution of blood flow, myocardial dysfunction, altered cellular nutrient utilization, and cellular apoptosis.

III. DIAGNOSIS

A. Clinical features of sepsis

1. Early: nonspecific-tachycardia, oliguria, and hyperglycemia.
2. Persistent sepsis: altered mental status, metabolic acidosis, respiratory alkalosis, arterial hypotension, and coagulopathy.
3. Decreased systemic vascular resistance with an elevated cardiac output is a prominent feature of sepsis, with persistently decreased cardiac output portending a poor prognosis.
4. Late manifestations: organ dysfunction, such as acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), acute renal failure, hepatic dysfunction, and refractory shock.

B. Identification of the inflammatory source

1. Identification is crucial to abolish the inciting stimulus.
2. The most common sites of infection in sepsis are the respiratory tract and the urinary tract (other sites are listed in Table 123-1).
3. The most common etiologic microbes, recently shifted from gram-negative to gram-positive organisms, jointly account for almost 90% of cases.
4. Etiology of the remaining 10% of cases is accounted for by fungi, anaerobes, and polymicrobial infections.
5. Imaging studies, as well as blood, urine, pleural, wound, and cerebrospinal fluid (CSF) cultures, should be performed to identify a potential organism.

C. Predisposition, infection, response, and organ dysfunction (PIRO) sepsis staging system

1. Stratifies patients by following criteria:
   a. *P*redisposing factors to sepsis, that is, comorbid conditions and genetic factors which may play a role in the development and severity of sepsis
   b. *I*nsulting infection, that is the site, type, and severity of infection and the organism susceptibility
   c. *R*esponse, that is, the degree of the host response to the insult
   d. The presence and severity of *O*rgan dysfunction
2. PIRO staging may facilitate individualization of treatment regimens, as well as aid in the prediction of outcomes and prevention of complications.

IV. TREATMENT (Table 123-2)

A. Early goal directed therapy (within the first 6 hours)

1. Therapeutic goals:
   a. CVP >8 (CVP >12 in mechanically ventilated Pts and those with increased abdominal pressure).
   b. Mean arterial pressure (MAP) ≥65 mm Hg.
   c. Urine output ≥0.5 mL/kg/hour.
   d. Central venous ($ScvO_2$) ≥70% of mixed venous SvO_2 ≥65% (Table 123-3).
   e. Fluid resuscitation, with a combination of crystalloids and colloids, should be initiated as soon as the diagnosis is suspected. Should the central or mixed venous saturation not be achieved with fluid resuscitation alone, packed red blood transfusion to a hematocrit ≥30% and/or the use of dobutamine (to a maximum of 20 μg/kg/minute) should be considered.

TABLE 123-1 Common Sites and Diseases Associated with Sepsis/SIRS

Organ system	Location	Disease
Respiratory	Upper respiratory tract	Sinusitis
		Mastoiditis
	Lower respiratory tract	Pneumonia
		Lung abscess
		Empyema
Gastrointestinal	Mediastinum	Esophageal rupture/perforation
	Hepatobiliary	Hepatic abscess
		Cholangitis
		Cholecystitis
	Intra-abdominal	Intestinal infarction/perforation
		pancreatitis
		Intra-abdominal/diverticular abscess
Cardiovascular	Mediastinum	Postoperative mediastinitis
	Native or prosthetic cardiac valve	Endocarditis
Genitourinary	Kidney, ureter, and bladder	Perinephric abscess
		Pyelonephritis
		Cystitis
Neurologic	Brain and meninges	Meningitis
		Intracranial abscess
Dermatologic	Traumatic wound, surgical wound, or burn site	Soft tissue abscess
		Necrotizing fasciitis
		Infected decubitus ulcer
		Full and partial thickness burn
Prosthetic	Central/peripheral venous catheter	Catheter infection
	Arterial catheter	
	Ventriculo-peritoneal shunt	
	Dialysis catheter	
	Articular prosthetic device	Infected prosthesis
	Dialysis graft/shunt	
Other	Vascular system	Septic thrombophlebitis

f. Resuscitation will usually require a CVC or large bore IV, while monitoring will usually require a CVC.

g. Monitoring of fluid resuscitation and pressor/inotrope utilization usually requires placement of an arterial line, as noninvasive blood pressure measurements are typically inaccurate in shock.

2. Diagnostic testing to identify an infectious source
   a. Radiographs
   b. Cultures: blood, sputum, urine, pleural, CSF, wound

3. Early antibiotic therapy
   a. Within the first hour of suspected diagnosis, initiate a multiagent empiric antibiotic regimen
   b. Appropriate antibiotic therapy within the first hour of sepsis results in an 85% improvement in survival, while each passing hour without antibiotic administration increases sepsis mortality
   c. Initial antibiotic choice should take into account the degree of penetration into the suspected infection site, local microbial resistance patterns, efficacy against the most likely organisms, and risks of side effects

TABLE 123-2 Important Things to Remember When Treating Sepsis

Early goal-directed fluid resuscitation	Within 6 hours, adequate access
Diagnosis/identification of source	Cultures before antibiotics, radiographic imaging
Antibiotics	Administer within the first hour of diagnosis Reevaluate daily and de-escalate
Monitoring	Need adequate monitoring with arterial line and CVP
Vasopressors	Norepinephrine and dopamine first Neosynephrine, vasopressin and epinephrine
Activated protein C	Know the contraindications
Glucose protocols	≤150 mg/dL
Blood products	
Ventilation and weaning protocols	
Sedation protocols	
DVT and ulcer prophylaxis	
Know when it is time to limit care	

CVP, central venous pressure; DVT, Deep venous thrombosis.

d. The antibiotic regimen should be reevaluated daily to minimize cost and potential toxicities
e. Antibiotic de-escalation should be considered as soon as feasible

4. Infectious source control
a. Therapeutic drainage of an infected space and removal of infected tissue
b. May serve to both establish the diagnosis and guide early antibiotic therapy

B. Subsequent therapy (after the initial 6-hour period)

1. Optimal fluid resuscitation
a. Crystalloid or colloid fluid challenges based on assessments of hemodynamic improvement
b. CVP >8 (CVP >12 in mechanically ventilated points and those with increased abdominal pressure)

2. Vasopressors and inotropes
a. Utilized to restore tissue perfusion and maintain MAP ≥65 mm Hg.
b. Norepinephrine and dopamine are the preferred initial agents.
c. Neosynephrine, vasopressin, and epinephrine are all acceptable agents.
d. Low-dose dopamine does not provide any benefit in terms of renal protection.
e. While it must be noted that many vasopressors are less effective in the setting of severe acidemia (pH <7.15), the administration of bicarbonate for pH ≥7.15 has been shown to worsen survival and the studies with pH <7.15 have been inconclusive.
f. Inotropic therapy with dobutamine is recommended to specifically treat sepsis-associated myocardial dysfunction.
g. Monitoring through an arterial line.
h. Pulmonary artery catheters do not improve outcome and should be carefully considered, given the increased cost and risks of complications.

3. Recombinant human activated protein C (rhAPC)
a. The administration of rhAPC has been shown to reduce sepsis mortality.
b. The administration of rhAPC inhibits the microvascular thromboses associated with sepsis (and other mechanisms of action may also exist).

TABLE 123-3 Endpoints for Resuscitation in Sepsis

Endpoint	Goal
Patient tolerance	Monitor patient response to resuscitation strategy (monitor for signs of fluid overload, arrhythmias, etc.)
Hemoglobin	Support with goal to optimize oxygen delivery
Cardiac output	Maximize with goal to optimize oxygen delivery
Sao_2	Maximize with goal to optimize oxygen delivery
Oxygen delivery	Support the hemoglobin, cardiac output, and Sao_2 to optimize the oxygen delivery
Mixed SvO_2	Maintain $SvO_2 \geq 70\%$
Heart rate	Maintain at levels that allow adequate diastolic cardiac filling
MAP	Maintain at ≥65 mm Hg
CVP	Maintain at 8–12 mm Hg (12–15 mm Hg in ventilated patients)
Serum lactate	Restore normal pH and monitor for resolution of lactic acidosis
Urine output	Maintain at urine output ≥0.5 mL/kg/h
Serum glucose	Maintain at ≤150 g/dL
Minute ventilation	Monitor ABGs closely for signs of inadequate respiratory compensation for metabolic acidosis Ventilatory support (if necessary)

Sao_2, hemoglobin saturation; SvO_2, venous oxygen saturation; MAP, mean arterial pressure; CVP, central venous pressure; ABGs, arterial blood gases.

c. The administration of rhAPC carries a low, but defined, risk of hemorrhage and the fact that the agent has not been well-studied in patients with known bleeding diatheses (such as chronic liver disease), patient selection, and monitoring of therapy is crucial.

d. The administration of rhAPC is recommended for adult patients with a high likelihood of death and an acute physiology and chronic health evaluation (APACHE) II score of ≥25, who have no contraindications.

4. Steroid replacement therapy
   a. Steroids have no demonstrated benefit in unselected patient populations, but studies suggest a high frequency of occult adrenal insufficiency in sepsis.
   b. Although the use of steroids in sepsis remains controversial, current guidelines recommend the use of hydrocortisone replacement in adults with severe sepsis whose hypotension is refractory to fluid resuscitation and vasopressors.
5. Insulin therapy
   a. Controlling blood glucose to levels ≤150 mg/dL improves outcomes in sepsis.
   b. Caution should be taken when evaluating point of care glucose measurements in the severely ill as they often overestimate the actual glucose level.
6. Prophylaxis
   a. Deep venous thrombosis (DVT) prophylaxis is indicated for all patients, in the absence of clinical contraindications.
   b. Stress ulcer prophylaxis is indicated for all patients, in the absence of clinical contraindications.
7. Limitation of care
   a. Careful consideration of the patient's and their family's wishes should be exercised regarding aggressive care in the setting of sepsis.

Suggested Reading

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MULTIPLE ORGAN DYSFUNCTION

Samir Fakhry and Paola Fata

124

I. BACKGROUND

A. Multiple organ dysfunction syndrome (MODS) has been described as a "disease of medical progress" or the unwanted outcome of successful shock resuscitation.

B. Develops in approximately 15% of medical and surgical intensive care patients.

C. It is the leading cause of death for all patients admitted to an intensive care unit (ICU).

D. In the ICU, the incidence of single-organ failure approaches 48%. The lung is the most common organ to develop obvious clinical failure, followed by the liver, kidney, gastrointestinal (GI) tract, and cardiovascular system.

II. DEFINITION

A. MODS refers to the presence of altered organ function in a severely ill patient so that homeostasis cannot be maintained without intervention.

B. The physiologic definition is severe acquired dysfunction of at least two organ systems lasting at least 24 to 48 hours in the setting of sepsis, trauma, burns, or severe inflammatory conditions. Both the number of dysfunctional organs and the duration of dysfunction are critical to the definition. The mortality increases proportionally with number and duration of dysfunctions.

C. Single-organ failure lasting more than 1 day results in a mortality risk of 20%; if two organs are involved, mortality increases to 40%; whereas persistent dysfunction (>72 hours) present in three organ systems can result in a mortality risk of 80%.

III. HISTORY

A. 1973: Tilney identifies a syndrome of sequential organ failure following rupture of abdominal aortic aneurysms.

B. 1977: Eiseman first introduced the term "multiple organ failure" as a consequence of technical complications related to clinical management in almost 60% of patients.

C. 1980: Fry and colleagues proposed that infection is the probable cause for development of this syndrome.

D. 1985: Goris found, in contrast, that bacterial sepsis was found in 65% of intra-abdominal sepsis patients but only in 33% of trauma patients diagnosed with multiple organ failure and therefore sepsis is probably not the essential cause of MODS; rather an uncontrolled hyperinflammatory response is responsible.

IV. SCORING SYSTEMS

A. A number of scoring systems have been developed to predict mortality from organ dysfunction, and they are useful as a baseline severity assessment.

B. Changes in score may reflect recovery or deterioration of organ function and may be employed across ICUs as a quality performance marker.

C. Two most frequently employed clinical measurement systems are the sepsis-related organ failure assessment (SOFA) and the multipleorgan dysfunction score (MODS) (Table 124-1).

TABLE 124-1 Clinical Measurement Systems to Assess Organ Dysfunction

Parameter	SOFA	Score	MODS	Score
Respiratory	Pao_2/Fio_2 Ventilation	0–4	Pao_2/Fio_2	0–4
Coagulation	Platelet number Cell number	0–4	Platelet number	0–4
Hepatic	Bilirubin	0–4	Bilirubin	0–4
Cardiac	Blood pressure Vasopressor use	0–4	Blood pressure Heart rate Central venous pressure	0–4
CNS	Glasgow coma scale	0–4	Glasgow coma scale	0–4
Renal	Creatinine urine output	0–4	Creatinine urine output	0–4
Aggregate score	Add worst daily score	0–24	Add worst daily score	0–24

V. PATHOPHYSIOLOGY. An evidence-based understanding of the pathophysiology is still pending, and various mechanisms have been proposed.

A. Uncontrolled infection

1. Earlier reports suggested MODS was caused by occult or uncontrolled infection, commonly pneumonia or peritonitis. Infection in patients with MODS is common, and nosocomial infection is rare in patients without organ dysfunction. Infection, however, is not necessarily present.

2. Endotoxin can be absorbed through the GI tract or lung and has been postulated to play an important role in MODS. In the clinical setting, however, this correllates poorly with culture proven infection.

B. Gut hypothesis

1. Splanchnic hypoperfusion is common in critical illness.

2. High susceptibility of the GI tract to diminished tissue perfusion and ischemia results in:

a. Mucosal atrophy with increased permeability

b. Altered immune function

c. Bacterial translocation

d. Bacteria in the systemic circulation activate the inflammatory response, resulting in organ dysfunction

C. Tissue hypoxia: Diminished oxygen delivery at the cellular level inhibits the normal physiologic activity of the cell, which is a common pathway for organ dysfunction.

D. Microvascular coagulopathy

1. Inflammation and inappropriate activation of coagulation may be related to the development of organ dysfunction through abnormal microvascular thrombosis.

2. Endotoxin and inflammatory cytokines activate tissue factor. Tissue factor activates the coagulation pathway as well as gene expression for the proinflammatory cytokines, such as tumor necrosis factor (TNF).

3. Alterations in factor levels determining the balance between coagulation and fibrinolysis precede organ dysfunction.

E. Systemic inflammation

1. Defined as the activation of circulating leukocytes, endothelial cells, and chemical mediators, which are normally suppressed by anti-inflammatory mediators.

2. When the patient's inflammatory response process is uncontrolled, MODS ensues:
   a. The initiating event may be severe tissue trauma or intra-abdominal sepsis, which results in massive activation of inflammatory mediators. Then systemic damage to vascular endothelia, permeability edema, and impaired oxygen availability to the mitochondria occurs (despite adequate arterial oxygen transport).
   b. Increased circulating levels of cytokines TNF, interleukin-1 (IL-1), and interleukin-6 (IL-6) are associated with organ dysfunction and increased mortality.
   c. Systemic inflammation seems to be the initiating event or final common pathway of the previous four hypotheses.

F. MODS cannot be traced to a single cause for most patients. A single theory about the development is not enough to explain the clinical syndrome. Tissue hypoxia, splanchnic hypoperfusion, microvascular coagulopathy, and systemic inflammation are the integrated responses to severe injury resulting in clinical organ dysfunction (Fig. 124-1).

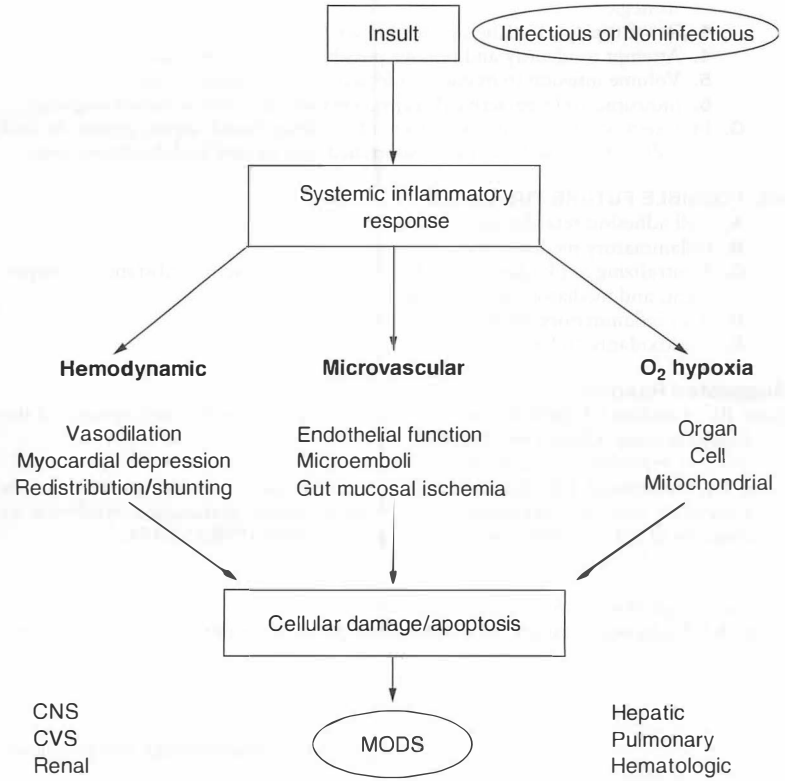

Figure 124-1. Multiple organ dysfunction syndrome (MODS) etiologic factors. CNS, central nervous system; CVS, cardiovascular system.

VI. THERAPY

- **A.** The capacity to treat MODS when it is diagnosed is limited despite therapeutic advances in critical care. *The mortality rate remains unchanged.*
- **B.** Multiple clinical trials have evaluated the use of anti-inflammatory agents (methylprednisolone, intravenous ibuprofen, anti-TNF monoclonal antibodies), and all have thus far been ineffective. Recent data suggest that activated protein C can decrease the mortality of sepsis and MODS.
- **C.** Selective decontamination of the digestive tract to decrease bacterial translocation has yielded varying results and remains controversial.
- **D.** It is important to address the underlying causes in patients at risk for MODS (i.e., identify and treat infection early, aggressive shock resuscitation, damage control rather than definitive operations in emergent situations, correcting acidosis, hypothermia, and control of bleeding).
- **E.** Resuscitation with hypertonic saline attenuates neutrophil infiltration in the lung, as well as plasma levels of nitric oxide and IL-1, and shows early promise in prevention and treatment.
- **F.** Supportive therapy is used to treat MODS when it is diagnosed:
  1. Modern ventilation techniques for acute lung injury
  2. Support of each failing organ system with the most current evidence-based strategies
  3. Renal replacement therapy for kidney failure
  4. Attempt to identify and remove possible precipitating causes
  5. Volume infusion to maintain adequate cardiac filling pressure
  6. Inotropic and vasoactive therapy as needed after resuscitation ongoing
- **G.** In recent studies, implementation of evidence-based sepsis protocols and "bundles" improved outcomes, shortened time to care and decreased costs.

VII. POSSIBLE FUTURE THERAPIES

- **A.** Cell adhesion retardation
- **B.** Inflammatory mediator reduction
- **C.** Neutralizing antibodies directed at cytokines, vasoactive substances, complement, and mediators of coagulation
- **D.** Anti-inflammatory protein induction
- **E.** Antioxidants and antiproteases

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XII

Neurologic Problems in the Intensive Care Unit

125

AN APPROACH TO NEUROLOGIC PROBLEMS IN THE INTENSIVE CARE UNIT

David A. Drachman

I. GENERAL PRINCIPLES

A. Patients with neurologic problems present in the intensive care unit (ICU) as primary neurologic problems or as neurologic complications secondary to medical or surgical disorders. Only a few common neurologic *situations* occur in the ICU, although they can be caused by many *diseases*.

1. Depressed state of consciousness, coma
2. Altered mental function
3. Required support of respirations or other vital functions
4. Monitoring: increased intracranial pressure (ICP), respirations, consciousness
5. Determination of brain death
6. Prevention of further damage to the central nervous system (CNS)
7. Management of seizures or status epilepticus
8. Evaluation of a neurologic change occurring in a known medical disease
9. Management of medical disease developing during neurologic illness

B. **Primary neurologic problems** in the ICU include:

1. Stroke
2. Guillain–Barré syndrome
3. Status epilepticus

4. Myasthenia gravis
5. Head trauma

C. Neurologic complications of medical disease are far more common than primary neurologic problems. They include:
1. Impaired consciousness following cardiopulmonary resuscitation
2. Altered mental status with metabolic disorders
3. Development of delirium
4. Critical care neuromyopathy
5. Focal neurologic deficits in a patient with multisystem disease

D. Indications for neurologic consultation in the ICU
1. *Depressed state of consciousness.* Depressed consciousness ranges from lethargy to coma and raises many questions:
   a. Is there a focal brainstem lesion or diffuse cerebral involvement?
   b. Is there an anatomic lesion or a metabolic disorder?
   c. Have vital brainstem functions been impaired?
   d. Is ICP increased?
2. The most common *primary neurologic causes* of depressed consciousness include:
   a. Head trauma
   b. Intracranial hemorrhage
   c. Nonconvulsive seizures
3. The *secondary conditions* seen most often are:
   a. Metabolic–anoxic disorders
   b. Drug intoxications
   c. Diabetic acidosis
4. It is crucial to establish whether depressed consciousness is the result of:
   a. Intrinsic brainstem damage
   b. Increased ICP
   c. Toxins
   d. Widespread anoxia/ischemia
   e. Other, less common causes

II. DIAGNOSIS

A. In the patient with depressed consciousness, it is particularly important to identify *as rapidly as possible* the component(s) that may be treatable!
1. **Neurologic examination of patients with stupor or coma.** Examination of the patient with depressed consciousness includes: evaluation of (a) mental status, (b) cranial nerve functions, (c) motor functions and coordination, (d) reflexes, (e) sensation, and (f) vascular integrity; supplemented by appropriate laboratory studies.
   a. *Mental status*
      i. Detailed evaluation of memory and cognitive function is rarely possible in lethargic patients and is impossible when stupor or coma is present.
      ii. Estimate the responsiveness of the patient, including vital functions, respiratory pattern, eye opening, response to painful stimuli, and speech.
   b. *Cranial nerve evaluations*: Vision (e.g., blink to threat), pupils (size and response), corneal reflexes, "doll's eyes" responses, and, if absent, ice water caloric response, cough, facial movements to pain, and gag reflex are tested.
   c. *Motor function*: Evaluate by observing all limbs for spontaneous movement, symmetry, and adventitious movements. Pinch or other noxious stimulus may help evaluate purposeful defensive movements.
      i. Decerebrate (four-limb extensor) or decorticate (upper limbs flexor, lower limbs extensor) rigidity is observed.

ii. Tone is assessed for spasticity or rigidity.

d. *Reflexes*: Deep tendon reflexes; grasp, suck, snout, and plantar reflexes are evaluated.

e. *Sensation*: Pain is often the only testable sensation; withdrawal from pinprick in the feet must be distinguished from an extensor plantar response.

f. *Vascular status*: Listen for bruits over the carotid, subclavian, and vertebral arteries.

2. Laboratory studies

a. Imaging studies: Magnetic resonance imaging (MRI) or computed tomography (CT) can reveal evidence of stroke, hemorrhage, trauma, tumor, and so forth, despite the difficulty of obtaining these studies.

b. Electroencephalography (EEG): This reveals seizure activity, functional state, symmetry, certain toxic-metabolic conditions. Can be performed at the bedside.

c. Metabolic studies: Electrolytes, ammonia, pH, O_2 saturation, renal function, hepatic function, toxic substances, and others.

3. Interpretation. This examination reveals the patient's state of consciousness, the integrity of brainstem reflexes, the presence of focal versus diffuse neurologic deficits, and provides information on specific metabolic disorders.

B. Management of patients with depressed consciousness depends on determining the cause and applying the appropriate techniques for eliminating toxins, reducing ICP, and maintaining vital functions.

1. Altered mental function: In the awake patient, disorders that affect mental function can produce patterns of: confusion, delirium, aphasia, dementia, or isolated memory impairment. Ask the following questions:

a. Is the abnormal mentation a recent change or longstanding?

b. Did the change develop abruptly after surgery, cardiac arrest, or other event?

c. Is the mental change improving, worsening, or stable?

2. Confusion and delirium: often result from *metabolic* or *toxic* disorders; they are commonly reversible.

3. Persistent aphasia and *isolated* memory impairment: suggest focal anatomic damage to the brain. Neurologic examination for localization and imaging studies are useful.

4. Dementia/cognitive impairment: can be assessed *only* in patients with a clear sensorium; it cannot be evaluated in patients with depressed consciousness, confusion, or delirium. Cognitive impairment can indicate either *reversible* (drug-induced, depression-related) conditions or *irreversible* damage (diffuse anoxia, ischemia, strokes; or a degenerative dementia).

Recent change of mental status in the ICU requires evaluation by an experienced neurologist as early as possible!

C. Support of respiration and other vital functions

1. Respiratory support is needed for neurologic patients with:

a. Loss of brainstem control of respiration

b. Impairment of effective transmission of neural impulses to respiratory muscles.

Brainstem lesions produce characteristic respiratory patterns, depending on the site of damage (e.g., central neurogenic hyperventilation, Cheyne–Stokes or periodic breathing, apnea). Transmission of respiratory impulses can be impaired at the cervical spinal cord, anterior horn cells, peripheral nerves, neuromuscular junctions, or muscles of respiration. Traumatic cervical cord injuries, amyotrophic lateral sclerosis, the Guillain–Barré syndrome, myasthenia gravis, and muscular dystrophy interfere with breathing at different levels. Some conditions

are transitory (Guillain–Barré syndrome) or treatable (myasthenia gravis), with *complete recovery* if respiration is successfully maintained.

D. Monitoring ICP and state of consciousness. Head trauma, subarachnoid hemorrhage, tumor, and stroke may require neural monitoring.

1. Lethargic patients should be observed for increased ICP caused by cerebral edema, intracranial (subdural, epidural, intracerebral) hemorrhage, or both.
2. Once uncal or tonsillar *herniation* with brainstem compression occurs, the secondary brain injury may far outweigh the initial damage (methods for monitoring ICP and assessing consciousness with the Glasgow coma scale are described elsewhere (Chapter 144 and Appendix).

E. Determination of brain death

1. Death of the brain and brainstem is equivalent to death of the patient.
   a. Brain death is specifically a determination that the brain *and* the brainstem are already dead—*not* a *prediction* of unlikely useful recovery.
   b. The mnemonic *CADRE* is useful to remember the criteria for brain death: **c**oma, **a**pnea, **d**ilated fixed pupils, **r**eflex (brainstem) absence, and **E**EG silence.

F. Preventing further damage to the CNS

1. In stroke, thrombolytic treatment or mechanical clot removal can reverse the ischemic process, and neuroprotective agents may prevent further damage.
2. Spinal cord compression by tumor requires decompression and/or radiation therapy to avoid cord transection.
3. *Cerebral ischemia, anoxia, hemorrhage, increased ICP, spinal cord compression, and other acute neurologic disorders require prompt institution of treatment.*

G. Managing status epilepticus. Status epilepticus threatens lasting deficits or death if not controlled.

1. Patients with *continuous* or *recurrent* seizures that cannot be promptly arrested must be treated in the ICU.
2. Therapy ranging up to general anesthesia or artificial ventilation may be required.

H. Evaluating secondary neurologic disease in severe medical illness. Patients in the ICU with myocardial infarctions, subacute bacterial endocarditis, cardiac arrhythmias, pneumonia, renal disease, and so forth may develop neurologic changes during treatment for the medical problem. These neurologic findings may result from the underlying disease or be coincidental; a neurologist should evaluate such patients.

I. Managing secondary severe medical disease in neurologic illness. Patients with chronic neurologic disorders often develop unrelated medical illness: for example, myocardial infarcts occurring in demented patients or septicemia in patients with multiple sclerosis. Early recognition of a change in the neurologic patient's condition is often critical to a successful outcome.

III. PROGNOSTIC AND ETHICAL CONSIDERATIONS

A. When severe damage involves the brain, physicians and their families often need guidance regarding the probable outcome. Three critical questions should be addressed:

1. Will the patient survive?
2. Has irreversible brain damage occurred?
3. What is the likely degree of residual disability?

B. The most important consideration is whether *irreversible damage* has affected crucial brain areas, rather than the level of consciousness. The probability of neurologic recovery declines with age, size, and location of the lesion, and duration of the deficit. (Some reported statistical guidelines are of value in estimating recovery; see, e.g., Levy D, Caronna J, Singer B, et al. in Suggested Reading.)

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ALTERED CONSCIOUSNESS

Majaz Moonis, David A. Drachman, and Lawrence J. Hayward

126

I. OVERVIEW

A. Introduction. Many diseases lead to acute impairment of consciousness, including some that are potentially life threatening but treatable if recognized early, and require a systematic and complete evaluation:

1. Rapid determination of the type of mental status change
2. Administration of life support measures when needed
3. Obtaining a detailed history, physical examination, and ancillary studies
4. Initiation of definitive treatment based on this assessment

B. Pathophysiology

1. Altered sensorium (state of consciousness) results from damage to the reticular activating system (RAS) in the brainstem and diencephalon, and/or their projections to *both* cerebral hemispheres.
2. Many structural/physiological disorders can affect these structures and impair consciousness (Table 126-1).

C. Prognosis. Depends on the cause of coma and any secondary complications (see later).

D. Diagnosis. Distinguishes among normal sleep, coma, status epilepticus, akinetic mutism, locked-in state, and aphasia.

E. Treatment. Depends on the underlying cause and the presence or absence of cerebral edema.

II. THE PATIENT WHO APPEARS UNCONSCIOUS

A. General principles. Some patients appear to be unconscious. The differential diagnosis includes the following.

1. Normal sleep (can be aroused to complete wakefulness by verbal or physical stimulation)
2. Impaired consciousness and brain death (sustained arousal by stimuli cannot be obtained)
3. Locked-in state (awake and can communicate by vertical eye movements)
4. Psychogenic coma (demonstrate clinical and electroencephalographic [EEG] evidence of wakefulness)
5. Nonconvulsive status epilepticus (impaired consciousness with EEG evidence of continuous seizures)

B. Prognosis

1. Depressed consciousness: Prognosis depends on the underlying cause, degree of reversibility, and presence of secondary brain damage from effects of raised intracranial pressure (ICP).
2. Locked-instate: Patients usually have permanent paralysis but can communicate through blinks. Acute locked-in state can sometimes be reversible with treatment of the underlying cause (thrombolytic therapy for a basilar artery stroke).
3. Status epilepticus: Usually reversible with antiepileptic drugs but may sustain permanent damage after prolonged seizure activity. When seen in anoxic coma, indicates a poor prognosis for recovery.

TABLE 126-1 Localization of Brain Dysfunction in Patients with Apparent Change in Consciousness

Clinical state	Area of dysfunction
Depressed consciousness	RAS
Drowsiness	RAS
Stupor/coma	RAS and bilateral cerebral hemispheres
Acute confusional state	Bilateral cerebral hemispheres
Akinetic mutism	Bilateral frontal lobes; diencephalon bilaterally
Persistent vegetative state	Bilateral cerebral hemispheres

RAS, reticular activating system.

C. Diagnosis

1. Rapid evaluation for the presence of neck rigidity (meningitis or subarachnoid hemorrhage), needle marks (drug overdose), or asymmetric dilated pupils (impending herniation) should be a priority before a more detailed examination.
2. Detailed history of onset, preceding events, and past medical conditions and medications and drugs is crucial to establishing the correct diagnosis.
3. In mild brain dysfunction (drowsiness, hypersomnolence), mild sensory stimulation results in orientation and appropriate responses are made. In more severe brain dysfunction (stupor), more severe and sustained sensory stimuli are required to achieve transient arousal. Patients may have purposeful movements when aroused but lack normal content of consciousness.
4. Severe brain dysfunction results in coma, from which patients cannot be aroused.
5. If spontaneous blinking is present in a paralyzed patient, appropriate responses may be elicited to questions, indicating normal cortical function (locked-in syndrome).
6. Apparently comatose patients demonstrating active resistance, rapid closure of the eyelids, pupillary constriction to visual threat, fast phase of nystagmus on oculo-vestibular or optokinetic testing, and avoidance of self-injury may have psychogenic coma.
7. Nonfocal neurologic examination is suggestive of a toxic-metabolic coma, with some exceptions (meningoencephalitis, subarachnoid hemorrhage, bilateral subdural hematomas, or thrombosis of the superior sagittal sinus) (Table 126-2).
8. Presence of focal neurologic signs (cranial nerves or motor system) suggests a *structural lesion* as the underlying cause of coma.
9. Brain death is the irreversible destruction of the brain (total absence of all cortical and brainstem function), although spinal cord reflexes may remain.
   a. Pupils are in midposition, are round, and do not respond to light.
   b. The Apnea Test. No inspiratory effort (i.e., central apnea) even when arterial carbon dioxide tension (PCO_2) is raised to levels that should stimulate respiration. Sedating medications, drug intoxications, metabolic disturbances, hypothermia, and shock should be excluded as complicating conditions in determining brain death.

D. Ancillary tests

1. Computed tomographic (CT) or magnetic resonance imaging (MRI) scan without contrast demonstrates intracranial hemorrhage and hydrocephalus; contrast enhancement is required for infections or neoplastic masses. MRI demonstrates ischemia within minutes after stroke onset.

TABLE 126-2 Classification of Causes of Altered Consciousness Based on Most Common Clinical Presentation

1. Depressed consciousness or acute confusional state *without* focal or lateralizing neurologic signs and without signs of meningeal irritation.[a]
   - Metabolic disorders: hepatic failure, uremia, hypercapnia, hypoxia, hypoglycemia, diabetic hyperosmolar state, hypercalcemia, thiamine or cobalamine deficiency, hypotension
   - Drug intoxications or poisoning: opiates, alcohol, barbiturates, tricyclic antidepressants, amphetamines, anticholinergic agents, other sedatives, carbon monoxide, heavy metal toxins
   - Infectious and other febrile illnesses: septicemia, pneumonia, rheumatic fever, connective tissue diseases
   - Nonconvulsive status epilepticus or postconvulsive lethargy
   - Situational psychoses: intensive care unit, puerperal, postoperative, or posttraumatic psychoses; severe sleep deprivation can be complicating factor
   - Abstinence states (i.e., withdrawal states): alcohol (delirium tremens), barbiturates, benzodiazepines
   - Space-occupying lesions: bilateral subdural hematoma, midline cerebral tumors (e.g., lymphoma, glioma), abscess
   - Hydrocephalus
2. Altered consciousness *with* signs of meningeal irritation
   - Infectious disorders: meningoencephalitis (bacterial, viral, fungal, parasitic)
   - Subarachnoid hemorrhage: brain contusion, ruptured aneurysm, or other vascular malformation
   - Rheumatologic conditions: meningeal granulomatous disorders (e.g., sarcoid, Wegener granulomatosis)
3. Altered consciousness with *focal or lateralizing neurologic signs*[b]
   - Space-occupying lesion: neoplasm, hemorrhage, inflammatory process (e.g., abscess, autoimmune encephalitis)
   - Cerebral ischemia or infarction: stroke, hypertensive encephalopathy

[a] Meningismus is often absent in deeply comatose patients with meningeal inflammation.
[b] Metabolic derangements can produce focal signs, for example ocular motility disturbance due to thiamine deficiency; focal deficits with hypoglycemia.

2. Comprehensive metabolic profile, blood gases, and toxic screen must be performed, especially if CT and MRI fail to demonstrate a structural lesion.
3. The cerebrospinal fluid must be examined if meningoencephalitis or subarachnoid hemorrhage is suspected.
4. EEG is most useful in suspected seizures, as a confirmatory test for brain death, in suspected infections (herpes encephalitis, Creutzfeldt–Jakob disease), and to demonstrate normal rhythm and reactivity in locked-in syndrome and psychogenic coma.

E. Treatment

1. Definitive treatment of altered consciousness depends on the underlying cause (Table 126-2).
2. Reversal of depressed consciousness with intravenous thiamine, glucose, and naloxone often provides rapid diagnostic clues about unsuspected thiamine deficiency, hypoglycemia, or opioid overdose, respectively.
3. Fluid replacement, oxygenation, suctioning, positioning, nutrition, corneal protection, and bowel and bladder care are essential.

Sedating drugs confound the accurate monitoring of the patient's neurologic condition and *should be avoided or minimized whenever possible*.

4. In ischemic/hypoxic cases due to cardiac arrest-induced hypothermia may limit neurologic damage and improve outcome (see Chapter 128).

III. THE PATIENT APPEARS AWAKE BUT IS CONFUSED OR NONCOMMUNICATIVE

A. General principles. Patients with this clinical presentation may have acute confusional state, delirium, nonconvulsive seizures, receptive aphasia, or akinetic mutism.

1. Acute confusional state: Easily distracted, poor attention span with resultant poor recall, and short-term memory.
2. Delirium
   a. Behave as in acute confusional state
   b. Autonomic hyperactivity with hypervigilance
   c. Delusions and often visual hallucinations
3. Nonconvulsive status epilepticus. Signs that are suggestive of this diagnosis are episodic staring, eye deviation or nystagmoid jerks, facial or hand clonic activity, and automatisms.
4. Receptive aphasia
   a. Unable to respond to command or repeat
   b. Fluent but jargon speech with paraphasias (word substitution)
5. Akinetic mutism
   a. Brainstem function is intact and sleep–wake cycles may be present.
   b. Little evidence is seen of cognitive function. Patient may open eyes to auditory stimulation or track moving objects, but only a paucity of spontaneous movement occurs. *Persistent vegetative state* is similar but more severe and usually follows prolonged coma. Complex subcortical responses are absent, but decorticate or decerebrate posturing and other rudimentary subcortical responses (e.g., yawn, cough) are seen.

B. Diagnosis

1. The history is critical in determining the cause of the patient's condition, and efforts to locate family members, witnesses, and medication lists are almost always fruitful.
   a. Knowledge of preexisting cerebral dysfunction (e.g., dementia, multiple sclerosis, mental retardation) is important in determining the degree of depressed consciousness or confusion expected for a specific systemic derangement (e.g., hyponatremia, sepsis, drug intoxication).
   b. A reliable account of the tempo of loss of consciousness is important. For example, truly sudden coma in a healthy person suggests drug intoxication, intracranial hemorrhage, brainstem ischemic stroke, meningoencephalitis, or an unwitnessed seizure.
2. Focal neurologic signs suggest a structural cause of altered consciousness, although focal weakness or partial motor seizures sometimes occur in metabolic encephalopathies (e.g., hypoglycemia). Other falsely localizing signs include sixth nerve palsies caused by transmitted increased ICP, and visual field cuts caused by compression of the posterior cerebral artery. Conversely, a nonfocal examination does not invariably indicate toxic-metabolic encephalopathy, although it often will cause symmetric neurologic dysfunction (Table 126-2).
3. Treatment. Refer to treatment of impaired consciousness

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Ropper AH, Brown RH. *Adams and Victor's principles of neurology*, 8th ed. New York: McGraw-Hill, 2005.
A lucid and comprehensive review of disorders of consciousness (Chapter 17) and acute confusional states (Chapter 20).

127 METABOLIC ENCEPHALOPATHY

Paula D. Ravin

I. BACKGROUND

A. Metabolic encephalopathy is defined as global brain dysfunction caused by a biochemical derangement.

B. There is often a fluctuating level of consciousness with nonfocal signs. Patients can present with:

1. Delirium (confusion, inattentiveness, sleeplessness, hallucinosis).

2. Depressed level of consciousness (drowsiness, stupor, coma).

C. Metabolic encephalopathy is common in illnesses that cause multiorgan failure (see Table 127-1 for typical patient profile).

D. The following increase the risk of developing metabolic encephalopathy:

1. Age older than 60 years

2. Systemic infection

3. Temperature dysregulation

4. Chronic disease of the central nervous system (CNS)

5. Organ failure

6. Endocrine disorders

7. Multiple CNS-acting drugs

8. Nutritional deficiency

9. Alcoholism

10. History of perinatal injury

11. Sleep deprivation, sensory deprivation

E. In cases of a correctible metabolic disorder, prompt treatment may result in reversal of encephalopathy.

F. Progression to stupor or coma may lead to prolonged encephalopathy and complications, with a poor neurologic outcome.

II. ETIOLOGY

A. Drugs and toxins (50%)

B. Hepatic, renal, or pulmonary failure (12%)

C. Endocrine or electrolyte disturbances (8%)

D. Other causes: thiamine deficiency (exacerbated by glucose loading), prolonged hypoglycemia, hypoperfusion during cardiac bypass, hyperthermia (> 105°F), hyperammonemia

III. PATHOGENESIS

A. Altered substrate (glucose/oxygen) for neurotransmitter function

B. CNS depressant drug accumulation due to abnormal volume of distribution (decreased protein, high lipophilicity)

C. Impaired cerebral blood flow

D. Abnormal cerebrospinal fluid (CSF) dynamics

E. Altered neuronal function due to temperature and/or ionic changes

IV. DIAGNOSIS. Metabolic encephalopathy should be considered when a patient exhibits altered cognition or alertness. The clinical examination should include:

A. General physical examination:

1. Vital signs, breathing pattern, pulse oximetry

TABLE 127-1 Patient Profile in Metabolic Encephalopathy

- Gradual onset over hours
- Progressive if untreated
- Waxing and waning level of consciousness
- Patient treated with multiple CNS-acting drugs
- Patient with organ failure, postoperative state, electrolyte or endocrine imbalance
- No evidence of CVA, brain tumor: nonfocal examination
- Can be heralded by focal or generalized seizures
- Increased spontaneous motor activity

CNS, central nervous system; CVA, cerebrovascular accident.

2. Fundoscopy, to evaluate for papilledema (increased intracranial pressure), septic emboli
   a. Cardiovascular examination: global cerebral hypoperfusion may result from congestive heart failure
3. Bowel sounds: obstruction/perforation may cause agitation and changes in mental status
4. Bladder distention: retention can lead to agitation

B. Neurologic examination
1. Behavioral changes: inattention, diminished speech, disorientation, impaired short-term memory, indifference, blunted affect, waxing and waning consciousness, hallucinosis.
2. Abnormal extraocular eye movements should raise suspicion of brainstem stroke or thiamine deficiency; pupils are usually small and reactive, although they may be dilated in some toxic encephalopathies related to adrenergic excess (e.g., thyroid storm, cocaine overdose).
3. Respiratory pattern can be deranged in a variety of ways, including hyperventilation (e.g., acidosis), Cheyne–Stokes respiration, hypoventilation, gasping, apneic episodes (central or obstructive), hiccoughing.
4. Abnormal motor activity: tremors, myoclonus, asterixis, restlessness, chorea, muscle spasms, rigidity, rigors.
5. Hyperreflexia and Babinski signs may be present.
6. Dysautonomia with widely fluctuating blood pressure and core temperature should raise suspicion of sepsis.

C. Metabolic encephalopathy should be distinguished from:
1. Brainstem stroke (see Chapter 130)
2. Increased intracranial pressure from an expanding mass lesion in the brain
3. Meningoencephalitis (e.g., herpes)
4. Occult head trauma
5. Nonconvulsive status epilepticus

D. Metabolic encephalopathy due to thiamine deficiency (Wernicke-Korsakoff syndrome) should be suspected in all encephalopathic patients who are malnourished and/or have a history of alcohol abuse. Patients with the syndrome can present with oculomotor paresis, nystagmus, pupillary abnormalities. Administration of glucose without parenteral thiamine can lead to severe exacerbation of encephalopathy and lead to permanent CNS injury.

V. LABORATORY STUDIES

A. Body fluids
1. Toxicology screen, especially in patients with history of major depression, substance abuse. Include salicylates, barbiturates, opioids, amphetamines, alcohol, benzodiazepines, caffeine, and theophyllines.

2. Drug levels: digoxin, anticonvulsants, lithium.
3. Metabolic panel: blood urea nitrogen (BUN), creatinine, electrolytes, complete blood count (CBC), platelet count, thyroid-stimulating hormone (TSH), calcium, phosphate, arterial ammonia, blood gases, serum and urine osmolality, blood glucose.
4. When indicated, CSF analysis for infection, inflammation, subarachnoid blood.
5. Urinalysis, urine culture, blood cultures.

B. Electroencephalogram (EEG): Background slow wave activity or frontal triphasic waves are seen in metabolic encephalopathy. Epileptiform activity raises possibility of nonconvulsive status epilepticus.

C. Imaging studies
1. Computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain, to evaluate for an acute structural lesion.
2. Chest radiographic films, to evaluate for occult pneumonia.
3. Abdominal radiographic films, to evaluate for bowel obstruction.

VI. TREATMENT

A. Correction of the underlying metabolic disturbance. Acute encephalopathy due to thiamine deficiency is a medical emergency. If suspected, give thiamine 100 mg intravenously daily for at least 3 days; the oral route is not suitable for rapidly repleting thiamine.

B. Improvement in cognition and arousal may lag behind the improvement in metabolic parameters by days to weeks in some cases.
1. With underlying neurodegenerative disease, patients may not recover to their baseline level despite stabilized metabolic values.
2. Avoid adding CNS-acting drugs, such as stimulants and sedatives, for the behavioral changes of metabolic encephalopathy before addressing the inherent causes.

VII. CONCLUSIONS

A. Metabolic encephalopathy is a common cause of altered neurologic function in the intensive care unit (ICU) setting.

B. It should be suspected when there is a fluctuating or impaired mental status, bouts of restlessness, and a nonfocal examination.

C. The causes are varied, but vigilant correction of metabolic disorders, reduction in CNS-acting drugs, and general supportive measures improve the outcome in most patients.

D. Patients in the ICU commonly have poor nutritional status and global encephalopathy. These patients should be treated empirically for acute thiamine deficiency.

Suggested Reading

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128 GENERALIZED ANOXIA/ISCHEMIA OF THE NERVOUS SYSTEM

Majaz Moonis and Carol F. Lippa

I. GENERAL PRINCIPLES

A. Failure of blood flow (cardiac arrest) or reduced oxygenation to the brain (respiratory failure, carbon monoxide, or cyanide poisoning) for 4 to 5 minutes results in brain damage because the brain tolerates oxygen deprivation poorly.

B. Anoxia resulting from respiratory failure from any cause is better tolerated than when the primary event is cardiac arrest.

II. PROGNOSIS. Many factors determine the prognosis after anoxic brain insult. These include the cause of the anoxic/ischemic insult, effective time to establish recirculation (arrest time [AT] + cardiopulmonary resuscitation [CPR] time), level of consciousness, age of patient, and neurological signs present at 24 to 72 hours.

A. Favorable prognostic indicators include:

1. Retained consciousness during the anoxic/ischemic insult.
2. Primary respiratory failure carries a better prognosis than primary cardiac arrest.
3. Recovery of multiple brainstem responses within 48 hours of arrest (pupillary, corneal, and oculovestibular).
4. Return of purposeful motor movements within 24 hours (localization of pain).
5. Young age (children may do well even beyond this time period).
6. Hypothermia at AT (cold water drowning).

B. Poor prognostic indicators in patients with persistent coma after 72 hours include:

1. The absence of pupillary responses or motor response to pain at 72 hours.
2. Presence of diffuse cerebral edema on computed tomography (CT) scan with loss of gray-white junction.
3. Certain abnormal electroencephalogram (EEG) patterns including burst suppression, α coma, low voltage unreactive delta activity.
4. Absent cortical evoked potential N20 response after 72 hours of coma. If the cortical N20 responses can be elicited, the chances of improvement are increased to 25%.
5. Cerebrospinal fluid (CSF) neuron-specific enolase >24 ng/mL at 24 hours or a creatine kinase-BB >50 U/L at 48 to 72 hours.

III. ETIOLOGY

A. Cardiac arrest from any cause

B. Respiratory failure from any cause

C. Poisoning (carbon monoxide, cyanide, others)

IV. PATHOPHYSIOLOGY. Following these injuries, excess glutamate release results in activation of the excitotoxic cascade, calcium influx into neurons, and cell death.

V. DIAGNOSIS

A. History

1. Cardiac arrest
2. Respiratory failure

3. Drowning
4. Drug intoxication/poisoning

B. Examination: Patients are comatose without focal neurological deficits. Rarely soft neurological signs have been documented

C. Imaging and laboratory studies

1. Computerized tomography scan to rule out structural lesions such as stroke, hemorrhage within a tumor or brain herniation.
2. Blood glucose, liver function tests including ammonia, blood urea nitrogen, and creatinine should be obtained to rule out hypoglycemia or other causes of metabolic encephalopathy. Toxic screen should be obtained when the cause of coma is unknown. An immediate EEG if nonconvulsive status is suspected.

VI. TREATMENT

A. Adequate oxygenation (Pao_2 at or over 100 mm Hg) and mean arterial blood pressure (90 to 110 mm Hg) should be maintained.

B. Patients should be kept slightly hypovolemic and the head of the bed elevated to 30 degrees.

C. Underlying causes such as toxins or drug ingestion should be treated.

D. Cardiac arrhythmias should be controlled.

E. A diligent search for infections should be done and treated appropriately.

F. Patients should not be allowed to become hyperthermic.

G. All other toxic, metabolic, or structural causes of comas should be ruled out.

H. Vital signs, hematocrit, electrolytes, blood sugar, and serum osmolarity should be maintained within the normal range.

I. Seizures (25%): Fosphenytoin at 20 phenytoin equivalents/kg intravenously (IV) or intramuscularly (low risk of inducing hypotension and can be given intramuscularly if there is no IV access). Alternatively, phenytoin in the same doses can be given with careful blood pressure and cardiac monitoring. If serious acute underlying cardiac arrhythmias exist, IV phenobarbital is preferred. Intravenous valproate or intravenous levetiracetam are options, levetiracetam especially in cases where there is significant liver dysfunction

J. EEG monitoring

1. If seizures are controlled, a delayed EEG is done after 48 hours.
2. Continuous EEG monitoring is required for status epilepticus.

K. Controlling brain edema

1. There is no role for the use of steroids or high-dose barbiturates, and hyperosmolar agents are seldom helpful in anoxic or hypoxic coma.
2. Controlled hyperventilation with a PCO_2 of 25 to 28 mm may be effective in the short term to avoid impending herniation.

L. Hypothermia: In two prospective randomized and controlled trials, induced hypothermia (IH) with rapid cooling to 33°C for 12 to 24 hours resulted in significant improvement in outcome after coma due to cardiac arrest compared with patients allowed to maintain normothermia. Increased vascular resistance and decreased cardiac output were important complications. However, the incidence of cardiac arrhythmia was similar in the hypothermic and normothermic groups. Larger trials with better methods of rapid cooling should be explored; in some medical centers, IH is currently considered the standard of practice. Based on the published evidence to date, the International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support (ALS) Task Force has made the following recommendations: Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32° C to 34° C for 12 to 24 hours when the initial rhythm was ventricular fibrillation (VF). Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest.

M. Mobilization: Once coma begins to lighten, early mobilization should be the goal to prevent other complications.

VII. COMPLICATIONS

A. Delayed brain damage: Seen rarely, 3 to 30 days after the initial recovery, especially following carbon monoxide poisoning, a late functional decline occurs with irritability, lethargy, and increased muscle tone. Pathologically, widespread demyelination is found. Most patients survive this second insult.

B. Intention myoclonus is another delayed consequence. This can be distinguished from seizures by the absence of corresponding EEG changes.

C. Persistent vegetative state: No cortical function, although the patient appears awake and retains many bodily functions (feeding, sleep–wake cycle).

D. Brain death: The clinical criteria of brain death is defined in chapters 125 and 138. Total absence of electrocerebral activity, not associated with sedative hypnotic drugs or hypothermia, is helpful in confirming brain death in difficult cases. Similarly, a brain scan showing absence of blood flow is strongly suggestive of brain death.

Suggested Reading

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better outcome for recovery. The rationale of IH and benefits and risks are discussed.

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A summary of the literature concerning reliable indicators of death or a vegetative state following acute anoxia.

129 STATUS EPILEPTICUS

Catherine A. Phillips

I. DEFINITIONS

A. *Status epilepticus* is defined as:

1. Usually, one or more epileptic seizures lasting 30 minutes or longer without recovery between attacks (formal definition); or

2. Seizure activity lasting 5 minutes or longer (operational definition); or

3. Two or more seizures with incomplete recovery of consciousness between them.

B. *Myoclonic status* is repetitive, asynchronous myoclonic jerks with variable clouding of consciousness, usually in the setting of severe encephalopathy such as cerebral anoxia; patients are usually comatose.

C. *Simple partial status* is continuous or repetitive focal seizures without loss of consciousness. This includes *epilepsia partialis continua*, with continuous localized clonic seizure activity that does not generalize and in which consciousness is maintained.

D. *Nonconvulsive status* is a confusional state of 30 minutes or more.

1. In *absence status*, consciousness varies with subtle myoclonic facial movements and automatisms of face and hands.

2. *Complex partial status* involves either a series of complex partial seizures, separated by a confusional state, or a prolonged state of partial responsiveness and semipurposeful automatisms.

II. ETIOLOGY

A. Symptomatic status—status caused by a neurologic or metabolic insult—is more common than idiopathic status.

B. Status can be caused by stroke (ischemic or hemorrhagic), anoxic brain injury, electrolyte disturbances (e.g., hyponatremia, hypomagnesemia, hypoglycemia, hyperglycemia, uremia, sepsis), drug or other toxicity, alcohol or other drug withdrawal, and decreasing antiepileptic medication.

C. Viral encephalitis from Epstein–Barr syndrome or herpes simplex virus can have an abrupt onset heralded by status epilepticus.

III. PROGNOSIS AND SEQUELAE

A. Overall, mortality rate is 7% to 25%. Advanced age and prolonged status are poor prognostic factors.

B. Status caused by anoxia has the highest mortality rate followed by hemorrhage, tumor, metabolic disorders, and systemic infection. Status caused by alcohol withdrawal and antiepileptic drug discontinuation, and idiopathic status, have lower mortality rates.

C. In one study, duration >60 minutes was associated with a mortality rate of 32%, compared with 3% for duration <60 minutes.

D. Long-term sequelae may include intellectual deterioration, permanent focal neurologic deficits, and chronic epilepsy. Aspiration pneumonia is a common complication of status.

E. Generalized tonic—clonic status epilepticus is the most common form of status with the most severe neurologic sequelae.

IV. INITIAL ASSESSMENT

A. Patients with generalized tonic—clonic status usually do not convulse continuously, and observation is necessary to determine that generalized seizures occur without recovery of consciousness.

B. In nonconvulsive or focal motor status, the diagnosis requires 30 minutes of continuous clinical (or electrical) seizure activity. When status epilepticus presents with a change in mental status only, an electroencephalogram (EEG) is required for confirmation.

V. INITIAL MANAGEMENT AND MEDICAL STABILIZATION

A. Initial assessment and treatment should begin within 5 minutes of onset of seizure activity (Table 129-1).

TABLE 129-1 Management Protocol for Generalized Status Epilepticus

Minutes: 0–10

1. If diagnosis is uncertain, observe recurrence of generalized seizures without subsequent recovery of consciousness.
2. Assess cardiopulmonary status; establish airway, administer O_2, initiate cardiac monitoring.
3. Start IV line with normal saline.
4. Draw blood for complete blood count and differential, glucose, blood urea nitrogen, creatinine, electrolytes, calcium, liver function tests, antiepileptic drug levels, toxicology screen; perform bedside glucose determination.
5. Give glucose (D50) 50 mL and thiamine 100 mg IV if hypoglycemia is present.
6. Monitor respirations, blood pressure, ECG, oximetry, and, if possible, EEG.
7. Give lorazepam (0.1 mg/kg) IV bolus, <2 mg/min (may use 2–4 mg initial dose, and complete dose as needed).

Minutes: 10–30

1. Start phenytoin or fosphenytoin (20 mg/kg) IV, 50 mg/min (fosphenytoin 150 mg/min), with slower rate if hypotension develops.
2. Give additional boluses of phenytoin or fosphenytoin (5 mg/kg), to a maximum of 30 mg/kg, if patient is still having seizures.

Minutes: 30–90

1. If status continues after phenytoin infusion is completed, immediately start phenobarbital (20 mg/kg) IV at ≤100 mg/min; intubation is necessary either before or during phenobarbital infusion.
2. If status persists, induce coma using one of the agents listed below (items a–c). Continuous EEG is needed to monitor seizure control and level of anesthesia. Monitor EEG hourly once burst-suppression pattern is present.
   a. Pentobarbital: 5 mg/kg IV load, given slowly; give additional 5-mg/kg boluses as necessary to produce burst-suppression pattern. Maintenance infusion of 0.5 to 5 mg/kg/h.
   b. Midazolam, 0.1 to 0.3 mg/kg IV load, infusion rate 0.05 to 2 mg/kg/h.
   c. Propofol, 1 to 5 mg/kg load, infusion rate 1 to 15 mg/kg/h.

12 H: Slowly withdraw medication at 12 h; if seizures recur, resume infusion for 24 h, then slowly taper off again; continue this process as necessary.

IV, intravenous; ECG, electrocardiogram; EEG, electroencephalogram.

B. History: include information on a preexisting chronic seizure disorder and antiepileptic drug use.

C. Examination: signs of systemic illness (e.g., uremia, hepatic disease, infection); illicit drug use; trauma; focal neurologic abnormalities.

D. Administer glucose for hypoglycemia (hypoglycemic status is rare but easily reversible; can cause irreversible central nervous system [CNS] damage untreated). Thiamine should be given because glucose can precipitate Wernicke–Korsakoff syndrome with marginal nutrition.

E. Intravenous (IV) infusions should consist of saline solution, because some antiepileptic drugs precipitate in glucose solutions.

F. Hyperthermia caused by status: treat with alcohol sponge baths, cooling blankets, or ice packs.

G. Oxygenation must be maintained.

H. Metabolic acidosis often develops early in status but usually resolves spontaneously once seizures stop; treatment with bicarbonate is usually not necessary.

I. Blood pressure must be monitored; if hypotension occurs, the brain is vulnerable to inadequate perfusion. Pharmacologic intervention for the seizures can exacerbate hypotension.

J. When a metabolic disorder causes status, pharmacologic intervention alone is not effective.

K. Exclude systemic and CNS infections; lumbar puncture (LP) is often necessary; leukocytosis, fever, and cerebrospinal fluid pleocytosis may be caused by status itself.

L. Only short-acting paralytic agents should be used, if these agents are absolutely required; otherwise, ongoing EEG monitoring will be necessary.

M. Contrast-enhanced head computed tomography (CT) scan may demonstrate a structural cause, but scan should be done after the patient has been stabilized and the seizures controlled. Magnetic resonance imaging (MRI) is preferred but often not practical in the emergent setting.

VI. PHARMACOLOGIC MANAGEMENT OF GENERALIZED STATUS EPILEPTICUS

A. Goals: stop seizures early; prevent recurrence; try to determine the cause. Generalized convulsive status is a medical emergency.

B. A benzodiazepine drug is the initial therapy for status. Diazepam has a brief duration of action (10 to 25 minutes). Lorazepam is equally effective with a much longer duration of action (2 to 24 hours). Both benzodiazepines have essentially the same cardiac, respiratory, and CNS depressant side effects. Respiratory depression and apnea can occur abruptly with the initial doses, especially when given IV, and previous administration of sedative drugs and increasing age potentiate cardiorespiratory side effects.

1. Lorazepam should be given 0.1 mg/kg IV at 2 mg/minute; a 2- to 4-mg dose may be given initially. A total dose of up to 0.2 mg/kg may be given if necessary. The dose of diazepam is 0.15 mg/kg, with an additional 0.1 mg/kg if necessary.
2. Hypotension may be partially caused by the propylene glycol solvent in IV diazepam and lorazepam.
3. Rectal diazepam is an alternative. For adults, 7.5 to 10 mg of the IV preparation or 0.2 mg/kg of the rectal gel preparation is administered per rectum (PR). The incidence of significant respiratory depression is lower with PR compared to IV administration.
4. Intramuscular (IM) absorption of these agents is delayed and incomplete; this route is unsuitable for treating status.
5. Midazolam can also be effective but has an extremely short duration of action and a high recurrence rate of seizures.

C. *Phenytoin* IV is very effective in generalized status. Phenytoin should *not* be given IM. A 20-mg/kg load is given at a maximal rate of 50 mg/minute, with an additional 10 mg/kg if the initial load is not effective.
   1. Hypotension, electrocardiographic (ECG) changes and respiratory depression can occur partly from the propylene glycol diluent. Cardiac monitoring should be performed and the drug given more slowly (25 mg/minute) in elderly patients or in those with a history of cardiac arrhythmias, compromised pulmonary function, or hypotension. The most common adverse effect is hypotension.
   2. Severe tissue injury can also occur if phenytoin extravasates into tissue.

D. *Fosphenytoin*: a water-soluble prodrug of phenytoin, rapidly converted to phenytoin. In many centers fosphenytoin is now used in place of phenytoin, but should be used when IV access not available or phenytoin poorly tolerated at the infusion site.
   1. Fosphenytoin has greater aqueous solubility than phenytoin; it may be used IV or IM, is nonirritating, and is rapidly and completely absorbed by either route.
   2. Therapeutic phenytoin concentrations are attained in 10 minutes with rapid IV infusion and in 30 minutes with slower IV infusion or IM injection.
   3. Fosphenytoin is dosed in "phenytoin equivalents" (PE) units (same as for phenytoin [load 20 mg/kg PE]); administered at rates up to 150 mg/minute PE.
   4. Cardiac monitoring is required with IV fosphenytoin.

E. Phenobarbital is as effective as the combination of benzodiazepines and phenytoin for initial therapy, but CNS depression is a major side effect.
   1. If status persists 10 minutes after phenytoin load is complete, IV phenobarbital should be given (10 mg/kg) as an initial dose, then repeated if seizures continue (up to 20 mg/kg).
   2. Phenobarbital can be administered up to 100 mg/minute.
   3. *Respiratory depression is a major side effect*, especially if benzodiazepines have been used, and it is imperative to monitor respirations and ensure an adequate airway.
   4. In some cases, treatment of the status proceeds directly to induction of anesthesia as described in subsequent text, without using phenobarbital.

F. Refractory status epilepticus. If status continues after full loading doses of phenytoin and phenobarbital, a drug-induced coma to suppress electrical seizure activity completely is indicated.
   1. Intubate patient; close hemodynamic monitoring. Pressors are frequently needed. Ileus is also common.
   2. Simultaneous EEG monitoring is required to monitor electrical seizure activity and assess depth of anesthesia.
   3. Barbiturates (e.g., pentobarbital), benzodiazepines, and propofol are commonly used to achieve drug-induced coma. Phenobarbital is not used for this purpose because it causes very prolonged coma.
   4. Drug dose is increased until a burst-suppression pattern (flat background punctuated by bursts of mixed-frequency activity) is seen on the EEG. If the bursts contain electrographic seizure activity, the coma should be deepened, at times to virtual electrocerebral silence.
   5. Goal: *terminate electrical seizure activity*, not just to produce a burst-suppression pattern.
   6. Maintenance doses of phenytoin and phenobarbital are continued and serum levels followed.
   7. Drug-induced coma is continued for 12 to 24 hours, then anesthesia is slowly withdrawn. If electrical seizures recur, the process is repeated for a longer period of time.

8. If midazolam is used to induce coma and status is not terminated within 48 hours, substitute a different drug (e.g., pentobarbital, propofol) because the effects of midazolam tolerance will complicate therapy.

VII. PHARMACOLOGIC MANAGEMENT OF PARTIAL AND ABSENCE STATUS EPILEPTICUS

A. Absence status is not associated with the severe adverse sequelae of convulsive status, but should be treated promptly.

B. IV lorazepam is recommended, followed by more definitive treatment for absence epilepsy.

C. Partial status may lead to neuronal injury and should be treated aggressively, using the same protocol as for generalized status but with longer time allotments for each phase of the protocol, particularly before the induction of generalized anesthesia.

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CEREBROVASCULAR DISEASE

Majaz Moonis, John P. Weaver, and Marc Fisher

130

I. GENERAL PRINCIPLES

A. Cerebrovascular disease includes:
  1. Stroke caused by thrombotic or embolic ischemia (IS)
  2. Intracerebral hemorrhage (ICH) and extracerebral hemorrhage (subarachnoid hemorrhage and subdural) (hemorrhagic shock [HS])

B. Admission to the intensive care unit (ICU) is often warranted because of the severity of the disease or institution of newer therapies.

C. This chapter focuses on both ischemic cerebrovascular disease (ICVD) and ICH.

II. ICVD

A. Prognosis

1. Altered sensorium (state of consciousness), conjugate gaze paresis, and early radiologic signs of *large* infarction predict a poor outcome.

2. Lacunar stroke has a better prognosis (70% to 80% recovery).

3. Transient ischemic attack (TIA) patients have a 5.5% chance of stroke within 48 hours.

B. Etiology

1. ICVD results from restriction of blood flow to the brain, usually because of arterial occlusion.

2. Cardioembolic stroke is due to ischemic heart disease, atrial fibrillation, or cardiomyopathy.

3. Atherothrombotic stroke is caused by occlusion of a large intra/extracranial portion of the carotid/vertebrobasilar system from local stenosis and occlusion.

4. Lacunar stroke is due to small blood vessel occlusion.

5. Watershed territory strokes result from systemic hypotension, with resulting border zone infarction (areas between anterior and middle cerebral artery (MCA), or middle and posterior cerebral artery distributions).

C. Diagnosis

1. History—helps to determine type of stroke:
  a. Cardioembolic more common during the day with acute onset.
  b. Atherothrombotic more often during sleep.
  c. Intracranial hemorrhage often starts with a headache and deficit may progress for considerable time.
  d. TIA is defined as a neurologic/retinal deficit, recovering within 60 minutes in the absence of imaging abnormalities.

2. Examination
  a. Aphasia, hemiparesis or hemiparesthesia, and monocular visual loss suggest carotid system infarct.
  b. Vertigo, cerebellar ataxia, and crossed deficits (ipsilateral cranial nerve and contralateral hemiparesis or hemianesthesia) suggest involvement of the vertebrobasilar system.
  c. Pure motor hemiparesis, pure sensory stroke, ataxic hemiparesis, and dysarthria—clumsy hand syndrome suggest the diagnosis of lacunar stroke.

3. Laboratory and radiologic evaluation
   a. *Neuroimaging*: An essential procedure!
      i. To exclude ICH or subarachnoid hemorrhage.
      ii. To select patients for acute thrombolytic therapy.
      iii. Diffusion-weighted magnetic resonance imaging (DW-MRI) can demonstrate ischemic lesions within minutes of onset, whereas perfusion imaging (PI) demonstrates the area at risk of eventual infarction. A DW-PI mismatch demonstrates the penumbra (salvageable tissue). Perfusion computed tomography (CTP) and CT angiography (CTA) are accurate, faster, and, therefore, more practical when thrombolytic therapy is anticipated.
   b. An *electrocardiogram* (ECG) and telemetry in all patients with IS.
   c. *Echocardiography*, transesophageal echocardiogram is preferred.
   d. *Carotid ultrasound* and transcranial Doppler ultrasound are used in patients with contraindications to CTA/MR angiography (MRA).
   e. *Blood studies*, at a minimum, should include: a complete blood count (CBC), fasting lipid and blood glucose and homocysteine levels. Hypercoagulable workup and anticardiolipin antibodies may be obtained in younger patients or those with prior venous thrombosis, recurrent abortions, thrombocytopenia, and migraine (lupus antiphospholipid antibody anticoagulant syndrome).

D. Treatment

1. Identify patients who are candidates for thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) (Table 130-1). Thrombolysis: 33% greater probability of being free of any disability at 3 months, 10-fold *relative* increased risk of intracranial bleeding).
   a. Patients presenting within 3 hours of onset of ischemic stroke should have an urgent CT scan to rule out hemorrhage and large infarcts (>one-third the MCA territory). Wherever available, a CT angiogram and CTP or alternatively MRI (DW-PI) and MRA should be performed.
   b. In the absence of a large infarct, if CTP or DW-PI demonstrates a mismatch, there may be grounds to consider thrombolysis, later than 3 hours post stroke.
   c. In patients with large vessel stroke (Internal Carotid, Basilar of Middle Cerebral Artery proximal occlusion) suggested by a high NIHSS score and confirmed by CT Angiography, intravenous thrombolysis can be initiated at community hospitals; with no improvement, rapid transfer to a tertiary hospital for possible additional intraarterial interventional therapy. The same strategy is applicable at tertiary stroke centers where if there is no time delay, intraarterial therapy may be initiated as a primary measure for these large vessel stroke identified on CTA or MRA.
   d. A signed consent is desirable but not necessary in the first 3 hours as thrombolysis within the first 3 hours is considered standard of care (Table 130-1).
2. Blood pressure should be lowered to <185/110 mm Hg before thrombolytic therapy is initiated. For other patients, blood pressure can be observed in the absence of malignant hypertension; it should not be excessively lowered unless it exceeds 220/120 mm Hg or end-organ failure (congestive heart failure [CHF], renal) is present. If blood pressure has to be lowered, the goal should be a 15% to 20% reduction.
3. Subcutaneous heparin/enoxaparin/compression boots should be considered in immobilized patients.
4. Elevated temperature and hyperglycemia should be aggressively treated.
5. Oral feedings should be delayed until swallowing evaluation is performed.

TABLE 130-1 Thrombolytic Therapy of Acute Ischemic Stroke

A. Inclusion criteria

1. Age older than 18 yr
2. Time from stroke onset <3 h

B. Exclusion criteria

Absolute contraindications

1. Evidence of intracranial hemorrhage on pretreatment CT
2. Active internal bleeding
3. Known bleeding diathesis, including but not limited to:
   a. Platelet count <100,000/mm
   b. Patient has received heparin within 48 h and has an elevated aPTT >35 s
4. Current use of oral anticoagulants (e.g., warfarin sodium) or recent use with an INR >1.6
5. Within 3 mo any significant intracranial surgery, serious head trauma, or previous stroke
6. Clinical presentation suggestive of subarachnoid hemorrhage, even with normal CT
7. Blood pressure (systolic >185 mm Hg, diastolic >110 mm Hg) refractory to antihypertensive therapy
8. Known cerebral arteriovenous (AV) malformation, or aneurysm
9. Recent major intracranial hemorrhage

Relative contraindications (use best medical judgment – assess risk vs. benefit)

1. Only minor or rapidly improving stroke symptoms
2. Patient has had major surgery or serious trauma excluding head trauma in the previous 14 d
3. History of gastrointestinal or urinary tract hemorrhage within 21 d
4. Recent arterial puncture at a noncompressible site
5. Recent lumbar puncture
6. Abnormal blood glucose (<50 or >400 mg/dL)
7. Postmyocardial infarction pericarditis
8. Patient observed to have seizure at the time of onset of stroke (perform CT angiogram: if arterial occlusion, proceed to thrombolysis)

CT, computed tomography; aPTT, activated partial thromboplastin time; INR, international normalized ratio.

6. Cardioembolic stroke can be treated with delayed warfarin therapy. There is currently no clear role for the use of full intravenous heparin or heparinoids in secondary stroke prevention or to improve outcome.
7. Antiplatelet therapy should be considered in patients who do not have a clear embolic source. Extended-release dipyridamole and aspirin (ERDP/ASA; Aggrenox) is U.S. Food and Drug Administration (FDA) approved and is 23% more effective in reducing recurrent stroke compared with aspirin. The results for a recently completed international trial (PROFESS) suggests that clopidogrel may be as effective as ERDP/ASA).
8. Treatment with statins to reduce low-density lipoprotein (LDL) cholesterol to preferably <70 mg/dl and antihypertensive therapy with Angiotensin converting enzyme inhibitors (ACEI) and or Angiotensin Receptor Inhibitors (ARBs) further reduce risk of recurrent stroke by 30% to 40%.

9. Large strokes with worsening sensorium are treated with short-term mannitol and at times with intracranial pressure (ICP) monitoring. Early decompressive hemicraniectomy for large MCA stroke with altered sensorium is associated with a >50% reduction in mortality and >25% more patients achieve a better functional outcome.

III. ICH

A. General principles. ICH often requires management in the ICU. The leading cause is hypertensive ICH. Other causes include rupture of saccular aneurysms or arteriovenous malformations (AVMs), and ICH due to amyloid angiopathy.

B. Prognosis. The prognosis for ICH is worse for larger lesions. Pontine ICH has the highest mortality, followed by cerebellar and then basal ganglia ICH. Lobar ICH carries the most favorable outlook for survival and functional recovery.

C. Etiology

1. Hypertensive ICH results from rupture of arterial branch-point acquired microaneurysm (Charcot-Bouchard aneurysms). Surrounding edema exerts a mass effect and blood may block ventricles, causing hydrocephalus.
2. Nonhypertensive hemorrhage.
   a. Amyloid angiopathy.
   b. Rupture of AVM/aneurysm.
   c. Bleeding or coagulation disorders causing thrombocytopenia, loss of factors involved in coagulation (leukemia, idiopathic thrombocytopenia, severe liver disease, disseminated intravascular coagulation [DIC]), and other rare disorders of coagulation.
   d. Anticoagulation and antiplatelet use.

D. Diagnosis

1. History: The presentation of ICH is abrupt and often associated with headache and progressive neurological deficits over minutes to hours.
2. Examination
   a. Helpful clinical hints to suggest ICH include deficits that extend beyond the distribution of a single artery and presence of altered sensorium.
   b. Localization
      i. Putamen (hemiparesis, hemiesthesia)
      ii. Pons (hyperthermia, coma, pinpoint pupils)
      iii. Thalamus (hemihypesthesia, disconjugate vertical gaze)
      iv. Cerebellum (ataxia, nystagmus, head tilt, vomiting)
      v. Cerebral cortex (if cortical signs are present in a nonhypertensive ICH, suspect cerebral amyloid angiopathy)
3. Radiologic and laboratory tests
   a. CT scan demonstrates the site and size of the hematoma with great accuracy.
   b. MRI is as sensitive to detect blood and may demonstrate underlying pathology such as a vascular malformation or tumor.
   c. Angiography should be considered if an underlying aneurysm or AVM is suspected.
   d. Lumbar puncture is contraindicated in ICH because of the risk of transtentorial herniation.
   e. Coagulation profile and CBC to exclude underlying bleeding disorder.

E. Treatment

1. Correct any predisposing systemic hemorrhagic factors to prevent further clinical deterioration.
2. Lower systolic blood pressure in the acute phase of ICH to between 110 and 160 mm Hg. β-Blockers are the agents of choice. Intravenous nicardipine is a safe alternative. Vasodilators (e.g., nitroprusside [Nipride]) should be avoided because they can promote cerebral edema and elevate ICP.

3. Acute increases in ICP may require hyperventilation and hyperosmolar agents, such as mannitol. Treatment of ICH with steroids can be detrimental.
4. Elevation of ICP from hydrocephalus is treated with ventriculostomy.
5. Surgery may be indicated for large superficial lobar ICH and cerebellar ICHs. Early surgical intervention is indicated for lesions >2.5 cm associated with changes in mental status. Decompressive hemicraniectomy may be lifesaving but the quality of life will depend on the extent of brain damage and potential for reversibility.

   Prophylactic anticonvulsants are not routinely used in ICH.
6. Four-vessel angiography may be performed in patients without history of hypertension, or if the bleeding is in an atypical location.

Suggested Reading

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131 SUBARACHNOID HEMORRHAGE

Wiley Hall, John P. Weaver, and Majaz Moonis

I. GENERAL PRINCIPLES

A. Frequency and morbidity of subarachnoid hemorrhage (SAH)

1. Aneurysmal SAH accounts for 80% of nontraumatic SAH.

2. Perimesencephalic and other mechanisms of nontraumatic SAH account for the remaining 20% of cases and have lower incidences of morbidity and mortality from rebleeding and delayed ischemic deficits.

3. Intracranial hemorrhage secondary to the rupture of saccular aneurysms accounts for 2% to 5% of all new strokes and accounts for 21,000 to 33,000 new cases in the United States annually.

B. Management of SAH caused by a ruptured aneurysm includes:

1. Early aneurysm repair to limit rebleeding

2. A calcium antagonist to ameliorate cerebral injury secondary to vasospasm

3. Hemodynamic and endovascular intervention to treat and overcome vasospasm

II. PROGNOSIS. Prognostic indicators:

A. Aneurysms >10 mm in size and smaller aneurysms at the basilar tip are more likely to rupture as compared with smaller aneurysms in other locations.

B. Decerebration or coma at onset (Hunt and Hess grades 4 and 5) are associated with worse outcome.

C. Up to 51% of patients with SAH die, many before reaching medical care, and most of the remainder in the first 2 weeks of care. Up to 33% of survivors need long-term care and up to 46% of survivors suffer some form of long-term cognitive dysfunction.

III. PATHOGENESIS

A. Saccular (berry) aneurysms are distinguished from other types of intracerebral aneurysms caused by trauma, vascular dissection, or mycotic lesions and those related to tumors.

B. Of saccular aneurysms, 85% are located in the anterior circulation and 15% in the posterior circulation. Multiple aneurysms can occur in families or with systemic diseases such as polycystic kidney, Marfan syndrome, Ehlers–Danlos syndrome, pseudoxanthoma elasticum, fibromuscular dysplasia, and coarctation of the aorta.

C. Risk factors include tobacco use, heavy alcohol use, cocaine abuse, hypertension, and history of intracranial aneurysm in a first-degree relative.

IV. DIAGNOSIS

A. History

1. Severe headache, usually described as the worst headache ever; abrupt onset and peaks in intensity immediately.

2. Sudden loss of consciousness, nausea, vomiting.

3. Facial pain, pupillary dilation and ptosis (from oculomotor nerve compression), and visual field defects (from optic nerve or chiasm compression).

4. A warning leak, or sentinel hemorrhage, which occurs in approximately 20% of patients, can be misdiagnosed. The physician should have a high

index of suspicion for aneurysmal expansion or warning leak because such events precede major hemorrhage.

B. Examination

1. Neck stiffness
2. Altered sensorium
3. Focal signs (hemiparesis, oculomotor palsy, visual loss, paraparesis)

C. Laboratory studies

1. A noncontrast head computed tomography (CT) is used to identify, localize, and quantify the hemorrhage. Modern CT is approximately 95% sensitive for SAH on the first day of hemorrhage.
2. Lumbar puncture (LP) is indicated if CT is nondiagnostic in a case with strong clinical suspicion.
3. When CT and LP are negative, in some cases escalation to computed tomography angiography (CTA) or conventional catheter angiography may be performed.
4. If surgery is emergent, CT angiography is the preferred study.
5. Four-vessel cerebral angiography is the most precise imaging study to localize the aneurysm(s), define the vascular anatomy, and assess vasospasm. Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) can be performed to reveal aneurysms larger than 4 mm.
   a. Imaging the upper cervical spine with angiography and MRI is important when cerebral angiography fails to reveal the source of hemorrhage.
   b. If the initial angiogram fails to demonstrate the source of SAH, angiography may be repeated in 1 to 2 weeks. If clinically stable, patients may be discharged home after the second negative angiogram. In some cases, a third angiogram may be performed in several months' time.

V. TREATMENT

A. Management

1. Preoperative medical management includes bed rest, head elevation to improve cerebral venous return, pulmonary toilet, thrombophlebitis prophylaxis, antiemetics, anticonvulsant prophylaxis, and pain control.
2. Rebleeding is a serious complication of SAH, postulated to be caused by breakdown of the perianeurysmal clot. The peak incidence of rebleeding occurs during the first day after SAH and one-half to two-thirds of patients who rebleed die. Key preventative measures include early repair of the aneurysm and blood pressure control.
3. Systolic blood pressure is maintained below 160 mm Hg with β-blocking agents, which also reduce the risks of cardiac arrhythmias. Nicardipine may be used when bradycardia exists. Nitrates are avoided due to their potential to raise intracranial pressure (ICP). No consensus exists on upper limits for blood pressure after aneurysm repair when vasospasm dominates morbidity; 200 to 220 mm Hg is a common upper limit.
4. Hypothalamic damage can cause cardiac dysrhythmias from excessive sympathetic stimulation. Myocardial ischemia may occur from increased sympathetic tone, as can global myocardial depression.
5. Hydrocephalus can develop within the first 24 hours after SAH because of impaired cerebrospinal fluid (CSF) resorption by the arachnoid granulations or intraventricular blood obstruction of CSF outflow. Ventricular drainage or shunting may be emergently indicated.
6. Hyponatremia can develop from hypothalamic dysfunction, causing a salt-wasting syndrome. This is commonly confused with syndrome of inappropriate antidiuretic hormone (SIADH); the two are distinguished by urine output and electrolyte levels. Hyponatremia is treated with normal or hypertonic saline. Fluid restriction is not indicated. Euvolemia is maintained throughout the course.

B. Repair of ruptured aneurysm

1. Standard surgical management is craniotomy with clip occlusion of the aneurysm neck, usually within 48 hours of rupture in most noncomatose patients.
   a. Unique problems that dictate the use of specialized techniques included vertebral–basilar system aneurysms, giant aneurysms (>25 mm), and multiple aneurysms.
   b. Follow-up angiography is performed to evaluate occlusion of the aneurysm and patency of the surrounding vessels.
2. Endovascular repair includes coil embolization of appropriately shaped aneurysms.
   a. Some lesions require balloon or stent-assisted techniques due to aneurysm neck morphology.
   b. In cases where embolization and surgical clipping are not possible, balloon or coil occlusion of the parent artery may be considered.
3. Surgical clipping is definitive, but a higher percentage of patients may develop epilepsy post repair. Endovascular repair is less invasive but patients may require multiple coilings due to aneurysm recanalization and patients may have higher incidence of vasospasm due to lack of drainage of blood during craniotomy.

C. Neurologic complications

1. **Cerebral vasospasm** is a major cause of morbidity and mortality. Noted angiographically in 70% of patients, vasospasm causes symptoms because of cerebral ischemia in only 36% of cases. Vasospasm occurs progressively: it may be apparent as early as the third day after hemorrhage, with a peak between days 4 and 12. It occurs more frequently in patients with a poor clinical condition, thick focal blood clots, or a diffused layer of blood in the subarachnoid space. Neurologic deficits are correlated with the areas of cerebral ischemia. Vasospasm is diagnosed by angiography or noninvasively by transcranial Doppler (TCD).
   a. **Calcium antagonists.** The calcium antagonist nimodipine reduces delayed neurologic deficits caused by vasospasm. Nimodipine exerts a beneficial effect by decreasing postinjury intracellular calcium; dilating leptomeningeal vessels; improving collateral circulation to ischemic areas; improving erythrocyte deformability; or exerting an antiplatelet aggregating effect. Nimodipine (60 mg) is given orally every 4 hours for 21 days from the onset of SAH. If hypotension occurs, the dose is divided in half and administered every 2 hours.
   b. **Hyperdynamic therapy.** The current mainstay of therapy for symptomatic vasospasm is hypervolemic, hypertensive, hemodilution therapy to augment cerebral blood flow (CBF). Elevation of arterial pressure increases CBF; volume augmentation provides hemodilution, decreases viscosity, and improves cerebral microcirculation.
      i. Criteria to initiate treatment include increased TCD blood flow velocity, focal neurologic deficits, or impaired consciousness without hydrocephalus.
      ii. Vasopressors are used to keep systolic blood pressures elevated, and plasma volume is maintained with fluids and occasionally albumin.
      iii. Hematocrit is often maintained at approximately 30, though controversy exists regarding the risk/benefit of transfusion to this goal.
      iv. Risks of therapy include myocardial infarction, congestive heart failure, dysrhythmias, hemorrhagic infarcts, rebleeding, hyponatremia, and hemothorax.
   c. Endovascular treatments for vasospasm may improve outcome. Options include intra-arterial injection of vasodilators such as nicardipine,

verapamil, or papaverine. For proximal vessel vasospasm, balloon angioplasty may be performed.

d. Emerging technologies such as brain tissue oximetry, microdialysis, and CBF monitoring may in the future permit earlier detection and more targeted treatment of vasospasm.

2. Treatment of intracranial hypertension may require an ICP monitor and/or CSF drainage. Mannitol and hypertonic saline may be used, but strict attention to euvolemia is required.

3. Unresponsive patients should undergo electroencephalography (EEG) monitoring. Subclinical seizures have been reported in up to 20% of such cases.

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The Guillain–Barré Syndrome

Isabelita R. Bella and David A. Chad

132

I. GENERAL PRINCIPLES

A. Until recently, the term *Guillain–Barré syndrome* (GBS) has been used synonymously with acute inflammatory demyelinating polyradiculoneuropathy (AIDP), an immunologically mediated disorder producing multifocal demyelination of nerve roots and cranial and peripheral nerves that occur at all ages.

B. In recent years, the recognition of primary axonal forms of GBS has broadened the spectrum of GBS to include both the demyelinating form (AIDP) and axonal variants: acute motor axonal neuropathy (AMAN) and acute motor-sensory axonal neuropathy (AMSAN).

C. All present similarly with rapidly progressive weakness, areflexia, and elevated spinal fluid protein without pleocytosis.

D. GBS is the most common cause of rapidly progressive weakness and can be fatal because of respiratory failure and autonomic nervous system abnormalities.

E. AIDP is the most common subtype in developed countries, whereas axonal forms are more common in northern China.

II. DIAGNOSIS

A. Clinical features of AIDP

1. The major clinical features of AIDP are rapidly evolving weakness (usually over days) and areflexia, heralded by dysesthesias of the feet or hands, or both.

- **a.** Weakness classically ascends from legs to arms but can start from the cranial nerves or arms and descend to the legs.
- **b.** Proximal muscle involvement is seen early in the course of the disease.
- **c.** In severe cases, respiratory and bulbar muscles are affected.

2. Patients can become quadriparetic and respirator dependent within a few days, or can have only mild weakness of the face and limbs.

3. Weakness typically does not progress beyond 1 month.

- **a.** Progression beyond 4 weeks but arresting within 8 weeks has been termed *subacute inflammatory demyelinating polyneuropathy (SIDP)*.
- **b.** Progression beyond 2 months is designated "chronic inflammatory demyelinating polyradiculoneuropathy" (CIDP), a disorder with a natural history different from GBS.
- **c.** A small percentage (2% to 5%) of patients present with recurrent GBS.

4. Approximately two thirds of patients have an antecedent infectious event 1 to 3 weeks before the onset of GBS.

- **a.** Often there is a prodromal flu-like or diarrheal illness caused by a variety of infectious agents, including cytomegalovirus, Epstein–Barr and Herpes simplex viruses, *Mycoplasma, Chlamydia*, and *Campylobacter jejuni*.
- **b.** Also associated with human immunodeficiency virus (HIV) infection are Hodgkin's disease, systemic lupus erythematosus, immunization, general surgery, and renal transplantation. Lyme disease can mimic GBS.

B. Physical examination

1. There is symmetric weakness in both proximal and distal muscle groups associated with attenuation or loss of deep tendon reflexes.

2. Objective sensory loss is usually mild.
3. Between 10% and 25% of patients require ventilator assistance within 18 days after onset. Patients must be followed carefully with serial vital capacity (VC) measurements until weakness has stopped progressing.
4. Mild to moderate bilateral facial weakness often occurs in addition to bulbar difficulties.
5. Ocular signs
   a. Ophthalmoparesis is unusual unless seen in the Miller Fisher variant (characterized by ophthalmoplegia, ataxia, and areflexia, with little limb weakness).
   b. Pupillary abnormalities and papilledema are rare.
6. Autonomic nervous system disturbances are seen in more than 50% of patients and include cardiac arrhythmias, orthostatic hypotension, hypertension, transient bladder paralysis, increased or decreased sweating, and paralytic ileus.

C. Clinical features in axonal forms

1. Patients with axonal forms (AMAN and AMSAN) present similarly to AIDP with rapidly progressive weakness, areflexia, and albuminocytologic dissociation, but they differ in the following ways:
   a. AMAN patients lack sensory abnormalities, and this form is more commonly found in northern China during summer months among children and young adults.
   b. AMSAN is generally associated with a more severe course and longer time to recovery.

D. Laboratory studies

1. Cerebrospinal fluid (CSF)
   a. An elevated CSF protein without an elevation in cells (albuminocytologic dissociation) is characteristic of GBS.
   b. CSF protein may be normal within the first 48 hours but often is elevated within 1 week of onset; rarely, it remains normal several weeks after the onset of GBS.
   c. The cell count rarely exceeds 10 cells/cm^3 and is mononuclear in nature.
   d. When GBS occurs as a manifestation of HIV infection or Lyme disease, the CSF white cell count is generally increased (25 to 50 cells).
   e. The CSF glucose is always normal.
2. Electrodiagnostic studies in AIDP
   a. Typically disclose slowing (<80% of normal) of nerve conduction velocity, with prolonged distal motor and sensory latencies.
   b. The amplitude of the evoked motor responses may be reduced and is frequently dispersed.
   c. Early in the course of GBS, routine nerve conduction studies can be normal, with the exception of prolonged F responses or absent H reflexes. The presence of a normal sural nerve sensory response, with an abnormal upper extremity sensory response is also characteristic of early GBS. Electromyography may demonstrate only decreased numbers of motor unit potentials firing on voluntary effort.
   d. Active denervation changes may be seen several weeks later if superimposed axon loss has occurred.
3. Electrodiagnostic studies in axonal forms
   a. In AMSAN, nerve conduction studies may reveal inexcitable motor and sensory nerves.
   b. In AMAN, nerve conduction studies reveal low amplitude to absent motor responses with normal sensory responses and conduction velocities.
   c. Needle examination may reveal denervation potentials in both axonal forms.

4. Autoantibodies to glyconjugates
   a. Approximately 90% of Miller Fisher syndrome patients have high titers of ganglioside (GQ1b) antibodies.
   b. Although 25% to 60% of GBS patients have been reported to have anti-GM1 antibodies, their significance is unclear. Several studies suggest they occur more frequently in the pure motor form of GBS, in axonal variants, and in those with poor prognosis, whereas others have found no relationship between the presence of antibodies and outcome or pattern of disease.
   c. Antibodies to GD1a, GM1, GM1b, and GalNac-GD1a are particularly associated with the AMAN subtype of GBS.

E. Differential diagnosis

1. A number of conditions causing rapidly progressive weakness must be differentiated from GBS.
   a. Neuromuscular junction disorders: myasthenia gravis and botulism.
   b. Disorders of peripheral nerve: tick paralysis, shellfish poisoning, toxic neuropathy, acute intermittent porphyria, diphtheritic neuropathy, and critical illness polyneuropathy.
   c. Motor neuron disorders: amyotrophic lateral sclerosis and poliomyelitis.
   d. Disorders of muscle: periodic paralysis, metabolic myopathies, inflammatory myopathies, and critical illness myopathy if the patient is in intensive care.

III. PATHOGENESIS

A. AIDP is thought to be produced by immunologically mediated demyelination of the peripheral nervous system.
1. It is likely that both humoral and cellular components play a role.
2. In AIDP, the immune attack appears to be directed to epitopes on the Schwann cell, but the exact antigens have not been identified.

B. In axonal forms, the immune response is targeted toward epitopes on the axolemma.
1. Gangliosides GD1a, GM1, GM1b, and GalNac-GD1a may be the epitopes targeted in the immune response.

C. The concept of molecular mimicry, in which an immune attack occurs on the epitope shared by the nerve fiber and infectious organism, is thought to be a possible mechanism for *C. jejuni*-associated GBS.

D. Pathologic studies in AIDP have usually shown endoneurial mononuclear cellular infiltration with a predilection for perivenular regions and segmental demyelination. The inflammatory process occurs throughout the length of the nerve (from the level of the root to distal nerve twigs).

IV. TREATMENT

A. Close observation for potential respiratory and autonomic nervous system dysfunction is required, preferably in an intensive care unit (ICU).
1. Forced VC and maximal inspiratory pressure (MIP) should be followed at frequent intervals.
2. A baseline arterial blood gas should be obtained.
3. Ropper and Kehne suggest intubation if any one of the following criteria is met:
   a. Mechanical ventilatory failure with reduced VC of 12 to 15 mL/kg
   b. Oropharyngeal paresis with aspiration
   c. Falling VC over 4 to 6 hours
   d. Clinical signs of respiratory fatigue at a VC of 15 mL/kg
4. Consider elective intubation in those with respiratory factors highly associated with progression to respiratory failure:
   a. VC < 20 mL/kg

   b. MIP <30 cm H_2O
   c. Maximal expiratory pressure (MEP) <40 cm H_2O
   d. A reduction of >30% of VC, MIP, or MEP in 24 hours
5. Tracheostomy should not be performed at the outset of the disease because patients can improve rapidly.

B. Because of potential autonomic dysfunction, careful monitoring of blood pressure, fluid status, and cardiac rhythm are essential in managing patients with GBS. Hypertension can be managed with short-acting α-adrenergic blocking agents, hypotension with fluids, and bradyarrhythmias with atropine.

C. Immunotherapy

1. Patients can be treated with plasmapheresis or intravenous immunoglobulin (IVIG). Both are equally efficacious, but because IVIG is easier to administer, it is more commonly used as the initial treatment.
2. Plasmapheresis
   a. GBS study group recommends exchanging 200 to 250 mL/kg in three to five sessions over 7 to 14 days.
   b. Requires good venous access and can induce hypotension; requires caution in patients with cardiovascular disease.
3. IVIG
   a. Dose administered is 400 mg/kg/day for 5 consecutive days.
   b. Easier to administer but can produce side effects such as flu-like symptoms, headache, and malaise.
   c. Should be avoided in patients with immunoglobulin A (IgA) deficiency and renal insufficiency.
4. Corticosteroids
   a. Treatment with IV or oral corticosteroids alone is not beneficial in GBS.
   b. Although the combination of IVIG and IV methylprednisolone (500 mg/day for 5 days) showed no significant difference over IVIG alone unless adjusted for various factors, there was a trend toward shortened time to independent ambulation with combination treatment.
5. Treatment with plasmapheresis followed by IVIG has not been found to be superior to either treatment used alone.

V. OUTCOME

A. Most patients recover over weeks to months.

B. Approximately 15% have no residual deficits, 65% are restored to nearly normal function, and 5% to 10% are left with severe residual weakness or numbness.

C. Poor prognostic factors include those with electrodiagnostic evidence of axon loss and a higher disability grade at nadir.

D. Despite close monitoring in the ICU, mortality rates range from 3% to 8%.

E. Causes of fatal outcomes include dysautonomia, sepsis, acute respiratory distress syndrome, and pulmonary emboli.

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133 MYASTHENIA GRAVIS

Randall R. Long

I. GENERAL PRINCIPLES

A. Myasthenia gravis (MG) is an autoimmune disorder characterized by muscle weakness and exaggerated muscle fatigue.

B. Prevalence is 1 in 20,000 with 3:2 female-to-male predominance.

C. Incidence in women peaks in the third decade; in men in the fifth to sixth decades.

D. Oculomotor and bulbar muscles are most commonly affected; proximal muscles usually are more affected than distal muscles; variability over time in both severity and distribution of weakness is common.

E. Myasthenic crisis reflects limiting bulbar and respiratory muscle weakness, constituting a medical emergency and requiring intensive care.

F. Factors commonly associated with myasthenic crisis include systemic infection, electrolyte imbalance, anesthesia, and drugs that impair neuromuscular transmission (Tables 133-1 and 133-2).

II. PATHOPHYSIOLOGY

A. Circulating autoantibodies bind with acetylcholine receptors in postsynaptic muscle membrane.

B. Receptors may be blocked, and receptor density decreases due to accelerated degradation and turnover.

C. Miniature end-plate potentials are normal in number (indicating normal quantal release of acetylcholine) but decreased in amplitude.

III. PROGNOSIS

A. Available therapies offer effective treatment for the vast majority of patients.

B. Aggressive airway management and respiratory support during myasthenic crises minimize morbidity and mortality.

C. Elective thymectomy favorably alters the natural history of the disease.

IV. DIAGNOSIS

A. Clinical presentation

1. MG should be considered in any patient with unexplained weakness, especially when weakness fluctuates or involves bulbar muscles.
2. Normal sensation, tendon reflexes, pupillary reflexes, and mental status distinguish MG from most other acute and subacute paralytic illnesses.

B. Antiacetylcholine receptor antibodies

1. 80% of patients have serum antibodies to acetylcholine receptors.
2. Among "seronegative" patients, some will have anti–muscle-specific tyrosine kinase (MuSK) antibodies.

C. Tensilon (edrophonium HCl) test

1. Pretreat with 0.5 mg atropine.
2. Give 2 mg (0.2 mL) edrophonium HCl intravenous (IV) predose; monitor for bradyarrhythmia.
3. Give 8 mg (0.8 mL) edrophonium HCl IV test dose; observe for 1 to 5 minutes for transitory increase in muscle strength.

TABLE 133-1 Conditions that may Contribute to Myasthenic Crisis

Intercurrent systemic infection
Electrolyte imbalance (NA, K, Ca, P, Mg)
Thyrotoxicosis or hypothyroidism
Anesthesia
Medication effects (Table 133-2)
Cholinergic crisis (discontinue cholinesterase inhibitors)

4. Equivocal result is a negative result.
5. Adjust dose in children (0.03 mg/kg).

D. Electrodiagnostic studies
1. Decrement (≥15%) in compound muscle action potential amplitude with 2 to 3/second supramaximal stimulation.
2. Increased "jitter" on single-fiber electromyograph (EMG).
3. Electrodiagnostic studies may support—but never exclude—the diagnosis of MG.

E. Chest imaging: All patients with MG should be screened for thymic hyperplasia or thymoma.

TABLE 133-2 Medications that may Accentuate Myasthenic Weakness

Antibiotics	**Neuromuscular blockers and muscle relaxants**
Amikacin	Anectine (succinylcholine)
Clindamycin	Norcuron (vecuronium)
Colistin	Pavulon (pancuronium)
Gentamicin	Tacrium (atracurium)
Neomycin	Benzodiazepines
Polymyxin	Curare
Streptomycin	Dantrium (dantrolene)
Tobramycin	Flexeril (cyclobenzaprine)
Tetracyclines	Lioresal (baclofen)
Trimethoprim/sulfamethoxazole	Robaxin (methocarbamol)
	Soma (carisoprodol)
	Quinine sulfate
Antiarrhythmics and antihypertensives	**Antirheumatics**
Lidocaine	Chloroquine
Quinidine	D-penicillamine
Procainamide	**Others**
β-Blockers	Opiate analgesics
Calcium channel blockers	Oral contraceptives
Antipsychotics	Antihistamines
Lithium	Anticholinergics
Phenothiazines	
Tricyclics	

V. TREATMENT. Immunosuppressive therapy is indicated for most patients with MG, but benefits are often delayed. Plasmapheresis and intravenous immune globulin (IVIG) offer a more rapid, but transitory, benefit. Cholinesterase inhibition is a useful adjunctive therapy.

A. Plasmapheresis
1. Exchange 50 mL/kg/day for 3 to 7 days
2. Response within 48 to 72 hours

B. IVIG
1. 400 mg/kg/day for 5 days
2. Response within 7 to 10 days

C. Corticosteroids
1. Response rate >80%.
2. 25 mg/day (single dose), increasing by 5 mg/day every third day to 60 mg/day.
3. Beware of increased weakness at the outset of steroid treatment.
4. After maximal response (2 to 3 months), gradually shift to equivalent alternate day dose; then taper slowly by decreasing alternate day dose by 5 mg each month to 25 mg every other day target.
5. Complete discontinuation, with maintained response, is rare.
6. Azathioprine, cyclosporine, mycophenolate mofetil (Cellcept), and other immunosuppressants can be considered in patients who are steroid intolerant or unresponsive.

D. Cholinesterase inhibition (Table 133-3 shows dose equivalencies)
1. Pyridostigmine (Mestinon) and neostigmine (Prostigmine) are useful adjuncts.
2. IV neostigmine infusion can be used in patients who can take nothing by mouth; begin with an hourly rate equivalent to 2% of the prior 24 hour total oral dose of cholinesterse inhibitor(s); increase or decrease gradually according to clinical response versus cholinergic side effects (see subsequent text).
3. Cholinergic crisis is increased weakness due to excess cholinergic stimulation; fasciculation, diaphoresis, and diarrhea are concomitants.

E. Supportive care in the intensive care unit (ICU) and recovery room
1. Avoid incentive spirometry!
2. Maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and forced vital capacity (FVC) are the best indicators of respiratory muscle function; O_2 saturation is a poor indicator.
3. Early intubation is prudent in the event of declining respiratory muscle function.
4. Cholinesterase inhibition will increase oral and airway secretions.

F. Thymectomy: Elective thymectomy through median sternotomy is indicated for all but the most elderly, frail myasthenic patients. Results are best when done within 5 years of onset.

TABLE 133-3 Cholinesterase Inhibitors and Dose Equivalencies

Agent	Commercial name	Route and dose (mg)	
		Oral	Parenteral
Pyridostigmine bromide	Mestinon	60	
Neostigmine bromide	Prostigmin	15	
Neostigmine methylsulfate	Prostigmin		0.5

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134 ACQUIRED WEAKNESS IN THE INTENSIVE CARE UNIT

David A. Chad

I. GENERAL PRINCIPLES

A. A recent large prospective cohort study found the incidence of severe acquired weakness in the intensive care unit (ICU) to be 25%.

B. Although preexisting neuromuscular disorders may cause weakness in ICU patients, two of the most common causes of *newly acquired* weakness arising in the ICU setting are critical illness myopathy and critical illness polyneuropathy.

C. Both disorders may cause severe generalized weakness—a syndrome of flaccid, generalized weakness (quadriplegia) with failure to wean from mechanical ventilation. The two disorders are known to occur separately or in combination. The most common form of weakness acquired in the ICU is critical illness myopathy.

D. A major risk factor for the development of critical illness myopathy is exposure to intravenous corticosteroids (CS) and neuromuscular blocking agents (NMBAs); critical illness myopathy develops in one third of patients treated for status asthmaticus in the ICU.

E. Critical illness myopathy also develops in patients who have not received CS and NMBAs, but who have had severe systemic illness with multiorgan failure and sepsis; critical illness myopathy accounts for 42% of patients with weakness in the surgical and medical ICU setting.

F. The major risk factors for critical illness polyneuropathy are sepsis and multiorgan failure; of patients admitted to the ICU for at least 2 weeks, 50% show at least electromyography (EMG) evidence of an axon-loss polyneuropathy.

II. DIAGNOSIS OF CRITICAL ILLNESS MYOPATHY

A. Clinical features

1. Weakness is typically diffuse.
2. Weakness affects all limb muscles and neck flexors—a flaccid quadriparesis with a proximal > distal distribution.
3. Weakness may involve facial muscles, but extraocular muscles are rarely involved.
4. Tendon reflexes are often depressed or absent.
5. Weakness typically affects the diaphragm, causing failure to wean.

B. Laboratory studies

1. Serum creatine kinase (CK) is elevated in 50% of patients; the rise tends to occur early in the course of the illness.
2. EMG
   - **a.** Nerve conduction studies reveal low amplitude or absent motor responses; sensory responses are relatively preserved, or may be reduced.
   - **b.** The needle electrode examination discloses fibrillation potential activity in weak muscles in some, but not all, patients.
   - **c.** Voluntary muscle contraction reveals early recruitment of motor unit potentials (MUPs) that may be short in duration, low in amplitude, and polyphasic in form.

d. Motor unit potential analysis is difficult owing to severe weakness or encephalopathy, or both (no motor units may be available for analysis).
e. Stimulation of the phrenic nerves with diaphragm recording evokes low motor responses.
f. Direct muscle stimulation may demonstrate electrical inexcitability of the muscle membrane.
g. Direct stimulation of muscle and direct nerve stimulation yield comparably reduced muscle responses (in contrast to the results found in critical illness polyneuropathy [*vide* infra]).

3. Muscle biopsy
   a. Characteristic finding: selective loss of myosin, with central area of pallor or lack of histochemical reactivity to myosin adenosine triphosphatase (ATPase)
   b. Muscle fiber atrophy (especially type II fibers)
   c. Mild to moderate muscle fiber necrosis in some patients

III. PATHOGENESIS

A. Loss of myosin thick filaments, with multifactorial causation including an increase in muscle apoptosis, upregulation of calpain, and upregulation of the transforming growth factor β/mitogen-activated protein kinase (TGF-β/MAPK) pathway.

B. Muscle is inexcitable in critical illness myopathy due to dysregulation of the sodium channels, with inactivation of sodium channels at the resting membrane potential.

IV. TREATMENT

A. Treatment is essentially symptomatic.

B. Strive to prevent the development of this disorder by using CS, NMBAs, or both as sparingly as possible.

C. Intensive insulin therapy (with target blood glucose concentrations of 80 to 110 mg/dL) may lower the incidence of critical illness myopathy (and critical illness polyneuropathy).

V. OUTCOME

A. Most patients recover over weeks to months, although patients may be left with residual weakness depending upon the initial severity and duration of weakness.

VI. DIAGNOSIS OF CRITICAL ILLNESS POLYNEUROPATHY

A. Clinical features

1. Distal more than proximal symmetrical weakness and sensory loss
2. Deep tendon reflexes are attenuated or lost
3. Cranial nerve innervated muscles are typically spared
4. There is often a concomitant encephalopathy (the encephalopathy of sepsis)

B. Laboratory studies

1. Serum CK levels are typically normal
2. Cerebrospinal fluid (CSF) studies are normal (normal protein)
3. EMG
   a. Nerve conduction studies reveal reduced *amplitude* or absent sensory and motor responses and reduced phrenic motor amplitudes.
   b. Nerve conduction *velocities* are within the range of normal or mildly reduced (the classical pattern for axon-loss polyneuropathies). There is typically no evidence for conduction block or prolonged F-waves.
   c. After 2 to 3 weeks, needle electrode examination may reveal abnormal insertional activity: fibrillation potentials and positive sharp waves.

These are more likely in distal muscles. In the first 2 to 3 weeks of the illness, fibrillation potentials may be absent.

d. Reduced recruitment of MUPs on voluntary activation; for a few weeks MUPs may be normal, but after weeks to months they become complex or polyphasic, and increased in size.

e. Direct needle stimulation of muscle elicits a relatively higher amplitude response than the muscle response after nerve stimulation.

4. Muscle biopsy

a. Neurogenic atrophy

VII. PATHOGENESIS

A. Inadequate perfusion of peripheral nerves as a result of the systemic inflammatory response, causing injury to the microcirculation of distal nerves, nerve ischemia, and axon-loss.

B. As in critical illness myopathy, there is evidence for dysregulation of sodium channel gating in peripheral nerve leading to nerve inexcitability and generalized weakness.

VIII. TREATMENT

A. Stabilize and treat the underlying critical illness; especially vigorous treatment of sepsis.

B. Intensive insulin therapy (with target blood glucose concentrations of 80 to 110 mg/dL) may lower the incidence of critical illness polyneuropathy.

IX. OUTCOME

A. Recovery of sensory and motor function occurs over weeks to months depending on the severity of the underlying polyneuropathy.

X. DIFFERENTIAL DIAGNOSIS OF ACQUIRED WEAKNESS IN THE ICU

A. Guillain–Barré syndrome (see Chapter 132)

B. Acute intermittent porphyric neuropathy

1. Generalized weakness (symmetrical or asymmetrical) in the context of abdominal pain, psychiatric disorder, and prominent dysautonomia.

2. Triggered by drugs that induce the hepatic cytochrome P-450 system (e.g., barbiturates).

3. May be associated with respiratory failure.

4. EMG: marked motor axon-loss polyneuropathy without conduction block.

5. Diagnosis suggested by presence of urinary porphyrin precursors—aminolevulinic acid.

6. Respond to oral or parenteral carbohydrate loading and to IV hematin therapy.

C. Prolonged neuromuscular blockade by muscle relaxants

1. Associated with renal or hepatic failure

2. Elevated levels of vecuronium metabolite in some instances (3-desacetylvecuronium)

3. No sensory deficits and normal reflexes

4. Normal sensory and motor nerve conduction studies

5. On EMG, decremental response at slow rates of stimulation (3 Hz)

6. Transient improvement after infusion of acetylcholinesterase inhibitors

D. Myasthenia gravis (see Chapter 133)

E. Lambert–Eaton myasthenic syndrome

1. Generalized weakness with autonomic symptoms and signs

2. Strength may *improve* with repetitive contractions

3. Approximately 50% of patients have an underlying neoplasm (typically small-cell lung cancer)

4. Presence of antibody to voltage-gated calcium channels in 80% of patients
5. EMG: very low motor amplitudes that increase after a short burst of isometric exercise; sensory studies are normal.

F. Botulism
1. Diffuse, symmetrical weakness; proximal > distal muscle involvement
2. Cranial nerve involvement
3. Dysarthria and dysphagia
4. Ptosis and ophthalmoparesis
5. Autonomic involvement
6. Dilated pupils
7. Bradyarrhythmias
8. Hypotension
9. Urinary retention
10. Management is supportive care and trivalent (acute bacterial endocarditis [ABE]) antitoxin

G. Motor neuron disease
1. Scenario: an ICU patient admitted for pneumonia and ventilator support who fails to wean.
2. The examination classically reveals a combination of lower *and* upper motor neuron signs (atrophy/fasciculations and hyperreflexia/spasticity, respectively) in bulbar (especially tongue and palate) and limb muscles (often asymmetric, distal, and proximal) with a normal sensory examination.

H. Muscular dystrophies: uncommon scenario, but patients with certain muscular dystrophies are prone to respiratory muscle involvement and pneumonia. These include:
1. Myotonic dystrophy
   a. Percussion and grip myotonia
   b. Frontal balding/temporalis muscle atrophy
   c. Distal muscle weakness and wasting
   d. Cardiac conduction defects
   e. Central hypoventilation
2. Duchenne and Becker dystrophy (X-linked dystrophy—dystrophinopathy)
   a. Calf pseudohypertrophy
   b. Severe generalized weakness and wheelchair before age 12 (Duchenne); mild to moderate generalized weakness with ambulation to at least age 16 (Becker)
   c. Cardiomyopathy
   d. Elevated CK (10 to 50 times above normal)
3. Congenital myopathy (severe forms of nemaline rod and centronuclear)

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135 NEURO-ONCOLOGICAL PROBLEMS IN THE INTENSIVE CARE UNIT

Michael C. Muzinich and N. Scott Litofsky

I. OVERVIEW. Patients with primary brain, spinal cord, peripheral nerve, or metastatic tumors from distant primaries may require management in the intensive care unit (ICU) for the following problems:
- **A.** Increased intracranial pressure (ICP)
- **B.** Hydrocephalus
- **C.** Seizures
- **D.** Postoperative complications
- **E.** Spinal tumors
- **F.** Systemic complications secondary to brain tumors

II. INCREASED ICP

A. General principles
1. Increased volume in the closed intracranial space causes increased pressure.
2. May present initially or as a result of postoperative complication.
3. May be secondary to intracranial neoplasms.

B. Pathophysiology
1. Tumor mass
2. Secondary cerebral edema from increased permeability of blood vessels within and adjacent to the tumor
3. Hemorrhage
   - **a.** Spontaneously from tumor
   - **b.** Surgical complication
4. Hydrocephalus secondary to compression of cerebrospinal fluid (CSF) outflow tracts
5. Hypercarbia
   - **a.** Hypoventilation from increased ICP
   - **b.** Seizure activity
6. Cerebral ischemia from vascular compression by the tumor

C. Diagnosis

1. Clinical presentation
- **a.** Headache
  - **i.** "Bandlike" or "Pressure"
  - **ii.** Worse in the morning or on arising
- **b.** Vomiting
  - **i.** Projectile
  - **ii.** Often in the morning
- **c.** Papilledema is a chronic finding of ICP elevation
- **d.** Decreased level of consciousness
- **e.** Cognitive changes
- **f.** Pupillary dilatation as tentorial herniation develops
- **g.** Light-near pupillary dissociation
  - **i.** Retinotectal compression of the afferent limb of the pupillary light reflex
  - **ii.** Subtle finding of ICP elevation

- **h.** Diplopia secondary to abducens nerve (cranial nerve [CN] VI) compression, often worse with lateral gaze
- **i.** Cushing triad
  - **i.** Systolic hypertension with wide pulse pressures
  - **ii.** Bradycardia
  - **iii.** Respiratory depression
- **j.** Cheyne–Stokes respiration
  - **i.** Gradually increasing and decreasing tidal volumes
  - **ii.** Periods of apnea
  - **iii.** Often the first abnormal breathing pattern to appear

2. Radiologic studies

- **a.** Magnetic resonance imaging (MRI)
  - **i.** Better resolution than computed tomography (CT)
  - **ii.** May not be available
  - **iii.** Enclosed magnet complicates monitoring of critically ill/intubated patients
- **b.** CT-
  - **i.** More widely available than MRI
  - **ii.** Speed of scanning and open configuration are advantageous for critically ill/intubated patients
- **c.** Findings
  - **i.** Tumor signal is variable
  - **ii.** May enhance with contrast
  - **iii.** Edema surrounding tumor is hypodense
  - **iv.** Midline shifted away from tumor
  - **v.** Midbrain cisterns compressed

3. Laboratory studies

- **a.** Arterial blood gas for elevated P_{CO_2}
- **b.** Serum sodium for hyponatremia

D. Treatment

1. Head elevation
2. Hyperventilation (no longer than 24 hours) to achieve P_{aCO_2} <32 mm Hg and >25 mm Hg
3. Initial fluid restriction
4. Mannitol 1 g/kg IV initially, then 0.25 g/kg every 4 to 6 hours
   - **a.** Hold if serum osmolarity >320 mOsm
   - **b.** Continue until mass effect relieved
5. Furosemide 1 mg/kg IV single dose
6. Dexamethasone 10 to 20 mg IV initially, then 4 mg every 6 hours
   - **a.** Taper when mass effect relieved
7. Ventriculostomy
   - **a.** CSF drainage can reduce volume and pressure rapidly
   - **b.** Low-risk bedside surgical procedure
8. Hypertonic saline not routinely used

III. HYDROCEPHALUS

A. General principles

1. Increased ventricular size secondary to increased CSF volume and pressure
2. Consequence of tumor or surgical complication

B. Pathophysiology/etiology

1. Subarachnoid tumor
   - **a.** Leptomeningeal tumor infiltration in subarachnoid space can prevent absorption of CSF by arachnoid granulations
   - **b.** Metastasis—most often from lung, breast, lymphoma, or leukemia
   - **c.** Primary tumors—most often neuroendocrine tumors, medulloblastoma, ependymoma, and glioblastoma multiforme

2. Cerebellopontine angle tumors may compress the fourth ventricle
3. Intraventricular tumors may obstruct CSF pathways
4. Intraparenchymal tumors
   a. Basal ganglia and thalamic tumors may compress the foramen of Monroe
   b. Pineal region tumors may compress posterior third ventricle or cerebral aqueduct
   c. Brainstem or cerebellar tumors may compress fourth ventricle

C. Diagnosis

1. Clinical presentation
   a. Signs and symptoms of increased ICP (see Section II)
   b. May present acutely or progress slowly over time
   c. May occur after treatment of brain tumor with radiation or surgery

2. Radiologic studies
   a. MRI demonstrates better anatomic detail
   b. CT often more efficient
   c. Findings based on tumor site
      i. Lateral ventricle enlargement with prominent temporal horns
      ii. Rounded third ventricle unless compressed by tumor
      iii. Fourth ventricular dilatation with poor CSF absorption
      iv. Periventricular edema secondary to transependymal leakage

D. Treatment

1. Dexamethasone—10 to 20 mg IV initially with 4 mg every 6 hours
2. Ventriculostomy
   a. External CSF diversion in rapidly deteriorating patients
   b. Temporary solution since risk of infection increases for as long as the catheter remains
3. Tumor resection
   a. Decompression of CSF pathway
   b. May not be definitive treatment
4. Ventriculo-peritoneal shunt—permanent CSF diversion if hydrocephalus persists following treatment

IV. SEIZURES

A. General principles

1. May precipitate rapid deterioration when ICP is elevated
2. Consequence of tumor infiltration or chemical changes in adjacent brain

B. Pathophysiology/etiology

1. Tumor progression
2. Hemorrhage
3. Hypoxia
4. Hyponatremia
5. Hypoglycemia
6. Subtherapeutic anticonvulsants

C. Diagnosis

1. Clinical presentation
   a. Variable
      i. Generalized tonic-clonic
      ii. Focal movement
      iii. Speech arrest
      iv. Episodic numbness
      v. Transient visual obscurations
   b. May occur shortly following postoperative emergence from anesthesia

2. Radiologic studies. CT scan to evaluate for hemorrhage

3. Laboratory studies
   a. Anticonvulsant level

- **b.** Serum sodium
- **c.** Arterial blood gas
- **d.** Serum glucose

D. Treatment

1. Airway management
   - **a.** Oropharyngeal airway
   - **b.** Laryngeal mask airway
   - **c.** Nasopharyngeal airway
   - **d.** Endotracheal intubation
2. Ventilate to maintain P_{CO_2} between 25 and 32
3. Acute anticonvulsant medications
   - **a.** Lorazepam—2 mg every 5 minutes IV with an 8 mg maximum for status epilepticus
   - **b.** Phenytoin—15 mg/kg IV for seizure prophylaxis in perioperative period or concurrent treatment with lorazepam for status epilepticus
   - **c.** Fosphenytoin—15–20 mg/kg initially followed by 5 mg/kg/day as maintenance
   - **d.** Phenobarbitol—15 mg/kg IV as concurrent treatment with lorazepam for status epilepticus
4. Prophylactic anticonvulsant medications
   - **a.** Levetiracetam (Keppra)
   - **b.** Phenytoin
   - **c.** Carbamazepine
   - **d.** Phenobarbital—more sedating

V. POSTOPERATIVE COMPLICATIONS

A. General principles

1. Postoperative ICU care often required following brain tumor resection
2. Neurologic and medical conditions determine length of stay

B. Diagnosis

1. **Clinical presentation**
   - **a.** Headache
   - **b.** Hemiparesis
   - **c.** Aphasia
   - **d.** Decreased level of consciousness
   - **e.** Excessive fatigue
   - **f.** Fever
   - **g.** Polyuria/polydipsia
2. **Differential diagnosis**
   - **a.** Intracranial hemorrhage
     - **i.** Can be into tumor bed, subdural, or epidural space
     - **ii.** Risk factors include coagulopathy, hypertension, and "bucking" during emergence from anesthesia
   - **b.** Cerebral edema
     - **i.** Brain manipulation
     - **ii.** Overhydration
     - **iii.** Hypernatremia
   - **c.** Cerebral infarction
     - **i.** Vascular injury
     - **ii.** Hypercoagulability
     - **iii.** Vasospasm
   - **d.** Endocrinopathies
     - **i.** Often associated with sellar or perisellar tumors
     - **ii.** Diabetes insipidus
       - **(a)** Presents 18 to 36 hours postoperatively
       - **(b)** >200 mL/hour urine output for 2 consecutive hours

(c) Specific gravity <1.005
(d) Sodium >147 mEq/L
iii. Hypercortisolemia presents 1 to 2 days after stopping corticosteroids
iv. Hypothyroidism presents more than 1 week postoperatively
v. Hyponatremia
(a) Usually from syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
(b) Cerebral salt wasting uncommon with neoplastic processes; usually associated with subarachnoid hemorrhage
e. Central nervous system infection
i. Meningitis
(a) Low probability of 0.8% in a clean operative field
(b) Usually presents 2 days to 2 weeks postoperatively
ii. Cerebral abscess—is uncommon and presents several weeks to months postoperatively
iii. Bone flap infection
(a) Presents months postoperatively
(b) Frequently presents with wound drainage

3. Radiologic studies
a. Usually CT scan with and without contrast
b. MRI if concern for meningitis

4. Laboratory studies
a. Arterial blood gas
b. Serum sodium
c. Serum glucose
d. Complete blood count
e. Erythrocyte sedimentation rate
f. Fasting cortisol
g. Thyroid stimulating hormone—T3 and T4
h. Urine specific gravity
i. CSF electrolytes, Gram-stain and culture

C. Treatment
1. Intracranial hemorrhage
a. Correct coagulopathy
b. Maintain systolic blood pressure below 160
c. Surgery if hemorrhage is causing significant mass effect
2. Cerebral edema
a. Hyperventilation
b. Dexamethasone
c. Mannitol
3. Cerebral infarction
a. Maintain cerebral perfusion
b. Treat symptomatic edema
4. Endocrinopathies
a. Hydrocortisone for adrenal insufficiency
b. Levothyroxine for hypothyroidism
c. Desmopressin acetate (DDAVP) 1.0 ug twice a day for diabetes insipidus
5. Hyponatremia
a. Fluid restriction for SIADH
b. 3% NaCl if patient is symptomatic
c. Do not increase >12 mEq/day due to risk of central pontine myelinolysis
6. Central nervous system infection
a. Antibiotics
b. Removal of infected bone flap
c. Drain purulent infections

VI. SPINAL TUMORS

A. General principles

1. ICU care required after cervical spine tumor resection or transthoracic approaches secondary to ventilatory issues

B. Pathophysiology/etiology

1. Tumor compression of the spinal cord
2. Spinal cord ischemia and infarction
   a. Tumor compresses the anterior or posterior spinal arteries
   b. Blood vessels damaged due to surgical manipulation
3. Postoperative hemorrhage
4. Autonomic dysfunction

C. Diagnosis

1. **Clinical presentation**
   a. Respiratory insufficiency
      i. Paralysis of intercostals muscles with lesions to C6 and below
      ii. Decreased diaphragmatic function with lesions above C6
      iii. Atelectasis
   b. Other
      i. Ileus
      ii. Urinary retention
      iii. Hypotension
      iv. Bradycardia
2. **Radiologic studies.** MRI generally more specific than CT in diagnosis
3. **Tests/laboratory studies**
   a. Cervical spine tumors
      i. Vital capacities every 6 hours
      ii. Oxygen saturation—may decline rapidly
      iii. Frequent neurologic exams

D. Treatment

1. Intubation and mechanical ventilation if vital capacity <12 mL/kg of body weight
2. Nasogastric tube to decompress ileus
3. Foley catheter for urinary retention
4. Pressors to keep systolic blood pressure >90
5. Atropine versus pacing for bradycardia
6. Surgery
   a. Resection of mass to relieve spinal cord compression
   b. Arthrodesis (fusion) if structural instability
7. Orthosis (bracing) may be helpful to provide support during healing
8. Radiation therapy
   a. May be primary treatment of metastatic disease to vertebral column
   b. Often used for residual postoperative disease of malignant processes

VII. SYSTEMIC COMPLICATIONS SECONDARY TO BRAIN TUMORS

A. Pathophysiology

1. Immobility
2. Hypercoagulability

B. DIAGNOSIS

1. **Clinical manifestations**
   a. Deep venous thrombosis (DVT)
   b. Pulmonary embolus
   c. Systemic infection
   d. Urinary tract infection
   e. Pneumonia
   f. Line sepsis
   g. Meningitis

2. **Radiologic studies**
   a. Venous duplex scan for deep vein thrombosis
   b. Pulmonary embolus
      i. Ventilation perfusion scan
      ii. CT—pulmonary embolus protocol
      iii. CT angiogram of chest
   c. Chest radiograph for pneumonia
3. **Laboratory studies**
   a. Complete blood count
   b. Complete metabolic profile
   c. Urinalysis and culture
   d. Sputum Gram-stain and culture/bronchoalveolar lavage
   e. Line tip culture
   f. Blood Gram-stain and culture
   g. Lumbar puncture for CSF electrolytes, Gram-stain and culture

C. Treatment

1. DVT prophylaxis
   a. Thrombo-embolic-deterrent (T.E.D.) (antiembolism) hose
   b. Leg sequential compression devices
   c. Greenfield filter if patient is <2 weeks postoperative
   d. Low-molecular-weight heparin or Coumadin is generally safe if patient is >2 weeks postoperative and is not actively bleeding
2. Antibiotics
3. Discontinue central line for line sepsis

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www.emedicine.com. 2008
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www.uptodate.com. 2008
An online medical reference featuring topic specific articles written for clinicians by experts in the field including: seizure, hypernatremia, hyponatremia, meningitis, sepsis, and pulmonary embolus.

MISCELLANEOUS INTENSIVE CARE UNIT NEUROLOGIC PROBLEMS

Ann L. Mitchell, Nancy M. Fontneau, and Maryann C. Deak

136

I. OVERVIEW

A variety of disorders affecting the nervous system, not easily categorized otherwise, require management in the intensive care unit (ICU). These include:

- **A.** Suicidal hanging
- **B.** Electrical injuries
- **C.** Carbon monoxide poisoning
- **D.** Decompression syndrome ("the bends")
- **E.** Cerebral fat embolism
- **F.** Hiccups

II. SUICIDAL HANGING

A. Background

Third most common means of committing suicide

B. Pathophysiology

1. Death is usually by slow strangulation with compression of the jugular veins or carotid arteries.
2. Interruption of blood flow for more than a few minutes results in hypoxic–ischemic injury with neuronal death, cytotoxic and vasogenic edema, increased intracranial pressure (ICP), and altered mental status.

C. Prognosis

1. Delayed presentation to a medical facility and low Glasgow Coma Scale (GCS) score on presentation are associated with poor neurologic recovery and death.
2. Coma of >24 hours' duration portends major neurologic dysfunction in survivors.
3. Some recovery expected, but central cord syndrome, dementia, amnesia, Korsakoff syndrome and other neuropsychiatric sequelae, restlessness, myoclonus and other movement disorders can result.

D. Management

1. Cardiopulmonary resuscitation.
2. Cervical fracture should be ruled out or stabilized.
3. Monitor for paratracheal or laryngeal trauma, or acute respiratory distress syndrome; endotracheal intubation for airway obstruction.
4. Treat cardiac arrhythmias and seizures.
5. Raised ICP should be treated with hyperventilation-induced hypocarbia, which produces reflex cerebral vasoconstriction.

III. ELECTRICAL INJURIES

A. Background

In the United States there are 4,000 injuries and 1,000 deaths from electric shock annually.

B. Pathophysiology

1. Voltage related to severity of exterior burns, muscle necrosis, myoglobinuria and renal failure, closed-head injury, and fractures

2. Ventricular fibrillation and respiratory arrest, especially from alternating current
3. Nervous system tissues especially vulnerable to injury
   a. Common neurologic injuries involve cervical spinal cord and peripheral nerves of the arm, because current most often flows through one or both arms to ground.
   b. With electrical injury to brain, transient unconsciousness, seizures, confusion, cerebral edema, and brain hemorrhage.
   c. Keraunoparalysis may also result, which is a reversible, transient limb paralysis and vasospastic vascular compromise attributed to autonomic dysfunction following lightning injury.

C. Prognosis

1. Prognosis may only be reliable several days after electric shock, secondary to keraunoparalysis that causes reversible loss of brainstem reflexes and motor responses.
2. Patients may recover fully from their neurologic dysfunction.
3. Approximately 25% of patients have acute or chronic neurologic sequelae.

D. Management

1. Cardiopulmonary resuscitation.
2. Monitor for delayed cardiac arrhythmias.
3. Stabilize spine and long bone fractures.
4. Isosmotic fluid resuscitation and alkalization of the urine to prevent myoglobin nephropathy.
5. Compartment syndrome may require debridement and fasciotomy.
6. Extensive burns should be managed in burn units.
7. Tetanus prophylaxis.

IV. CARBON MONOXIDE POISONING

A. Background

1. Carbon monoxide (CO) gas is a colorless, tasteless, and odorless byproduct of incomplete combustion.
2. Atmospheric CO concentration is normally <0.001%; CO concentrations of 0.1% can be fatal.

B. Pathophysiology

1. Carboxyhemoglobin accumulation due to prolonged binding of CO to hemoglobin.
2. Clinical effects depend on the carboxyhemoglobin level (by percent).
   a. Less than 10: mild headache, dyspnea on exertion
   b. 10 to 20: headache, easy fatigability
   c. 20 to 30: pounding headache, impaired dexterity, blurred vision, irritability
   d. 30 to 40: weakness, nausea, vomiting, confusion, delirium, cherry red color
   e. 40 to 50: tachycardia, arrhythmias
   f. 50 to 60: seizures, respiratory insufficiency
   g. Greater than 60: coma
   h. 60 to 70: coma, death

C. Treatment

1. 100% oxygen by tight-fitting nonrebreathing face mask.
2. Goal carboxyhemoglobin level of <5%.
3. Hyperbaric oxygen therapy may be useful for treating cerebral edema, but remains controversial. No randomized controlled studies support its use.
4. Steroids are not indicated.

D. Prognosis

1. Approximately 75% recover well.
2. Approximately 10% to 30% develop memory impairment or extrapyramidal signs reminiscent of Parkinsonism. Basal ganglia and substantia nigra neurons are highly sensitive to CO exposure.

V. DECOMPRESSION SICKNESS ("THE BENDS")

A. Background

Decompression sickness can arise following:

1. Rapid ascent of scuba divers or tunnel workers
2. Decompression or high-altitude flying aircraft with inadequate cabin pressure
3. Flying *too soon* after scuba diving (sooner than 18 to 24 hours)

B. Pathophysiology

1. Decompression sickness occurs when gases dissolved in body fluids under high atmospheric pressure come out of solution under conditions of lower pressure.
   a. Small gas bubbles form in tissues and venous blood.
   b. Bubbles coalesce, causing local tissue ischemia or venous obstruction.
2. Neurologic symptoms are seen in approximately 80% of patients.
   a. Focal or diffuse paresthesia is the most frequent symptom, affecting the skin and joints.
   b. Weakness of one limb or more.
   c. Visual disturbances, vertigo, headache, lethargy, paralysis; unconsciousness less common.
   d. Abnormal brain magnetic resonance imaging (MRI) scan, with white matter hyperintensities, even in divers who do not get typical decompression syndrome.
3. Air embolism is a more severe and acute decompression illness.
   a. Overinflation of the lungs causes rupture and gas bubble formation in the pulmonary veins.
   b. Cerebral arterial embolism can result if a patent foramen ovale exists.
      i. Unconsciousness and stupor are the most common symptoms.
      ii. Onset is usually within 5 minutes of decompression.
      iii. Cardiopulmonary arrest can occur.

C. Treatment

1. Recompression is the definitive treatment.
   a. Begin recompression as quickly as possible. Results are best when recompression is done within 12 hours of symptom onset in decompression sickness and within 4 hours of symptom onset in air embolism.
   b. Move patient to the nearest decompression (hyperbaric) chamber.
   c. Interim management:
      i. Place patient in the Trendelenburg position on the left side.
      ii. Administer 100% oxygen (with air breaks to avoid pulmonary oxygen toxicity).
      iii. Intubation if pulmonary edema develops.
      iv. Pneumothorax or pneumomediastinum should be treated with chest tube drainage.
      v. Circulatory support with colloid and vasopressors may be required.
      vi. Although steroids are often used to reduce cerebral edema in decompression sickness, no role has yet been proved for them in these cases.

2. Emergency phone numbers: The Divers Alert Network consultation service:
   a. Daytime: Duke University, (919) 684-2948
   b. 24-hour emergency line: (919) 684-8111
   c. *Internet: www.diversalertnetwork.org*

D. Prognosis

1. Most patients improve when the gas bubbles redistribute to the venous circulation.
2. Remarkable recovery can occur after recompression.
   a. Recompression treatment can be effective even after delays of up to 2 weeks.
   b. Relapse requiring repeated decompression treatment occurs in 30% to 50% of patients.

VI. CEREBRAL FAT EMBOLISM SYNDROME

A. Background

1. Consequence of long bone fracture, particularly lower limb fractures
   a. Present in up to 2% of patients
   b. Present in 5% to 10% of multitrauma patients
   c. Begins 12 to 48 hours after trauma
2. Symptoms depend on location of fat emboli
   a. Hypoxemia from pulmonary insufficiency
   b. Neurologic
      i. Confusion
      ii. Impaired consciousness or coma
      iii. Seizures
      iv. Focal neurologic signs in approximately one third of patients
      v. MRI brain: T1 hypointensities and T2 hyperintensities. Diffusion-weighted images may also display lesions
   c. Fever
   d. Tachycardia
   e. Cutaneous petechiae
   f. Thrombocytopenia
   g. Anemia

B. Pathology

1. Microscopic fat emboli in the gray matter
2. Perivascular hemorrhages predominantly in cerebral and cerebellar white matter
3. Cerebral edema

C. Management

1. Rapid immobilization of fractures
2. Monitor and correct oxygenation
3. Fluid resuscitation
4. Computed tomography (CT) of the brain to rule out direct traumatic brain injury as the cause of neurologic symptoms
5. Raised ICP managed initially by hyperventilation
6. Steroid therapy not proved useful

D. Prognosis

1. Mortality rate: <10%
2. Permanent neurologic deficit: 25% of patients

VII. HICCUP

A. Background

1. Hiccups are usually a benign, self-limited condition.
2. Prolonged hiccupping can produce fatigue, sleeplessness, weight loss, difficulty in ventilation, and wound dehiscence.

B. Pathophysiology

1. Troublesome hiccup is most commonly associated with chest, abdomen, neck, and brainstem disorders.
2. Lateral medulla, phrenic nerve, or vagus nerve injury are usual causes.
3. Metabolic disorders (e.g., uremia) or toxins.
4. Gastroesophageal reflux disease.
5. Hiccups are associated with use of certain medications, such as α methyldopa, corticosteroids, benzodiazepines, and opioids.

C. Management

1. Find and treat underlying structural or metabolic disorder.
2. Core studies:
   a. Physical examination
   b. Radiographs, CT, or MRI
   c. Electrolytes, glucose, blood urea nitrogen, creatinine, and a toxic screen for alcohol and barbiturates
   d. Lumbar puncture if central nervous system infection suspected
3. Medications:
   a. Chlorpromazine (25 to 50 mg) by mouth or intramuscularly (IM) three to four times a day.
   b. Intravenous infusion of chlorpromazine (25 to 50 mg in 500 mL of normal saline) if oral or IM is ineffective.
   c. Metoclopramide (10 mg) orally four times a day.
   d. Haloperidol (5 mg) given three times a day may also prove effective.
   e. Gabapentin (100 to 400 mg) three times a day.
   f. Baclofen (10 mg) four times a day.
4. Mechanical treatments for hiccup alter the responsible reflex arc by direct stimulation of the posterior pharynx.
   a. Red rubber catheter inserted through the nares used to tickle the posterior pharynx
   b. Nasogastric intubation
   c. Swallowing dry granulated sugar
5. Refractory hiccup
   a. Surgical extirpation of phrenic nerve
   b. Transcutaneous stimulation of the phrenic nerve

VIII. PERIPHERAL NERVE DISORDERS

A. Critical illness polyneuropathy (see Chapter 134)

B. Compression neuropathies

1. **Background**
   Can result in significant delayed morbidity.
2. **Clinical features.** Compression of the peroneal nerve at the fibular head and the ulnar nerve at the elbow most common, with weakness and numbness in nerve distributions.
3. **Prevention.** Avoid compression by proper patient positioning.
4. **Treatment.** Supportive in most patients.

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Transplantation XIII

CRITICAL CARE OF ORGAN TRANSPLANT RECIPIENTS: OVERVIEW 137

Christoph Troppmann

I. GENERAL PRINCIPLES

A. The increased number of organ transplants during the last two decades has been paralleled by significant improvements in both patient and graft survival. These improvements can be attributed to several factors.

1. The availability of polyclonal and monoclonal antibody preparations to prevent and treat rejection episodes.

2. The introduction in the 1980s of a powerful immunosuppressant agent, cyclosporine, followed a decade later by tacrolimus and mycophenolate mofetil. More recently, additional new drugs have become available (e.g., sirolimus), augmenting the immunosuppressive armamentarium considerably and allowing for more individualized immunosuppression of organ recipients.

3. Improvements in organ preservation (e.g., introduction of the University of Wisconsin preservation solution in the late 1980s).

4. Thorough preoperative patient screening.

5. Increasing sophistication in postoperative intensive care, allowing also for transplantation of high-risk recipients with significant medical comorbidities.

6. Availability of potent, yet nontoxic antibacterial, antifungal, and antiviral agents has allowed for more effective prevention and treatment of opportunistic infections.
7. Refinements in surgical techniques.

B. Transplantation has therefore become the treatment of choice for many patients with end-stage failure of kidneys, liver, endocrine pancreas, heart, lungs, and small bowel. Criteria for potential recipients have been expanded to include infants, children, and individuals thought to be at higher risk for complications (e.g., patients with diabetes, elderly patients).

C. Current absolute contraindications to transplantation include malignancy (untreated, metastatic, or at high risk for recurrence); uncontrolled infection; and medical–surgical contraindications to undergo, or inability to recover from, a major surgery.

D. The gap between available organs and patients awaiting transplantation is widening. As a result, mortality on many transplant wait lists is increasing.

II. THE ORGAN DONOR SHORTAGE: POTENTIAL SOLUTIONS

A. Live donors:

1. Owing to the lack of deceased organ donors, and the development of a noninvasive (laparoscopic) nephrectomy technique, live donor kidney transplants have significantly increased over the last decade. In 2001, for the first time, live kidney donors outnumbered deceased kidney donors in the United States. Current initiatives (e.g., more widespread implementation of paired kidney donation) aim at increasing live donor transplant rates even further.
2. Live donor liver, small bowel, pancreas, and lung transplants are also done, but represent only a relatively small proportion (<10%) of each of those transplants.

B. Deceased organ donors:

1. As a result of a series of "Organ Donation Breakthrough Collaborative" initiatives launched in 2003 by the Health Resources and Services Administration (HRSA, a part of the U.S. Department of Health and Human Services), the number of decreased organ donors in the United States has increased by 35% during this decade (5,985 donors in 2000 vs. 8,089 in 2007).
2. Brain-dead donors: still by far the most common deceased donor type (92% of all deceased donors in the United States in 2006).
3. Donation after cardiac death (DCD) donors: an increasingly used donor type. Typically, families of unconscious patients with severe, irreversible terminal brain injury who do not fulfill the formal criteria of brain death, decide to forego any further treatment and then decide to donate the organs.
4. Maximizing donation within the currently underused pool of potential brain-dead and DCD donors carries the most significant potential for substantially increasing the number of available organs for transplantation. Critical care physicians and other intensive care health personnel play a crucial role in optimizing the rate of conversion from being a potential donor to being an actual donor (see also Chapter 138).

C. Unconventional donor organ sources (e.g., liver or heart domino transplants, reuse of already transplanted organs): they cannot *significantly* increase the number of available organs. Paying live organ donors is against federal law in the United States and is currently not an option in Western industrialized countries.

III. ORGAN-SPECIFIC CONSIDERATIONS

A. Kidney transplantation
1. Treatment of choice for nearly all patients of all ages with advanced chronic kidney disease.
2. Kidney transplants do not only improve quality of life, but also prolong life.
3. Less expensive from a socioeconomic standpoint than chronic hemodialysis.

B. Liver transplantation
1. Treatment of choice for patients with acute and chronic end-stage liver disease.
2. Dramatic improvement in graft survival after introduction of cyclosporine in the early 1980s. Currently, no reliable means exists to substitute for a failing liver other than with a transplant.
3. Attempts to alleviate the severe donor shortage include the increased use of marginal donors and innovative surgical techniques (e.g., living donor and split liver transplants).

C. Pancreas and islet transplantation
1. Indications: most pancreas and islet transplants are done for selected, medically suitable patients with type 1 diabetes who have developed significant secondary diabetic complications or have poor quality of life (e.g., due to severe hypoglycemic unawareness).
2. At present, pancreas transplantation is the only effective option to consistently restore normal glucose homeostasis and normalize glycosylated hemoglobin (HbA1c) levels.
3. Successful pancreas transplants significantly improve quality of life and decrease incidence and severity of secondary diabetic complications.
4. Most pancreas transplants are performed simultaneously with a kidney transplant in preuremic patients with significant renal dysfunction, or in uremic patients with end-stage diabetic nephropathy.

D. Small bowel transplantation
1. Indications: congenital or acquired short bowel syndrome, especially if liver dysfunction occurs because of long-term parenteral nutrition or if establishing or maintaining central venous access becomes difficult.
2. In patients who have also advanced liver disease, a combined liver–small bowel transplant may be indicated.
3. With refinement of surgical techniques, more specific immunosuppression, and better postoperative monitoring for rejection, graft survival has considerably improved over the last decade and approaches now that of other solid organ grafts (e.g., lung transplants).

E. Heart transplantation
1. Treatment of choice for patients with end-stage congenital and acquired parenchymal and vascular diseases of the heart after exhaustion of all conventional medical and surgical options.
2. Considerably improved results since introduction of cyclosporine in the early 1980s and refinements in diagnosing and treating rejection episodes.
3. Mechanical devices (e.g., total artificial heart, ventricular assist device) can serve as a temporary bridge between heart failure and transplant.

F. Heart-lung and lung transplantation
1. Effective treatment for patients with advanced pulmonary parenchymal or vascular disease with or without primary or secondary cardiac involvement.
2. Increase in lung transplants (most frequently done as single or bilateral single lung transplants) is in large part due to technical improvements, resulting in fewer surgical complications, and to advances in perioperative and postoperative care.

3. Mechanical ventilation or extracorporeal membrane oxygenation (ECMO) can be a temporary bridge to transplant.

G. Hematopoietic cell transplantation—see Chapter 144.

IV. FUTURE CHALLENGES IN ORGAN TRANSPLANTATION

A. Increase number of available donor organs.

B. Minimize rates of chronic graft failure (e.g., secondary to chronic rejection, graft atherosclerosis).

C. Develop immunosuppressive drugs and protocols that have fewer side effects and further improve long-term graft survival.

D. Develop tolerance-promoting protocols that would obviate need for chronic immunosuppression beyond the induction phase.

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CRITICAL CARE OF THE DECEASED ORGAN DONOR

138

Christoph Troppmann

I. GENERAL PRINCIPLES

A. The gap between available donor organs and those waiting for transplants is widening, and death on the waitlist are increasing.

B. Critical care physicians and other health care personnel play a key role in early identification of potential organ donors; early referral to Organ Procurement Organizations (OPOs); in a coordinated approach to the potential donor families for obtaining consent; and maintaining and optimizing organ function and viability for transplantation.

C. Predicted annual number of brain-dead potential organ donors ranges between 10,500 and 13,800, but in 2007, organs were recovered from only 8,089 deceased donors.

II. DONOR CLASSIFICATION

A. Brain-dead deceased donors

1. The most common deceased donor type (represented 92% of all deceased donors in the United States in 2006)

2. Unequivocal diagnosis of brain death is required before proceeding with organ procurement

B. Donation after cardiac death (DCD) donors

1. Currently <10% of all deceased organ donors, but the number is increasing.

2. Usually time and place of death are controlled (e.g., families of unconscious patients with severe irreversible terminal brain injuries, who do not fulfill the formal criteria of brain death, decide to forgo any further treatment, and then decide to donate the organs).

3. Life-supporting treatment is discontinued, and organ recovery is initiated in the operating room once death has been pronounced by a physician not belonging to the organ recovery and transplant team.

III. PATIENT SCREENING (FOR POTENTIAL BRAIN-DEAD DECEASED DONORS AND DONATION AFTER CARDIAC DEATH (DCD) DONORS)

A. Age 0 to 90 years

B. Severe neurologic injury (trauma, cerebrovascular accident, hypoxia, brain tumor), or near brain death or brain-dead; with or without impending withdrawal of support

C. Absolute contraindications

1. Current untreated severe viral, bacterial, fungal, or protozoan infection

2. Evidence of systemic sepsis syndrome

3. Viral encephalitis with severe systemic viral infection

4. Human immunodeficiency virus (HIV)-positive serology

5. Malignancy (except nonmelanoma skin cancers, primary brain tumors with little propensity to disseminate)

D. After identification of any potential donor, federal required-request legislation mandates that hospitals notify their local OPO in a timely manner

E. If local OPO address is unknown, a 24-hour access number to the United Network for Organ Sharing (UNOS) is available for further referral information: 1-800-292-9537

F. The OPO will assist with completing preliminary screening of the potential donor and coordinating the approach to the potential donor's family, and will consult with the transplant team(s) regarding use of marginal donors

IV. BRAIN DEATH DIAGNOSIS

A. "An individual who has sustained either irreversible cessation of circulatory and respiratory function, or irreversible cessation of all functions of the entire brain, including the brainstem, is dead. A determination of death must be made in accordance with accepted standards" (President's Commission for the Study of Ethical Problems in Medicine *Uniform Determination of Death Act*, 1981)

B. The clinical diagnosis of brain death rests on three criteria:

1. Irreversibility of the neurologic insult
2. Absence of clinical evidence of cerebral function
3. Most important, absence of clinical evidence of brainstem function

C. Clinical brain death examination and apnea test are outlined in Table 138-1

D. Spinal reflexes can be preserved and do not exclude the diagnosis of brain death

1. Confirmatory tests should be used when the observation period needs to be shortened (e.g., unstable donors); in equivocal situations (including age younger than 1 yr); or if one of the potential pitfalls (Table 138-2) cannot be ruled out. Tests must demonstrate absence of intracranial circulation by angiographic contrast or radioisotopic flow studies, transcranial Doppler ultrasonography, or electrocerebral silence documented by an electroencephalogram. Pursue donation after cardiac death if patient is unconscious, has suffered significant irreversible brain injury, but does not fulfill all formal criteria for brain death, and if patient's family wishes to withdraw care

V. OBTAINING CONSENT FOR ORGAN DONATION

A. Early involvement of the OPO in the potential organ donor screening and organ donation and consent process is crucial.

B. Consent rates are highest when an OPO representative or an OPO-designated requestor broaches the possibility of organ donation with the family.

C. Other important factors affecting the decision to donate include level of education, understanding and awareness of the irreversibility of severe brain injury (DCD donors) and brain death, amount of time spent by the OPO representative with the family, and covering discussion topics of importance to donor families (e.g., costs, funeral, choices regarding amount of tissue/organs donated).

VI. PERIOPERATIVE CARE OF THE BRAIN-DEAD ORGAN DONOR

A. General considerations

1. Once consent for organ donation is obtained, the focus switches from cerebral protection to preservation of organ function and optimization of peripheral oxygen delivery
2. Inadequate brain-dead donor management may result in loss of transplantable organs or even (in up to 15%) loss of the organ donor altogether
3. Pathophysiology of brain death maintenance phase
   - **a.** Hypothermia
   - **b.** Hypotension due to complete arterial and venous vasomotor collapse
   - **c.** Abolition of resting vagal tone secondary to destruction of the nucleus ambiguus, eliminating all chronotropic effects of atropine

TABLE 138-1 Brain Death Criteria and Clinical Diagnosis of Brain Death

1. Irreversible, well-defined etiology of unconsciousness
   a. Structural disease or metabolic cause (hypoxia)
   b. Exclusion of hypothermia; hypotension; severe electrolyte, glycemic, uremic, endocrine, or acid–base disturbance; hepatic encephalopathy; drug or substance intoxication
   c. Sufficient observation period (at least 6 h) between two brain death examinations
2. No clinical evidence of cerebral function
   a. No spontaneous movement, eye opening, or movement or response after auditory, verbal, or visual commands
   b. No movement elicited by painful stimuli to the face and trunk (e.g., sternal rub, pinching of a nipple or fingernail bed) other than spinal cord reflex movements
3. No clinical evidence of brainstem function
   a. No pupillary reflex: pupils are fixed and midposition; no change of pupil size in either eye after shining a strong light source in each eye sequentially in a dark room
   b. No corneal reflex: no eyelid movements after touching the cornea (not the conjunctiva) with a sterile cotton swab or tissue
   c. No gag reflex: no retching or movement of the uvula after touching the back of the pharynx with a tongue depressor or after moving the endotracheal tube
   d. No cough reflex: no coughing with deep tracheal irrigation and suctioning
   e. No oculocephalic reflex (doll's eyes reflex): no eye movement in response to brisk turning of the head from side to side with the head of the supine patient elevated 30 degrees
   f. No oculovestibular reflex (caloric reflex): no eye movements within 3 min after removing earwax and irrigating each tympanic membrane (if intact) sequentially with 50 mL ice water for 30–45 s while the head of the supine patient is elevated 30 degrees
   g. No integrated motor response to pain: no localizing or withdrawal response, no extensor or flexor posturing
4. Apnea testing
   a. Patient must be normothermic (>36.5°C) and normotensive (systolic blood pressure >90 mm Hg)
   b. Patient is preoxygenated with F_{IO_2} of 1.0 for 10–15 min while adjusting ventilatory rate and volume so that P_{aCO_2} reaches 40–45 mm Hg
   c. Obtain arterial baseline blood gas, disconnect patient from the ventilator, deliver O_2 at 6–8 L/min through a cannula advanced 20–30 cm into the endotracheal tube (cannula tip at the carina)
   d. Use continuous pulse oximetry for early detection of desaturation
   e. If brain dead, a P_{aO_2} >60 mm Hg is achieved within 3–5 minutes after withdrawal of ventilatory support; at this point the patient should be reconnected to the ventilator (or earlier, should hemodynamic instability, desaturation, or spontaneous breathing movements occur)
   f. Arterial blood gas sampling immediately before reinstitution of mechanical ventilation to confirm the P_{aCO_2} rise to >60 mm Hg
   g. Criteria for positive apnea test: No evidence of spontaneous respirations before reinstitution of mechanical ventilation in the presence of P_{aCO_2} >60 mm Hg or P_{aCO_2} increase of >20 mm Hg from the normal baseline value

TABLE 138-2 Pitfalls in Clinical Brain Death Testing and Potential Remedial Measures

Pitfalls	Remedial measure(s)
Hypotension, shock	Institute fluid resuscitation, use pressor agents
Hypothermia	Use warming blanket, warmed fluids, heated ventilator gases
Intoxication or drug overdose	If measurable, check drug levels and toxicology screens, or increase waiting time between brain death examinations administer specific antidotes (e.g., naloxone, flumazenil)
Neuromuscular and sedative drugs, which can interfere with elicitation of motor responses	Discontinue muscle relaxants and mood- or consciousness-altering medications, increase waiting time between brain death examinations
Pupillary fixation, which may be caused by anticholinergic drugs (e.g., atropine given during a cardiac arrest), neuromuscular blocking agents, or preexisting disease	Discontinue anticholinergic medications and muscle relaxants, increase waiting time between brain death examinations, obtain careful patient history
Corneal reflexes absent due to overlooked contact lenses	Remove contact lenses before brain death examination
Oculovestibular reflexes diminished or abolished after prior use of ototoxic drugs (e.g., aminoglycosides, loop diuretics, vancomycin) or agents with suppressive side effects on the vestibular system (e.g., tricyclic antidepressants, anticonvulsants, and barbiturates) or due to preexisting disease	Obtain careful medication history and patient history

d. Absence of pituitary hormones (including vasopressin)
e. Upregulation of proinflammatory and immunoregulatory pathways

B. Management principles
1. Monitoring
a. Core temperature, central venous pressure (CVP), systemic arterial blood pressure (arterial line), pulmonary artery (PA) catheter in selected donors, pulse oximetry
b. Foley catheter (urine output)
c. Frequent determination of electrolytes and arterial blood gases
d. Regular monitoring (every 12 hours) of blood urea nitrogen (BUN) and creatinine level, liver enzymes, amylase, lipase, and coagulation tests to help assess organ status and function
2. Maintenance therapy end points in brain-dead organ donors
a. Systolic blood pressure 100 to 120 mm Hg, mean arterial pressure (MAP) >60 mm Hg
b. CVP 8 to 10 mm Hg
c. Systemic vascular resistance (SVR) 800 to 1,200 dyne/second/cm^5
d. Dopamine <10 μg/kg/minute

TABLE 138-3 Differential Diagnosis of Hypotension in the Brain-Dead Organ Donor

Hypovolemia
Hypothermia
Cardiac dysfunction
Arrhythmia (ischemia, catecholamines, hypokalemia, hypomagnesemia)
Acidosis
Hypooxygenation
Excessive positive end-expiratory ventilatory pressure
Congestive heart failure due to excessive fluid administration
Hypophosphatemia
Hypocalcemia
Causes related to the injury that caused brain death (cardiac tamponade, myocardial contusion)
Myocardial sequelae of autonomic storm during brain herniation
Preexisting cardiac disease
Pneumothorax (traumatic or iatrogenic)
Drug side effect or overdose (e.g., long-acting β-blocker, calcium-channel antagonist, antihypertensive agent)

e. Urine output 100 to 300 mL/hour
f. Core temperature >35°C
g. Pa_{O_2} 80 to 100 mm Hg, Sa_{O_2} >95%, pH 7.37 to 7.45
h. Hemoglobin 10 to 12 g/dL, hematocrit 30% to 35%

3. Cardiovascular support: Hypotension most common, usually due to hypovolemia, but there is a wide array of other differential diagnoses (Table 138-3)
a. If hypotension persists despite euvolemia, use dopamine or α-adrenergic agents (e.g., phenylephrine)
b. Consider use of low-dose arginine vasopressin and T3 (see dosages under VI.B.8.) to reduce catecholamine requirements
c. Treat any hypertension with short-acting vasodilatory agents (e.g., sodium nitroprusside) or short-acting β-blockers

4. Respiratory maintenance
a. Vigorous tracheobronchial toilet with frequent suctioning; aspiration precautions
b. Positive end-expiratory pressure (PEEP) at 5 cm H_2O, tidal volumes 10 to 12 mL/kg, and peak airway pressures <30 cm H_2O. For potential lung donors, CVP should be kept at 6 to 8 mm Hg, pulmonary artery balloon occlusion pressure at 8 to 12 mm Hg
c. Steroid bolus treatments during the maintenance phase may exert potential beneficial effects (improved oxygenation and increased donor lung recovery rates; see dosage under VI.B.8.)

5. Renal function and electrolyte management
a. Goals (for potential kidney donors)
i. Maintain adequate systemic arterial perfusion pressure
ii. Maintain brisk urine output (>1 to 2 mL/kg/hour)
iii. Minimize use of vasopressors to maximize posttransplant graft function
iv. Insufficient urine production (<1 mL/kg/hour) after adequate resuscitation: give loop or osmotic diuretics (furosemide, mannitol)
v. Avoid nephrotoxic drugs

b. Polyuria
  i. Frequently observed in brain-dead donors
  ii. Etiologies
    (a) Osmotic diuresis (induced by mannitol administered to decrease intracranial pressure (ICP) during pre-brain death phase, or hyperglycemia)
    (b) Hypothermia
    (c) Diabetes insipidus
      (1) Diagnosis
        - Urine volumes >300 mL/hour (or >5 mL/kg/hour) with hypernatremia (serum sodium >150 mEq/L), elevated serum osmolality (>310 mOsm/kg), and low urinary sodium concentration
        - Not infrequently associated with other electrolyte abnormalities: hypokalemia, hypocalcemia, hypomagnesemia

      (2) Treatment
        - Vasopressin or vasopressin analogs (indicated once urine output exceeds 300 mL/hour). Desmopressin (deamino-8-D-arginine vasopressin [DDAVP]) has a long duration of action and high antidiuretic–pressor ratio, reducing undesirable splanchnic vasoconstrictor effects of arginine vasopressin. Dosage: 1 to 2 μg desmopressin are administered intravenous (IV) every 8 to 12 hours to titrate urine output to values of 100 to 300 mL/hour
        - Correct hypernatremia: Use infusion solutions with low or no sodium content (e.g., dextrose 5% in water [D5 W] solution [free water]). Take into consideration sodium content of other IV fluids (e.g., of 5% albumin solutions)
        - Adjunct measures: discontinue mannitol, correct coexisting hypovolemia, and hyperglycemia

6. Hypothermia
  a. After brain death, when the body becomes poikilothermic because of the loss of central temperature control mechanisms, hypothermia is further aggravated by peripheral vasodilatation. Hypothermia is observed in up to 80% of brain-dead bodies
  b. Adverse effects: Decreased myocardial contractility, hypotension, cardiac arrhythmias, cardiac arrest, hepatic and renal dysfunction, acidosis, and coagulopathy
  c. Therapy: Maintain donor core temperature at >35°C using warmed IV fluids and blood products, warming blankets, heated ventilator gases

7. Coagulation system
  a. Coagulopathy and disseminated intravascular coagulation are common findings in brain-dead donors, particularly after head injury
  b. Clinical findings: pathologic bleeding, abnormal prothrombin time (PT)/international normalized ratio (INR), thrombocytopenia, hypofibrinogenemia, increased fibrin/fibrinogen degradation products
  c. Treat coagulopathy using blood products as indicated by specific findings. Correct underlying pathophysiology (e.g., hypothermia, acidosis)

8. Hormonal/endocrine support
  a. Hyperglycemia
    i. Frequent in brain-dead donors
    ii. Etiology
      (a) Increased catecholamine release
      (b) Altered carbohydrate metabolism
      (c) Steroid administration for treatment of cerebral edema

(d) Infusion of large amounts of dextrose-containing IV fluids
(e) Peripheral insulin resistance

iii. Treatment: insulin (subcutaneously or continuous IV infusion) to maintain glucose levels 100 to 150 mg/dL
iv. Good glycemic control also prevents ketoacidosis and osmotic diuresis and may be beneficial for pancreas graft function in recipients

b. Recently published retrospective clinical evidence suggests that routine hormonal support may stabilize and improve cardiac function in brain-dead donors and may result in increased probability of kidney, heart, liver, lung, and pancreas recovery and transplantation (overall level of evidence is low; available data is not conclusive and awaits confirmation in prospective controlled trials). Recommended doses (based on American Society of Transplant Surgeons and American Society of Transplantation 2002 Consensus Conference Recommendations):
i. Triiodothyronine (T3: 4 μg bolus, 3 μg/hour continuous IV infusion): (effects: reversal of myocardial dysfunction, improved arterial pressure, decreased CVP, significant reduction of inotropic requirements)
ii. Methylprednisolone: 15 mg/kg/bolus IV (repeat every 24 hours) (effects: improved oxygenation and increased donor lung recovery; putative beneficial effects in the donor and the organ recipient from attenuation of the effects of proinflammatory cytokines released as a consequence of brain death)
iii. Arginine vasopressin: 1 unit bolus, followed by 0.5 to 4.0 unit/hour IV continuous infusion (titrate SVR 800 to 1,200 dyne/second/cm^5 if PA catheter in place) (effects: treatment of diabetes insipidus, reduces inotropic requirements; better kidney, liver, and heart graft function; beneficial effects are present even in unstable donors who do not have diabetes insipidus)

C. Intraoperative care
1. In brain-dead donors, full cardiovascular and ventilatory support is maintained throughout the donor operation until aortic cross-clamp and the start of the organ flush phase.
2. Maintain hemodynamic stability and ensure adequate fluid resuscitation, particularly in thoracic and abdominal organ donors when both body cavities are open and significant evaporative and massive third space fluid losses can occur.
3. Maintain normothermia.

VII. PERIOPERATIVE CARE OF THE DONATION AFTER CARDIAC DEATH (DCD) DONOR

A. Preoperative care of potential DCD donors (before obtaining consent for organ donation)
1. The therapy remains primarily aimed at treating the underlying pathology (e.g., head trauma, cerebrovascular accident)

B. Preoperative care of actual DCD donors (after having obtained consent for organ donation)
1. The focus switches from cerebral protection to preservation of organ function and optimization of peripheral oxygen delivery
2. Maintenance therapy end points are identical to those described earlier for brain-dead organ donors

C. Intraoperative care of DCD donors
1. Maintenance therapy as outlined in preceding text is continued until support is withdrawn and the patient is extubated
2. Any additional premortem interventions (e.g., surgical: insertion of femoral cannulas in preparation of organ recovery; pharmacologic: administration

of IV heparin, opioids, and phentolamine) must occur in strict accordance with local OPO/hospital DCD protocols and policies

3. Death is pronounced by a physician not belonging to the organ recovery and transplant team (usually the patient's intensive care physician)
4. After an additional postmortem waiting time (minutes) specified by the local OPO/hospital DCD protocol, surgical organ recovery begins
5. Disposition of the patient, if death does not occur within a specified postwithdrawal of support waiting time, is determined by the local protocol (e.g., return patient to a non–intensive care hospital floor for comfort care only)

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REJECTION, INFECTION, AND MALIGNANCY IN SOLID ORGAN TRANSPLANT RECIPIENTS

139

Brian J. Gallay

I. GENERAL PRINCIPLES. Immunosuppressive therapy must be balanced to prevent transplant rejection and minimize risk of infection and malignancy. The level of immunosuppression required varies depending on risk of rejection of the transplanted organ. Although the risk of complications varies among organ types, all transplants share characteristic features of rejection, infection, and malignancy.

II. REJECTION

A. The alloimmune response:

1. Highly polymorphic human leukocyte antigens (HLAs) expressed on cell surfaces.

2. Foreign HLA molecules expressed on transplants are recognized by recipient helper and cytotoxic T lymphocytes, B lymphocytes, and natural killer cells.

3. T lymphocytes are central to alloimmunity as well as immunity to viruses and malignant cells.

4. B lymphocytes produce anti–donor HLA antibodies. Sensitization to donor HLAs may have occurred in recipients who had prior transplants, blood transfusions, or pregnancies.

5. Immunosuppression targets T lymphocytes. Dual or triple maintenance therapy, usually with a calcineurin inhibitor, antimetabolite, and corticosteroids, permits lower drug doses while acting synergistically.

a. Corticosteroids inhibit lymphocyte activation and are cytolytic at high doses (side effects include fluid retention, psychosis, hyperlipidemia, weight gain).

b. Antimetabolites (azathioprine, mycophenolate mofetil, leflunomide) inhibit lymphocyte proliferation (side effects include neutropenia, anemia; adjust dose to maintain peripheral leukocyte count $>3{,}000/mm^3$).

c. Calcineurin inhibitors (cyclosporine, tacrolimus) inhibit production of interleukin-2 (IL-2), a critical signal for T lymphocyte activation (side effects include acute and chronic nephrotoxicity, hypertension, neurotoxicity [e.g., seizures, tremor]).

d. Mammalian target of Rapamycin (mTOR) inhibitors (sirolimus, everolimus) prevent entry of lymphocytes into the cell cycle after activation (side effects include thrombocytopenia, anemia, leukopenia, delayed wound healing, hyperlipidemia).

e. Induction immunosuppression depletes T lymphocytes (antithymocyte globulin; alemtuzumab; muromonab-CD3 [Orthoclone OKT3]; side effects include fever, myalgia, pulmonary edema [cytokine release syndrome]; neutropenia thrombocytopenia, and anemia [antithymocyte globulin, alemtuzumab]; dyspnea and bronchospasm [alemtuzumab], aseptic meningitis [Orthoclone OKT3]) or inhibits their activation by blocking the IL-2 receptor (basiliximab, daclizumab).

B. Acute rejection:

1. General: transplant dysfunction is a frequent presentation. The gold standard test for diagnosing and grading solid organ graft rejection is

biopsy. Systemic inflammatory symptoms are less common. Acute cellular rejection is characterized histologically by lymphocytic cellular infiltrate with active parenchymal injury. Humoral rejection is characterized by vascular endothelial cell injury with intravascular antibody deposition, fibrin formation, and complement activation. Therapy with high-dose corticosteroids or antilymphocyte antibody is required.

2. Kidney: acute rise of serum creatinine. Rule out drug nephrotoxicity, pyelonephritis, systemic infection, urologic obstruction, intravascular volume depletion, and vascular compromise.
3. Liver: acute rise in serum transaminases. Rule out recurrent disease, biliary complications, hepatic artery thrombosis, and drug toxicity.
4. Heart: acute decrease in left ventricular ejection fraction, or rejection identified on routine endomyocardial biopsy. Rule out infection.
5. Pancreas: acute serum amylase elevation and decreased urinary amylase excretion (bladder-drained pancreas grafts). Hyperglycemia is a late manifestation. Rule out vascular graft thrombosis, impaired exocrine drainage, drug toxicity, or infection.
6. Lung: acute decrease in ventilation and oxygenation, or rejection identified on routine bronchoscopic biopsy. Rule out infection, airway or vascular anastomotic complications, malignancy, and recurrent disease.

C. Chronic rejection occurs as coronary artery disease in heart, bronchiolitis obliterans in lung, or ischemia and fibrosis in kidney, pancreas, and liver grafts. Both immunologic and nonimmunologic risk factors are important, including frequency and severity of acute rejection, recurrence of original disease, drug toxicity, and infection. Therapy includes increased immunosuppression, avoidance of drug toxicity, or treatment of recurrent disease.

III. INFECTION

A. General

1. Because immunosuppression targets T lymphocytes, risk of opportunistic infection by pathogens controlled by T cell immunity is increased.
2. Risk decreases over time with reduction in immunosuppression intensity.
   a. Peritransplant infection due to nosocomial infection as in other postoperative patients
   b. Opportunistic infection most common 3 to 6 months after transplant
   c. Later infection generally community-acquired or persistent opportunistic infection
3. Antimicrobial prophylaxis and empiric therapy are guided by time after transplant and level of immunosuppression, but a wide differential diagnosis and rapid identification of pathogens are always required.

B. Bacterial

1. Peritransplant nosocomial infection: pneumonia, catheter infection, superficial or deep wound infection, or urinary tract infection.
2. Community-acquired respiratory and urologic tract pathogens predominate later.
3. Consider *Nocardia* or *Legionella* in pneumonia.
4. Consider *Listeria* in acute meningitis.
5. Tuberculosis may occur at any time and often presents as disseminated disease.

C. Viral

1. Cytomegalovirus (CMV):
   a. Active infection occurs by reactivation of latent virus or by *de novo* infection with transplant (CMV-negative recipients of CMV-positive donor organs at highest risk).
   b. Highest incidence in the first 6 months: pneumonitis, esophagitis, gastritis, colitis, hepatitis, nephritis, bone marrow infection, or febrile

syndrome. Diagnosis is confirmed by presence of viremia (polymerase chain reaction [PCR]) or biopsy.

c. Prophylaxis with oral ganciclovir or valganciclovir is maintained for at least 3 months, especially in high-risk recipients.

2. Epstein–Barr virus (EBV) is associated with posttransplant lymphoproliferative disease (PTLD). It may cause acute hepatitis or infectious mononucleosis.
3. Pneumonitis due to adenovirus, respiratory syncytial virus, and influenza virus requires rapid bronchoscopic diagnosis and specific antiviral therapy.
4. Hepatitis B and C viruses are most commonly acquired before transplant, but *de novo* infection at transplant can cause acute hepatitis and fulminant liver failure.

D. Fungal

1. Pneumocystis pneumonia presents as acute pneumonitis in the first 6 months after transplant. Prophylaxis with trimethoprim–sulfamethoxazole is highly effective.
2. Aspergillosis is often disseminated and associated with high mortality.
3. Cryptococcosis must be considered in meningitis.
4. Coccidioidomycosis, histoplasmosis, and blastomycosis should be considered after careful demographic evaluation to determine exposure risk. Meningitis, pneumonitis, and dermatitis are common presentations.
5. Candidiasis may present as disseminated infection, urinary tract infection, or intra-abdominal abscess.

E. Parasitic

1. Parasitic infection should be suspected in the setting of eosinophilia.
2. Strongyloidiasis may present in the first 6 months with abdominal symptoms, systemic inflammatory symptoms, or pneumonitis in patients harboring the organism at time of transplant.
3. Toxoplasmosis may present in the first 2 months with systemic inflammation, meningoencephalitis, pneumonitis, pericarditis, myocarditis, or retinitis. Prophylaxis with trimethoprim–sulfamethoxazole is effective.

I. MALIGNANCY

A. Skin cancer is the most common malignancy in all transplant recipients. Risk increases with increasing levels of sun exposure and immunosuppression. Squamous cell carcinoma is most common. Melanoma may present as metastatic disease with an unidentified primary lesion. Kaposi's sarcoma is common in patients of Mediterranean origin.

B. Solid organ cancers:

1. Recurrent disease in recipients with a remote cancer history is possible, especially with colon and breast cancer, and melanoma.
2. May present as metastatic disease, but a primary lesion is commonly identified.
3. Risk is increased approximately threefold over that for the general population.
4. Risk factors are similar to those for nonimmunosuppressed patients.

C. PTLD:

1. Presents typically as polymorphic non–Hodgkin B cell lymphoma, commonly associated with EBV infection. The primary lesion may arise in the small bowel, central nervous system, or allograft. Lymphadenopathy is easily identified on physical examination or radiologic imaging.
2. PTLD usually presents within 1 year of transplant but may also occur later. Risk is 2% for renal transplant recipients to 10% for heart and lung recipients.

3. Therapy:
   a. Reduce or discontinue immunosuppression.
   b. Cytotoxic chemotherapy or therapy with anti-CD20 antibody (rituximab) targeting B lymphocytes.
   c. Antiviral (anti-EBV) therapy with acyclovir or ganciclovir (limited evidence-based support).
   d. Consider surgical resection in cases with localized, limited involvement (e.g., allograft, gastrointestinal lymphoma).
   e. Radiation is most effective for central nervous system PTLD.

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CRITICAL CARE OF KIDNEY TRANSPLANT RECIPIENTS

140

Brian J. Gallay

I. GENERAL PRINCIPLES. Renal transplants are the most common solid organ transplants. They improve quality of life and survival compared to dialysis therapy for patients with chronic kidney disease. Diabetic and hypertensive nephropathy are the most common causes of chronic kidney disease leading to transplantation. Underlying disease and its pathophysiology must be considered in pretransplant evaluation and postoperative management.

II. PRETRANSPLANT EVALUATION. Chronic kidney disease is a risk factor for cardiovascular disease and infection. Special attention must be paid to these as well as acute metabolic abnormalities.

A. Cardiovascular

1. Assessment: history of coronary artery disease, symptoms of angina or congestive heart failure, recent change in exercise tolerance, new ischemic changes on electrocardiogram (ECG). Decreased pulse or bruit on peripheral vascular examination, new murmur on cardiac examination.

2. Prevention: perioperative cardioprotection with β-blockers (e.g., atenolol 5 mg intravenously (IV) preoperatively and 50 to 100 mg orally daily for at least the first postoperative week), with careful monitoring for hyperkalemia, bradycardia, and hypotension. Consider continuing or starting acetylsalicylic acid preoperatively for patients with multiple risk factors. If a drug-eluting coronary artery stent has been placed previously, clopidogrel should be resumed as soon as possible postoperatively to minimize risk of intrastent thrombosis.

B. Infection

1. Assessment: signs or symptoms of active infection. Careful assessment of indwelling hemodialysis or peritoneal dialysis catheters (including skin exit site) and hemodialysis access grafts. Culture and cell count of peritoneal fluid from peritoneal dialysis catheter.

2. Prevention: postpone transplant until active infection has been treated. Cephalosporins for perioperative antibacterial prophylaxis.

C. Preoperative dialysis

1. Assessment of hypervolemia by physical examination. Determine pretransplant daily urine output to facilitate interpretation of posttransplant urine output. Laboratory assessment for hyperkalemia or severe metabolic acidosis.

2. Acute dialysis treatment to correct electrolyte abnormalities and volume status, avoiding excessive volume removal.

III. INTRAOPERATIVE CARE

A. Careful attention to volume status is critical to avoid hypovolemia that will impair renal perfusion and contribute to delayed graft function (i.e., need for dialysis therapy during the first week after transplant, a risk factor for acute rejection).

B. Intravascular volume status should be maintained at adequate central venous pressures (CVPs) without predisposing to pulmonary edema. CVP monitoring is recommended to maintain CVP approximately between 5 and 12 cm H_2O.

C. Consider perioperative pulmonary artery catheterization to assess hemodynamics in patients with significantly decreased left ventricular function.

IV. POSTOPERATIVE CARE

A. Postoperative management is determined by initial allograft function. Chest radiograph and frequent electrolyte monitoring, including sodium, potassium, calcium, and magnesium levels are essential to help assess volume and metabolic status.

B. Oliguria (urine output <20 mL/hour) requires careful attention to intravascular volume status. If an oliguric patient is euvolemic or hypervolemic, then aggressive fluid resuscitation should be avoided and other complications such as urinary obstruction (e.g., transplant ureter, Foley catheter), vascular thrombosis, and acute tubular necrosis must be considered. Hyperkalemia must be diagnosed and treated promptly.

C. With immediate graft function, urine output can reach 1 L/hour. Careful fluid and electrolyte replacement is required to avoid hypovolemia and electrolyte depletion.

V. POSTOPERATIVE CONSIDERATIONS

A. Surgical complications

1. Hemorrhage
   a. Incidence 1.9% to 12%
   b. Increased risk for patients requiring continuation of preoperative antiplatelet therapy (e.g., acetylsalicylic acid, clopidogrel) or preoperative reversal of chronic warfarin anticoagulation
   c. Frequently due to vascular anastomotic bleeding, but in half of cases no obvious source is identified
2. Allograft thrombosis
   a. Risk factors
      i. Hypotension and hypovolemia
      ii. Hypercoagulable state (antiphospholipid antibody syndrome; factors C, S, or antithrombin III deficiency; factor V Leiden mutation; acute humoral rejection)
      iii. Severe peripheral vascular disease (increased risk of intimal flap and other anastomotic complications)
      iv. Multiple small renal arteries, preexisting donor vascular disease, excessive organ preservation time
   b. Presentation, diagnosis, and treatment
      i. Sudden oligoanuria (arterial thrombosis), gross dark hematuria, allograft pain, and swelling (venous thrombosis)
      ii. Doppler ultrasound documenting lack of flow in renal artery and vein confirms diagnosis
      iii. Almost always requires allograft nephrectomy
   c. Prevention
      i. Maintain adequate blood pressure and intravascular volume.
      ii. Acetylsalicylic acid for severe peripheral vascular disease.
      iii. IV heparin for hypercoagulable states. No definitive evidence-based guidelines are available, but therapeutic target partial thromboplastin time (PTT) of 1.5 to 1.9 times the upper limit of normal PTT range has been suggested with acceptable bleeding risk.
3. Urologic
   a. Significant hematuria with passage of clots may require continuous bladder irrigation. Avoid excessively high intravesical pressures that can lead to rupture of the ureteroneocystostomy.
   b. Urinary leak:
      i. Occurs at the ureteroneocystostomy due to anastomotic complication or distal ureteral ischemia and necrosis. Patient may

present with sudden oligoanuria or significant increase in wound drainage.

ii. Ultrasound may identify perigraft fluid collection (urinoma), nuclear medicine scan may identify extravasation of tracer from ureter, and increased creatinine level of wound drainage (when compared to serum creatinine) will confirm urine leak.

iii. In some cases, reinsertion of Foley catheter with bladder decompression and/or placement of a percutaneous nephrostomy tube are sufficient. Surgical reexploration with ureteral reimplantation and stent placement if not responding to less invasive treatment.

4. Wound
   a. Infection and dehiscence are infrequent complications (<5%). Risk is increased with obesity (body mass index >30), and combined use of sirolimus and steroids for immunosuppression (both impair wound healing).
   b. Lymphoceles requiring therapy occur in <5%. Patients can present with ureteral or venous obstruction of the graft, often associated with ipsilateral lower extremity edema. External drainage and sclerotherapy can be attempted first. Definitive treatment often requires laparoscopic internal drainage through a peritoneal window.

B. Medical complications
   1. Cardiovascular:
      a. Because of the increased risk of myocardial infarction in patients with end-stage renal disease (ESRD), a high index of suspicion is required, especially with prolonged intraoperative hypotension or postoperative pulmonary edema.
      b. Pericarditis occurs in approximately 2%. Causes include uremia and infection, especially cytomegalovirus (CMV; unusual in the immediate postoperative period).
   2. Metabolic:
      a. Hyperkalemia can occur with delayed graft function. Immediate therapy is required with calcium chloride, insulin and dextrose, and bicarbonate. Polystyrene sulfonate (Kayexalate) or dialysis is required if diuresis to eliminate potassium cannot be induced.
      b. Hypokalemia may occur with large-volume diuresis early postoperatively, requiring frequent monitoring and repletion.
      c. Hypocalcemia, hypophosphatemia, and hypomagnesemia can occur with large-volume diuresis and early renal tubular dysfunction. Frequent electrolyte monitoring (at least every 12 hours) and repletion are required.
   3. Infection in the early postoperative period is due to bacterial etiology similar to that for other surgical patients. Risk is greatest in patients with diabetes or those older than 60. Perioperative prophylaxis with cephalosporins is paramount.
   4. Neurologic:
      a. Stroke is a rare early postoperative complication. Risk is greatest in patients with any significant vascular disease. Stroke should be considered in the setting of a postoperatively unexplained altered level of consciousness or with other neurologic changes.
      b. New-onset seizure is also uncommon. Uremia in the setting of delayed graft function, electrolyte abnormalities, stroke, or drug toxicity are the most common causes.

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CRITICAL CARE OF PANCREAS TRANSPLANT RECIPIENTS

141

Christoph Troppmann

I. GENERAL PRINCIPLES

A. Currently, pancreas transplantation is the only diabetes treatment that consistently normalizes glycosylated hemoglobin (HbA1c) levels, positively influences the progression of secondary diabetic complications, significantly ameliorates quality of life, and may prolong life. Most pancreas transplants are done for selected, medically suitable patients with type I diabetes. Type II diabetes is a relatively infrequent indication (<10% of all pancreas transplants).

B. Depending on the recipient's native kidneys' functional status, pancreas transplants are performed in three recipient categories:

1. Simultaneous pancreas–kidney (SPK) transplants in preuremic and uremic patients.

2. Pancreas after kidney (PAK) transplants in posturemic recipients of a previous kidney transplant (from a deceased or a live donor).

3. Pancreas transplants alone (PTA) in nonuremic recipients with extremely labile diabetes but adequate native renal function.

C. Pancreas graft survival rates have significantly improved over the past decade, and now exceed 85% at 1 year and 70% at 5 years (SPK).

I. PRETRANSPLANT EVALUATION.

Patients admitted to the hospital for pancreas transplantation must be evaluated for the following risk factors for adverse perioperative outcomes:

A. Coronary artery disease: High incidence of coronary artery disease in diabetic patients (with and without end-stage renal disease [ESRD]). In the course of their transplant workup, prospective recipients will have been screened for coronary artery disease by noninvasive tests or coronary angiography. Immediately preoperatively, particular attention must be paid to new symptoms of angina, congestive heart failure, recent changes in exercise tolerance, and new, possibly ischemic, changes on the electrocardiogram (ECG).

B. Peripheral vascular disease: Decreased peripheral pulses or new bruits on peripheral vascular examination, when compared to baseline. Infected diabetic foot ulcers are generally a contraindication to transplantation. Check also for new signs and symptoms of stroke and ischemic cerebrovascular disease.

C. Infectious disease: Diabetes in combination with uremia is a significant risk factor for infection. Preoperatively, chest radiograph, urinalysis, and careful assessment of indwelling catheters and catheter exit sites (hemodialysis catheters, peritoneal dialysis catheters [including a peritoneal fluid cell count and culture]) and of vascular access grafts, are mandatory. Active infection is a contraindication to transplantation.

D. Metabolic and fluid status: Hyperkalemic uremic patients admitted for transplant may need therapy before the transplant operation (e.g., oral sodium polystyrene sulfonate [Kayexalate], intravenous [IV] insulin and glucose, dialysis). Hypervolemic recipients may need preoperative dialysis. Hyperglycemia with metabolic acidosis requires preoperative correction.

E. Absolute contraindications to transplantation:

1. Active sepsis

2. Active viral infection

3. Acquired immunodeficiency syndrome (AIDS)
4. Malignancy (except if treated, nonmetastatic, without recurrence, and with sufficient posttreatment follow-up)

III. INTRAOPERATIVE CONSIDERATIONS

A. Operative technique

1. Nearly all pancreas transplants currently performed are from deceased donors and entail transplantation of the entire organ with an attached segment of duodenum that serves as conduit for the exocrine secretions.
2. Management of pancreatic exocrine secretions: The exocrine secretions of most pancreas transplants are drained enterically through an anastomosis of the graft's duodenal segment to the recipient's small intestine. For PAK and PTA recipients, bladder drainage (creation of a duodenocystostomy) can provide a useful additional means to monitor for rejection (by measuring urinary amylase).
3. Venous pancreas graft drainage: The venous effluent of the pancreas graft can be drained systemically, into an iliac vein (done in >75% of all pancreas transplants), or portally, into the superior mesenteric vein. Portal drainage has theoretical, but clinically to date unproved advantages (host tolerance facilitation by portally delivered graft antigen; avoidance of potential systemic hyperinsulinemia sequelae).

B. Cardiovascular care and monitoring

1. Recipients may benefit from perioperative cardioprotection with β-blockers (e.g., atenolol, 5 to 10 mg IV started preoperatively, repeat every 12 hours, and then 50 to 100 mg by mouth every day for at least the first postoperative week).
2. Hemodynamic monitoring: central venous pressure (CVP) catheter and arterial line; pulmonary artery catheter if indicated (e.g., presence of moderate left ventricular dysfunction).
3. Maintain adequate intravascular volume status, avoiding high CVPs that can predispose pancreas grafts with systemic venous drainage to edema, while providing adequate preload for optimal perfusion of the kidney graft (SPK recipients). Judicious fluid management to avoid fluid overload and acute myocardial strain is paramount.

C. Foley catheter, nasogastric tube

D. Metabolic care: Frequent (at least hourly) intraoperative monitoring of blood glucose levels is important, because the pancreas graft often begins to function immediately postreperfusion, resulting in decreasing blood glucose levels and no further need for exogenous insulin.

IV. POSTOPERATIVE CARE

A. General: Immediate postoperative chest radiograph and frequent electrolyte monitoring; daily serum amylase and lipase levels.

B. Metabolic

1. In the few grafts that have delayed function, temporary administration of exogenous insulin may be necessary (initially, most easily by IV insulin infusion with hourly blood glucose monitoring; adjust infusion rate to maintain blood glucose levels 80 to 120 mg/dL).
2. Bladder-drained recipients must be monitored closely for fluid and electrolyte losses from the exocrine pancreas, which can result in dehydration and metabolic acidosis. Urine is collected over an 8-hour period on each postoperative day, and hourly urinary amylase production (expressed as amylase U/hour) is determined. With normal pancreas graft recovery from preservation and reperfusion injury, urinary amylase excretion should increase daily before reaching its baseline, usually after discharge of the recipient from the hospital.

C. Kidney graft monitoring and management (see Chapter 140)

D. Provision of adequate immunosuppression
  1. Immunosuppression may include a combination of any of the following: polyclonal or monoclonal anti–T-cell agents for induction therapy during the first week (e.g., antithymocyte globulin, alemtuzumab [depleting] or basiliximab, daclizumab [nondepleting]), steroids, calcineurin inhibitors (tacrolimus, cyclosporine), mycophenolate mofetil, mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus).
  2. Solitary pancreas transplants (PAK and PTA) are more immunogenic and do not have a kidney from the same donor (as SPK recipients do) that would more easily allow for rejection monitoring (i.e., by checking serum creatinine levels). They require, therefore, closer surveillance for rejection and often more induction and maintenance immunosuppression.

E. Antimicrobial prophylaxis
  1. IV broad-spectrum antibiotics for 3 to 5 days (e.g., cephalosporins)
  2. Antifungal prophylaxis with fluconazole for 7 to 28 days
  3. *Pneumocystis jirovecii* prophylaxis with trimethoprim–sulfamethoxazole (Bactrim)
  4. Cytomegalovirus (CMV) prophylaxis for 1 to 6 months (depending on donor–recipient CMV serostatus)

F. Graft thrombosis prophylaxis
  1. No prospective data are available to support current empiric practices.
  2. Some centers partially anticoagulate recipients perioperatively for the first 3 to 7 days (e.g., heparin infusion at 300 to 700 U/hour IV). Some of these recipients are then orally anticoagulated with warfarin for the first 6 months.
  3. Many transplant programs start recipients perioperatively on oral acetylsalicylic acid, which is continued indefinitely.

V. POSTOPERATIVE CONSIDERATIONS

A. Surgical complications
  1. Postoperative bleeding
    a. Diagnosis: by serial hemoglobin/hematocrit levels; hemodynamic changes (hypotension, tachycardia, decreased CVP, decreased left ventricular filling pressures).
    b. Most common bleeding sources: free intra-abdominal bleeding from the graft itself or the vascular anastomoses; intravesical bleeding with massive hematuria (from the duodenovesical anastomosis in bladder-drained grafts); gastrointestinal (GI) bleeding manifesting as lower GI bleeding (from the duodenoenteric anastomosis in enteric drained grafts).
    c. Check platelets, prothrombin time (PT), and partial thromboplastin time (PTT). Replace coagulation factors and platelets as indicated.
    d. For ongoing intra-abdominal bleeding, relaparotomy for hemostasis and evacuation of hematoma may be necessary.
  2. Pancreas graft thrombosis
    a. Most frequent serious surgical complication (incidence: 5% to 10%); results nearly always in graft loss.
    b. Symptoms: Sudden onset of otherwise unexplained hyperglycemia (arterial and/or venous thrombosis); graft tenderness and enlargement (venous thrombosis); dark, massive hematuria (venous thrombosis of bladder-drained pancreas grafts); markedly decreased or absent urinary amylase on spot urinary amylase check (bladder-drained grafts).
    c. Diagnosis
      i. Imaging studies: Doppler duplex ultrasonography, magnetic resonance angiography, computed tomographic angiography, graft scintigraphy, conventional angiography.
      ii. Diagnosis made during exploratory relaparotomy.
    d. Treatment: transplant pancreatectomy

3. Surgical wound infection
   a. Superficial wound infection
      i. Symptoms: fever, wound drainage, cellulitis, leukocytosis
      ii. Treatment: IV antibiotics and local incision and drainage; open wound care with daily dressing changes
   b. Deep wound infection (intra-abdominal abscess)
      i. Occurs usually within the first 30 days posttransplant; bacterial abscesses are diagnosed earlier than fungal abscesses. Of all intra-abdominal infections, 50% are diffuse and 50% are localized; 30% are associated with a leak.
      ii. Clinical presentation: ranges from nonspecific abdominal complaints to diffuse peritonitis, fever, ileus, nausea, vomiting, leukocytosis, hyperglycemia, and sepsis.
      iii. Risk factors: include donor age older than 45 years, retransplant, pretransplant peritoneal dialysis, and graft pancreatitis.
      iv. Diagnosis: abdominal computed tomography (CT) with oral and IV contrast (for bladder-drained grafts also with retrograde bladder contrast to rule out leak).
      v. Treatment:
         (a) Percutaneous catheter drainage is appropriate as first-line treatment in stable recipients with localized intra-abdominal abscess.
         (b) For unstable recipients and those with diffuse peritonitis, relaparotomy and open abscess drainage. If leak is present, relaparotomy in enteric drained recipients is mandatory, but in selected stable bladder-drained recipients, conservative treatment (prolonged Foley catheterization and percutaneous drainage of localized abscesses) may be attempted.
         (c) IV antibiotics; bowel rest and nasogastric tube if ileus is present.
4. Leaks
   a. Enteric drained grafts
      i. Incidence 5% to 10%
      ii. Symptoms: abdominal pain, peritonitis, ileus, fever, leukocytosis, hyperamylasemia
      iii. Diagnosis
         (a) Abdominal CT with oral contrast
         (b) Diagnosis made at exploratory relaparotomy
      iv. Treatment: relaparotomy is mandatory (anastomotic revision or, most frequently, transplant pancreatectomy)
   b. Bladder-drained grafts
      i. Incidence: 10% to 15%
      ii. Early leaks (≤4 weeks posttransplant) usually at the duodenocystostomy anastomosis, late leaks (>4 weeks post-transplant) typically from the graft duodenum (e.g., duodenal ulceration or perforation, CMV infection)
      iii. Symptoms: abdominal pain, distention, fever, vomiting, decreased urine output, peritonitis, improvement after Foley catheter placement. Differential diagnosis must include early ureteral anastomotic leak of a simultaneously transplanted kidney (SPK)
      iv. Diagnosis
         (a) Low-pressure cystography
         (b) CT with retrograde bladder contrast (most accurate)
      v. Treatment
         (a) Early leaks: prolonged bladder decompression using Foley catheterization, percutaneous drainage of all intra-abdominal fluid collections

(b) Infected leaks with peritonitis: relaparotomy and direct leak repair or transplant pancreatectomy
(c) Late leaks: usually require conversion from bladder to enteric drainage, irrespective of etiology

5. Graft pancreatitis
   a. Prolonged posttransplant hyperamylasemia observed in up to 35% of all pancreas transplant recipients
   b. Risk factors: donor quality (e.g., obesity, age, excessive inotropic requirements), prolonged preservation time (ischemia–reperfusion pancreatitis), pancreatic duct outflow impairment, bladder drainage ("reflux pancreatitis")
   c. Complications: (peri-)pancreatic abscess, pancreatic necrosis (sterile and infected), pancreatic fistula, pseudocyst
   d. Symptoms: abdominal pain, graft tenderness, nausea, vomiting, ileus. Serum amylase and lipase levels may be elevated but correlate poorly with severity of pancreatitis. Endocrine secretory capacity often is only mildly impaired, even with severe pancreatitis
   e. Diagnostic studies: CT with appropriately timed IV contrast bolus to assess pancreatic parenchymal viability and need for debridement of pancreatic necrosis.
   f. Treatment
      i. Moderate and severe pancreatitis: nasogastric tube, bowel rest, total parenteral nutrition. Relaparotomy with debridement of pancreatic necrosis as indicated (particularly in recipients with concomitant peripancreatic infection and pancreatic abscess). No definitive data available on the utility of the somatostatin analogue octreotide for prevention and treatment of established pancreatitis.
      ii. Reflux pancreatitis in bladder-drained recipients: insertion of a Foley catheter not only is diagnostic but also constitutes effective treatment. Repetitive episodes of reflux pancreatitis usually require conversion from bladder to enteric drainage.
      iii. Mechanical pancreatic duct obstruction: relaparotomy to address underlying surgical-technical problem.
6. Hematuria (bladder-drained recipients)
   a. Early postoperative hematuria: usually anastomotic and self-limited. Severe cases must be treated by continuous bladder irrigation and normalization of coagulation parameters.
   b. Late hematuria: frequently associated with duodenal pathology (e.g., CMV infection). Cystoscopy and graft duodenal segment biopsy may be required. Depending on pathology, conversion to enteric drainage and antiviral treatment may be necessary.

B. Medical complications
1. Rejection
   a. Acute rejection
      i. Symptoms may include: hyperamylasemia, fever, graft tenderness, decreasing urinary amylase; serum creatinine elevation in recipients of a simultaneously transplanted kidney (SPK). Hyperglycemia is a late symptom, usually indicative of an advanced rejection process with irreversible graft injury
      ii. Diagnosis confirmation: percutaneous imaging-guided graft biopsy (gold standard)
      iii. Treatment
         (a) High-dose IV steroids
         (b) Anti–T-cell therapy
   b. Chronic rejection
      i. Associated with graft fibrosis and graft vasculopathy; irreversible

   ii. Symptoms: decreasing glucose tolerance, hyperglycemia, increasing HbAlc levels; decreasing or absent urinary amylase (bladder-drained grafts)
   iii. Treatment
      (a) Symptomatic: oral antidiabetic agents, return to exogenous insulin therapy
      (b) Pancreas retransplantation
      (c) Graft pancreatectomy usually not necessary
2. Acute perioperative myocardial ischemia: diagnosed on postoperative ECG and by elevated troponin and creatine kinase-myocardial-band (CK-MB) levels. Treatment: as in any nontransplant patient
3. Metabolic complications
   a. Hyperkalemia (in SPK recipients) can occur with delayed kidney graft function and may require IV calcium chloride, insulin and dextrose, and bicarbonate. Potassium excretion can be augmented by IV loop diuretics; if diuresis cannot be induced, oral sodium polystyrene sulfonate (Kayexalate) and dialysis may become necessary
   b. Hypokalemia, hypocalcemia, hypophosphatemia, and hypomagnesemia all can occur as the consequence of large-volume diuresis of a simultaneous kidney graft (SPK). Monitor at least every 12 hours; substitute electrolytes as indicated
   c. Hyperglycemia may reflect transient delayed graft function and may require temporary exogenous insulin
4. Infectious complications: Most early posttransplant infections are bacterial or fungal. Viral and parasitic infections begin to emerge after 6 weeks post-transplant
5. Neurologic complications
   a. Seizures: overall rare; rule out electrolyte abnormalities, acute perioperative cerebrovascular event, drug side effects (e.g., muromonab-CD3 [Orthoclone OKT3], tacrolimus), central nervous system infection (may require lumbar puncture).
   b. Acute cerebrovascular events: must be considered in all patients with new onset of seizures or otherwise unexplained postoperatively altered level of consciousness or new onset of other neurologic symptoms.
6. Immunosuppressive drug side effects
   a. Hematologic: leukopenia or thrombocytopenia (e.g., secondary to anti–T-cell therapy with antithymocyte globulin, alemtuzumab; mycophenolate mofetil, sirolimus). Adjust or hold drug doses as necessary.
   b. Renal acute nephrotoxicity (calcineurin inhibitors [cyclosporine, tacrolimus]).
   c. Neurologic: seizures, tremor, peripheral neuropathic symptoms (calcineurin inhibitors), aseptic meningitis and seizures (Orthoclone OKT3).
   d. Pulmonary: pulmonary edema (cytokine release syndrome associated with polyclonal or monoclonal anti–T-cell therapy), interstitial pulmonary fibrosis (sirolimus).
   e. Endocrine: hyperglycemia (tacrolimus, steroids).
   f. Metabolic: hyperlipidemia associated with steroids, cyclosporine, tacrolimus, and sirolimus.
7. Posttransplant malignancies: posttransplant lymphoproliferative disease; increased incidence of skin cancers.

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142 CRITICAL CARE OF LIVER TRANSPLANT RECIPIENTS

Mark J. Hill and Ty B. Dunn

I. GENERAL PRINCIPLES. Liver transplantation has become the treatment of choice for patients with acute and chronic end-stage liver disease, selected liver tumors, and some liver-based metabolic disorders. Depending on the patient's condition and organ availability, options include whole organ deceased donor, split liver deceased donor, and living donor (partial liver) transplantation. Survival rates after liver transplantation currently exceed 85% at 1 year and 70% at 5 years.

II. PRETRANSPLANT EVALUATION

A. Chronic liver disease/cirrhosis

1. Most common diagnoses in patients who have undergone transplantation for chronic liver disease: hepatitis B and C, alcoholic liver disease, hepatocellular carcinoma, acute liver failure, primary sclerosing cholangitis (PSC), and primary biliary cirrhosis (PBC).

2. Signs of advanced and decompensated chronic liver disease include hepatic encephalopathy, refractory ascites and hepatohydrothorax, hepatorenal syndrome, hepatopulmonary syndrome, recurrent and refractory variceal bleeding, recurrent infections (e.g., spontaneous bacterial peritonitis), intractable pruritus, and significant malnutrition (weight loss, muscle wasting).

3. Medical comorbidities must be identified and optimized before transplant.

4. Psychiatric, chemical dependency, and compliance issues must be identified and addressed.

5. Patients with hepatic malignancy require additional imaging to rule out extrahepatic spread.

6. Absolute contraindications to transplantation include active extrahepatic infection, extrahepatic malignancy, severe pulmonary hypertension (mean pulmonary artery pressure [PAP] >45 mm Hg), and advanced cardiopulmonary disease.

B. Fulminant hepatic failure (FHF)

1. Defined as severe acute liver injury with onset of encephalopathy within 2 weeks of onset of jaundice. Accounts for approximately 5% of all liver transplants in the United States.

a. Most common etiology: acetaminophen toxicity (approximately 85%).

b. Other etiologies include infections (hepatitis A, B, E), metabolic disorders (e.g., Wilson's disease), autoimmune hepatitis, drug toxicity, and exposure to exogenous toxins.

2. FHF patients may decompensate quickly and require early referral to a transplant center.

a. Initial presentation: can include severe hepatic dysfunction, marked coagulopathy, rapid deterioration of mental status, serious metabolic derangements, acute renal failure

b. Poor prognostic indicators for spontaneous recovery from FHF: include factor V level <30%, pH <7.3, international normalized ratio (INR)

>6.5, stage 3 or 4 encephalopathy, lack of response to medical therapy within 24 to 48 hours

c. Monitoring and treatment of cerebral edema
   i. Consider intracranial pressure (ICP) monitoring.
   ii. Mannitol, hyperventilation, and thiopental have been used to lower ICP and maintain adequate cerebral perfusion pressure >60 mm Hg (prevention of serious irreversible neurologic complications that would constitute a contraindication to liver transplantation).

III. INTRAOPERATIVE CARE

A. Venous and arterial monitoring catheters and large volume infusion lines are placed in the operating room and can be a source of immediate morbidity (pneumo- or hemothorax, pericardial tamponade, arterial pseudoaneurysm, air embolism).

B. The transplant operation is divided into three phases:
   1. Preanhepatic—mobilization of the diseased liver in preparation for its removal
   2. Anhepatic—characterized by progressive coagulopathy and decreased venous return to the heart secondary to clamping of the inferior vena cava and portal vein
      a. Venovenous and/or portal-venous bypass may be used during this phase to avoid significant hemodynamic changes.
      b. After the native liver is removed, the donor liver is placed in an orthotopic position and vascular anastomoses are sewn.
      c. Hepatic venous drainage: caval replacement, side-to-side cavoplasty (piggyback technique), direct hepatic vein-to-recipient cava anastomosis (partial liver grafts).
      d. Biliary reconstruction: duct–duct anastomosis or hepaticojejunostomy.
   3. Postanhepatic—begins at time of reperfusion
      a. Reperfusion can lead to hypotension and arrhythmias.
      b. Hemodynamic changes may result from acidosis, electrolyte abnormalities, air embolus, or volume overload.
      c. Close monitoring, appropriate volume resuscitation, and electrolyte management are critical.

IV. POSTPERATIVE CARE

A. Immediate postoperative phase
   1. Postoperative course depends largely on the patient's preoperative status and the development of any complications. Initial posttransplant care includes continuous hemodynamic and respiratory monitoring. Mechanical ventilation is often required for the first 6 to 12 hours; some centers have implemented rapid extubation pathways, particularly for recipients with well compensated disease. The care of all patients involves:
      a. Stabilization and recovery of the major organ systems
      b. Monitoring for evidence of improving graft function: improving mental status and coagulation profile, resolution of hypoglycemia, clearance of serum lactate, and decreasing transaminases and bilirubin (48 to 72 hours)
      c. Provision of adequate immunosuppression
      d. Common pitfalls to avoid include: oversedation with benzodiazepines and narcotics, unaddressed hypotension (systolic blood pressure [SBP] <100 mm Hg) which may contribute to renal dysfunction and graft thrombosis, and too rapid correction of preexisting hyponatremia which may lead to demyelinating syndromes

e. Vigilant surveillance and management of early complications (see subsequent text)

B. Surgical issues
1. Hemorrhage
a. Postoperative bleeding common; can be exacerbated by coagulopathy, fibrinolysis, thrombocytopenia, and platelet dysfunction.
b. Signs of ongoing blood loss: hypotension, tachycardia, decreasing cardiac filling pressures, falling hemoglobin and increasing surgical drain output.
c. Surgical exploration is indicated if bleeding persists despite correction of coagulation deficiencies.
2. Vascular complications
a. Overall incidence: 8% to 12%.
b. Thrombosis is the most common early event; stenosis and pseudoaneurysm formation occur later.
c. Doppler ultrasound evaluation is the initial imaging study of choice.
d. Hepatic artery thrombosis (HAT):
i. Incidence: approximately 2% in adults and 10% in children.
ii. Detected early, up to 50% of grafts can be salvaged with urgent exploration, thrombectomy, or revision of the anastomosis.
iii. Approximately 50% of patients with HAT require retransplantation.
iv. Can also present less acutely with bile duct ischemia resulting in anastomotic bile leak or diffuse intrahepatic small duct strictures/bilomas.
e. Thrombosis of portal vein or hepatic veins, or stenosis of suprahepatic inferior vena cava anastomosis:
i. It is less common than HAT.
ii. It may be heralded by liver dysfunction, tense ascites, or variceal bleeding.
iii. Diagnosed early, operative thrombectomy, and revision of the anastomosis (e.g., for portal vein thrombosis) or endovascular stenting (e.g., for suprahepatic anastomotic caval stenosis) may be successful.
iv. In late portal vein thrombosis, liver function is frequently preserved because of collateral veins; retransplantation is then usually not necessary and attention is directed to treatment of portal hypertension.
3. Biliary complications
a. Incidence: 15% to 35%. Rate higher for partial graft recipients, largely due to cut surface leaks; may reach 60% in donation after cardiac death (DCD) graft recipients.
b. Bile leaks:
i. Typically occur early posttransplant
ii. Clinical features: fever, abdominal pain, leukocytosis, elevated bilirubin
iii. Diagnosis: computed tomography (CT) or ultrasound may demonstrate a fluid collection, but confirmation of active leak requires hepatoiminodiacetic acid (HIDA) scintigram or cholangiography
iv. Management: drainage and endoscopic stent placement; operative repair
c. Strictures:
i. Usually occur late posttransplant
ii. Generally anastomotic, likely related to local ischemia
iii. Clinical features: cholestasis, cholangitis
iv. Diagnosis: ultrasound, magnetic resonance cholangiopancreatography, cholangiography
v. Management: balloon dilatation and stent placement across the stricture; surgical revision reserved for endoscopic failures

vi. Diffuse ischemic-type intrahepatic biliary strictures (risk factors: long preservation time, DCD donor): frequently require retransplantation

4. Wound complications
   a. Infection, hematoma, and seroma (early posttransplant)
      i. Diagnosis: drainage, increasing pain, erythema, fluctuance.
      ii. Management: open wound, perform serial dressing changes, allow healing by secondary intention. If significant cellulitis or systemic symptoms present: administer intravenous (IV) antibiotics.
   b. Incisional hernias (later posttransplant)
      i. Associated with malnutrition, attenuated fascia, and degree of immunosuppression
      ii. Often require surgical repair, particularly if symptomatic
5. Primary nonfunction (PNF)
   a. Transplanted graft is incapable of performing its vital synthetic and metabolic functions; the recipient is retransplanted or dies within the first week.
   b. Incidence: approximately 3% to 5% in the current era.
   c. Donor risk factors: include donor age older than 50, macrosteatosis >30%, donor intensive care unit (ICU) stay >3 days, cold ischemia time >18 hours, and split liver grafts.
   d. Diagnosis: by exclusion. Must rule out HAT, accelerated acute rejection, and severe infection.
   e. Treatment options: IV prostaglandin E_1 (not supported by compelling evidence); early listing for retransplantation (only available definitive treatment).

B. Nonsurgical issues
1. Neurologic: postoperative neurologic changes are often related to degree of preoperative encephalopathy, medication side effects, metabolic derangements, or a poorly functioning graft.
   a. Clinical findings: persistently decreased level of consciousness, seizures, and focal neurologic deficits.
   b. CT or magnetic resonance imaging (MRI) may be required to rule out specific diagnoses: ischemic encephalopathy, central pontine myelinolysis, intracranial hemorrhage, or posterior reversible encephalopathy syndrome (PRES).
2. Cardiovascular: hyperdynamic state characterized by high cardiac output and low systemic vascular resistance frequently observed in liver transplant recipients.
   a. Likely related to alterations in nitric oxide (NO) metabolism; generally improves over time after transplant.
   b. If hemodynamic support is required, α-agonists may help in restoring vascular tone.
3. Pulmonary: dysfunction can be preexisting or *de novo*.
   a. Atelectasis: may result from hepatohydrothorax or mucus plugs. Treatment aimed at underlying cause(s).
   b. Pulmonary edema and pleural effusions: may be exacerbated by hypoalbuminemia. Treatment: careful fluid administration and judicious use of diuretics.
   c. Hepatopulmonary syndrome—associated with hypoxia, intrapulmonary shunts, and often normal pulmonary artery pressures; typically improves after transplantation.
   d. Portopulmonary hypertension—pulmonary hypertension that arises in the setting of severe liver disease. Distinct from hepatopulmonary syndrome and may be a contraindication to transplant if severe. Vasodilators may be necessary to prevent right ventricular overload and subsequent hepatic congestion and graft dysfunction.

e. Acute respiratory distress syndrome (ARDS)
   i. Low incidence, but high mortality
   ii. Commonly seen in association with sepsis or high transfusion requirements (transfusion related acute lung injury [TRALI])
   iii. Protective ventilation strategy to prevent barotrauma may reduce mortality
f. Respiratory infections
   i. Nosocomial and ventilator-associated pneumonias caused by typical microorganisms in the early postoperative phase.
   ii. Opportunistic organisms, resistant bacteria, and fungal infections predominate later in the course, but also may occur after a long preoperative ICU stay or during periods of increased immunosuppression.

4. Renal: dysfunction common in liver recipients and associated with increased perioperative mortality. Causes of renal failure:
   a. Pretransplant: hepatorenal syndrome, acute tubular necrosis, and medical comorbidity (diabetes)
   b. Posttransplant: hypovolemia, ischemic acute tubular necrosis (early); drug nephrotoxicity due to calcineurin inhibitors (early and late)
5. Immunosuppression complications: include posttransplant diabetes, hyperlipidemia, opportunistic viral and fungal infections, increased incidence of squamous and basal cell skin cancers, and posttransplant lymphoproliferative disease (PTLD).
6. Recurrence of primary liver disease may require treatment and can significantly impact graft and patient survival.
   a. Hepatitis B: highly effective peri- and posttransplant prophylactic protocols based on hepatitis B immunoglobulin (Ig) and/or nucleoside analogs (e.g., lamivudine, adefovir, entecavir) have significantly lowered recurrence rates.
   b. Hepatitis C: approximately 25% to 30% recurrent cirrhosis at 5 years posttransplant; well tolerated routine pharmacoprophylaxis not available; treatment regimen may include interferon and ribavirin, but is often poorly tolerated by the immunosuppressed recipients.
   c. Autoimmune liver diseases (including autoimmune hepatitis, PBC, PSC): low rates of clinically significant recurrence; potential, but unproven benefit of long-term posttransplant maintenance steroids.

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143 CRITICAL CARE OF HEART AND LUNG TRANSPLANT RECIPIENTS

Irene April Kim, Nathan William Skelley, and David D. Yuh

I. CARDIAC TRANSPLANT RECIPIENTS

A. General principles

1. Objective. The primary initial critical care management objective is to optimize cardiopulmonary function with inotropic support, afterload reduction, and judicious fluid management.

2. Monitoring:

a. Arterial and central venous monitoring lines and pulse oximetry. Pulmonary arterial catheters are frequently helpful early postoperatively to aid in maximizing cardiac output with inotropic support, intravenous (IV) fluids, and vasodilators and are essential when the recipient has known pulmonary hypertension or in cases of donor right ventricular dysfunction.

b. Foley bladder catheter with temperature probe for urine output and core temperature.

c. Temporary epicardial pacing wires placed intraoperatively are routinely connected to a backup setting at 60 beats per minute (bpm) for patients with adequate intrinsic cardiac graft rhythm.

d. Mediastinal and pleural drains are placed to 20 cm of underwater seal suction to monitor postoperative thoracic hemorrhage.

B. Pathophysiology

1. Cardiac allograft denervation

a. Autonomic regulation through antagonistic sympathetic and parasympathetic mechanisms is interrupted with transection of these pathways during allograft procurement.

i. Without this autonomic input, the sinoatrial node of the allograft fires at an increased intrinsic resting rate of 90 to 110 bpm.

ii. Denervation also affects therapeutic interventions mediated by autonomic mechanisms. For example, carotid sinus massage, Valsalva maneuvers, and atropine no longer affect sinoatrial node firing or atrioventricular node conduction.

b. The allograft relies on adrenergic mechanisms (chronotropic and inotropic, primarily endogenous catecholamine production) for its functional regulation. The allograft physiologic response to stress (e.g., hypovolemia, hypoxia, anemia) is delayed until circulating catecholamines can exert their positive chronotropic effects.

2. Early allograft failure

a. Early cardiac allograft dysfunction accounts for up to 25% of perioperative deaths. The most common etiologies include pulmonary hypertension, myocardial injury due to prolonged ischemia or inadequate preservation, and acute rejection.

b. Initial depletion of myocardial catecholamine stores resulting from donor inotropic support frequently triggers need for early posttransplant inotropic allograft support.

c. Right ventricular failure. Early right ventricular failure is almost always associated with moderate to severe pulmonary hypertension which stems

from chronic left ventricular failure. This is a leading cause of early mortality.

i. It manifests as a hypokinetic, dilated right ventricular cavity and left ventricular underfilling on echocardiography and elevated central venous pressures (CVP) (15 to 25 mm Hg) with low cardiac outputs.

ii. Initial management employs pulmonary vasodilators, including inhaled nitric oxide, nitroglycerin, and milrinone. Pulmonary hypertension refractory to these vasodilators often responds to prostaglandin E1 (PGE1).

iii. If refractory to these measures, temporary right ventricular assist device (RVAD) support may be implemented. The Abiomed BVS 5000 (Abiomed; Danvers, MA) is a frequently used device in this setting.

d. Left ventricular failure. Left ventricular failure is less frequently encountered than right ventricular failure.

i. It manifests as a hypokinetic, dilated left ventricular cavity on echocardiography and elevated left ventricular end diastolic pressures (LVEDP) with low cardiac output and systemic hypotension.

ii. Primary treatment centers on IV inotropic support (i.e., epinephrine, dobutamine, dopamine, milrinone), afterload reduction (i.e., nipride, milrinone), and preload management, avoiding overfluid resuscitation.

iii. Left ventricular failure refractory to pharmacologic support may require a temporary intra-aortic balloon pump (IABP) or a left ventricular assist device (LVAD).

3. Dysrhythmias

a. Bradycardia. Sinus or junctional bradycardia in >50% of heart recipients. Primary risk factors for sinus node dysfunction: prolonged preservation, mechanical trauma during implantation. Most bradyarrhythmias resolve over 1 to 2 weeks; recovery may be prolonged in recipients receiving amiodarone preoperatively.

i. Because cardiac output is primarily rate dependent after transplantation, the heart rate should be maintained between 90 and 110 bpm with parenteral inotropic agents or temporary atrial (DOO) or atrioventricular (DDD) epicardial pacing for the first several days.

ii. Isoproterenol (Isuprel) is an effective chronotrope.

iii. Thereafter, the allograft is permitted to contract at intrinsic rates between 70 and 90 bpm.

iv. Theophylline may help to achieve adequate heart rates during this early transitional period.

v. In rare cases of persistent bradycardia, permanent pacemakers may be employed.

b. Atrial fibrillation. Atrial fibrillation or flutter is treated with digoxin at higher doses than used with innervated hearts. Such arrhythmias may indicate acute allograft rejection.

c. Ventricular arrhythmias. Ventricular arrhythmias, primarily premature ventricular contractions (PVCs) and nonsustained ventricular tachycardia have been reported in up to 60% of recipients. In these cases, underlying etiologies should be aggressively discerned (e.g., acute rejection, electrolyte disturbances, acidosis, etc.).

4. Coagulopathy

a. Heart recipients are frequently coagulopathic early postoperatively. Predisposing factors include preoperative warfarin therapy, cardiopulmonary bypass, hepatic failure, and chronic renal insufficiency.

b. Immediately postoperatively, check prothrombin time (PT)/partial thromboplastin time (PTT), platelet count, and fibrinogen levels.

Therapy as indicated with fresh frozen plasma (FFP), platelets, cryoprecipitate, and/or protamine.

C. Management issues

1. Inotropic and fluid management
   a. Preload optimization. IV fluids (crystalloids or colloids) should be judiciously administered while continuously monitoring for adequate systemic perfusion.
      i. Clinical parameters include palpable distal pulses, warm extremities, adequate urine output (>0.5 mL/kg/hour) without diuretics, normal acid–base balance, and cardiac index >2.0 L/minute/m^2.
      ii. A CVP of 8 to 12 mm Hg and/or pulmonary capillary wedge pressure of 15 to 20 mm Hg in the setting of systemic vascular resistance between 1,000 to 1,400 dynes/second/cm^5 are indicative of adequate fluid resuscitation.
   b. Inotropic support. If the cardiac index remains below 2.0 L/minute/m^2 with 1 or more β-adrenergic agents in the presence of adequate preload. The phosphodiesterase inhibitor milrinone can dramatically improve myocardial function, particularly for the right ventricle and in recipients with high systemic afterload or pulmonary hypertension.
   c. Afterload management. Mean arterial pressures in excess of 80 mm Hg should be treated to avoid excessive ventricular wall stress.
      i. Early postoperatively, IV sodium nitroprusside or nitroglycerin is administered. Nitroglycerin is associated with less intrapulmonary shunting due to relative preservation of the pulmonary hypoxic vasoconstrictor reflex.
      ii. Afterload reduction should be titrated to achieve mean arterial pressures between 65 and 80 mm Hg and/or a calculated systemic vascular resistance between 1,000 and 1,400 dynes/second/cm^5.
      iii. If hypertension persists, an oral antihypertensive can be added to permit weaning of parenteral agents. β-Blockers are generally avoided early postoperatively.
      iv. Transient vasodilation with systemic hypotension, frequently seen early after cardiopulmonary bypass in patients previously taking angiotensin-converting enzyme inhibitors, is usually effectively managed with inotropes containing an α-adrenergic component, such as epinephrine or norepinephrine.
2. Respiratory management. The respiratory management of the cardiac transplant recipient follows the same principles used for the following routine cardiac surgery.
   a. Initial ventilator parameters on arrival in the intensive care unit (ICU): tidal volume of 10 mL/kg, ventilatory rate of 10 breaths/minute, positive end-expiratory pressure (PEEP) of 5 cm H_2O, and fraction of inspired oxygen (F_{IO_2}) of 1.0.
   b. Goals are to reduce the F_{IO_2} to 0.4, maintain oxygen saturation >90%, and sustain an arterial oxygen tension (Pa_{O_2}) >70 mm Hg.
   c. Ventilatory rate and tidal volume are adjusted to achieve partial arterial pressure (Pa_{CO_2}) between 30 and 40 mm Hg and normal pH (7.35 to 7.45).
3. Electrolyte balance and renal function:
   a. Management of fluid and electrolyte homeostasis of the transplant recipient follows the same principles used after routine cardiac surgery.
   b. Serum electrolytes are checked frequently. Maintaining normal K^+, Mg^{2+}, and Ca^{2+} levels is particularly important in reducing the frequency of arrhythmias.
   c. Serum glucose is monitored every 6 hours. Hyperglycemia is commonly observed, particularly in the first 24 to 48 hours after surgery due to

physiologic stress, inotropic support, and glucocorticoid administration. Insulin (subcutaneous or continuous IV infusion) is titrated to maintain serum glucose levels between 100 and 150 mg/dL.

- **d.** A daily fluid restriction of 2,000 mL is maintained for the first 3 to 4 days, depending on the recipient's preoperative fluid status and postoperative renal function.
- **e.** On initiation of immunosuppressant therapies, particularly cyclosporine, serum creatinine is followed closely to monitor for early nephrotoxicity.
- **f.** Diuresis with furosemide is usually initiated 24 to 48 hours postoperatively and continued to eventually achieve euvolemia, often indicated by a return to preoperative body weight.

4. Perioperative infection prophylaxis:

- **a.** First-generation cephalosporins (e.g., Kefzol, Ancef) or vancomycin for patients with β-lactam allergy, is administered 30 minutes before anesthetic induction and continued for 48 hours postoperatively.
- **b.** Routine strict isolation is no longer employed. Hand washing, gloves, and gowns are used to avoid infectious cross-transmission.
- **c.** Trimethoprim–sulfamethoxazole (TMP/SMX), or aerosolized pentamidine if TMP/SMX is not tolerated, is used as prophylaxis against *Pneumocystis jiroveci* pneumonia, *Toxoplasma gondii, Listeria, Legionella,* and possibly *Nocardia* infections.
- **d.** Nystatin or clotrimazole is usually used as prophylaxis for mucocutaneous candidiasis. Fluconazole is indicated for candidiasis refractory to these topical antifungal agents or involving the esophagus.
- **e.** Routine low-dose acyclovir to reduce frequency and severity of herpes simplex and varicella-zoster infections.
- **f.** Recipients with a positive purified protein derivative (PPD) skin test should be considered for isoniazid (rifampin) prophylaxis.
- **g.** Cytomegalovirus (CMV) is the most common causative pathogen in cardiac transplant recipients and is thought to play a role in chronic allograft rejection. Routine prophylaxis with IV ganciclovir for 1 to 2 weeks followed by oral maintenance dosing for 3 months is recommended, particularly for a CMV seronegative recipient/seropositive donor combination.
- **h.** *Aspergillus* infections in transplant recipients; air filtration is beneficial. High-risk patients, including those with isolated *Aspergillus* species in respiratory tract cultures, may additionally benefit from itraconazole (400 mg daily administered orally from day 5 after transplantation for 3 to 6 months).

5. Immunosuppression

- **a.** The primary objectives of immunosuppressive therapy include:
  - **i.** The selective modulation of the immune response to prevent allograft rejection
  - **ii.** Maintaining immunocompetence to prevent infection and neoplasia
  - **iii.** Minimizing toxicity associated with immunosuppressive agents
- **b.** The choice and combinations of immunosuppressive agents, doses, and schedules vary significantly among transplantation centers. Data from the 2007 Registry of the International Society for Heart and Lung Transplantation suggests that there is no consensus about immunosuppression therapy regimens. Most centers employ triple immunosuppressive therapy consisting of cyclosporine or tacrolimus, corticosteroids, and azathioprine or mycophenolate mofetil. Tacrolimus produces an effect comparable to cyclosporine in terms of average number of rejection episodes in the first year. Tacrolimus has also been associated with lower nephrotoxicity, hypertension, and hirsutism. An example of such a regimen is outlined in Table 143-1. Such multidrug regimens

TABLE 143-1 Immunosuppressive Regimen for Heart Transplantation at the Johns Hopkins Hospital

Preoperative preparation
Cyclosporine: 4–10 mg/kg PO (dosage based on serum creatinine)
Intraoperative management
Methylprednisolone: 500 mg IV (after administration of protamine)
Immediate postoperative therapy
Methylprednisolone: 125 mg/kg IV for three doses
Prednisone: 1 mg/kg PO qd tapered to 0.4 mg/kg by 2 wk
Cyclosporine: 0.5 mg/kg/d IV until taking PO, then 5–10 mg/kg/d PO
Postoperative maintenance therapy
Prednisone: 0.2 mg/kg PO qd
Mycophenolate mofetil: 1 g PO/IV bid
Cyclosporine: 5 mg/kg PO qd (dose adjusted to maintain serum levels between 200 and 350 ng/mL)[a]

[a] Cyclo Trac SP^{125} I RIA Kit, INCSTAR, Stillwater, MN, USA.
(Reproduced with permission from Bethea BT, Yuh DD, Conte JV, Baumgartner WA. Heart transplantation. In: Cohn LM, Edmunds LH Jr., eds. *Cardiac surgery in the adult*, 2nd ed. New York: McGraw-Hill, 2004; 1427–1459.)

are designed to exploit synergism between the different mechanisms of action, permitting lower doses of each component and reduced toxicities.

II. HEART-LUNG AND LUNG TRANSPLANT RECIPIENTS

A. General principles

1. Objectives

a. Early postoperative care is based on judicious fluid and ventilatory management.

b. The primary objectives during this period are to maintain adequate perfusion and gas exchange while minimizing IV fluids, cardiac work, and barotrauma.

2. Monitoring

a. Arterial and central venous monitoring lines and pulse oximetry.

b. Pulmonary arterial catheters are helpful in the early postoperative period in maximizing cardiac output with inotropic support, IV fluids, and vasodilators and are essential when the recipient has known pulmonary hypertension and donor right ventricular dysfunction.

B. Pathophysiology

1. Lung allograft denervation

a. Denervation of the lungs diminishes cough reflex and impairs mucociliary clearance. Therefore, lung recipients require aggressive postoperative pulmonary toilet.

b. Early pulmonary allograft function is impacted by ischemia, reperfusion injury, and disrupted pulmonary lymphatics; this leads to increased vascular permeability, interstitial edema, and elevated arterial-alveolar gradients.

2. Early allograft failure

a. Cardiac allograft dysfunction

i. As in cardiac transplant recipients, early cardiac dysfunction may develop in heart-lung recipients due to prolonged ischemia, inadequate preservation, or catecholamine depletion.

ii. Hypovolemia, tamponade, sepsis, and bradycardia may contribute to this early dysfunction and should be treated expediently if present.

Otherwise, management of early cardiac dysfunction in heart-lung transplant recipients is comparable to that of isolated cardiac transplant recipients.

b. Lung allograft dysfunction

i. Early lung graft dysfunction manifests as persistently marginal gas exchange (i.e., hypoxia, hypercarbia) and pulmonary hypertension in the absence of infection or rejection.

ii. Shortly after ICU admission, primary graft failure, occurring in <15%, is usually caused by ischemia-reperfusion injury and results in pulmonary capillary leak causing alveolar edema, impaired lung compliance, and elevated pulmonary vascular resistance.

(a) Particularly severe cases of pulmonary hypertension can lead to right ventricular failure.

(b) This syndrome resembles acute respiratory distress syndrome (ARDS) with a severe arterial-alveolar gradient (Pa_{O_2}:F_{IO_2} ratio <150 mm Hg), diffuse interstitial infiltrates on early postoperative chest radiographs, and diffuse alveolar damage on histology.

(c) It has been observed that the degree of pulmonary edema is inversely related to the quality of preservation although the development of severe ischemia-reperfusion injury is still largely unpredictable.

c. Early lung graft dysfunction is managed by increased F_{IO_2}, PEEP, sedation, neuromuscular blockade, and careful diuresis to maintain fluid balance and reduce pulmonary edema.

d. In cases of persistently severe graft dysfunction refractory to standard ventilatory and medical management, extracorporeal membrane oxygenation (ECMO) and inhaled nitric oxide may be used to stabilize gas exchange.

i. Nitric oxide acts to relax preconstricted pulmonary vascular smooth muscle and is justified in recipients with pulmonary infiltrates, poor oxygenation, and mild to moderate pulmonary hypertension early postoperatively.

ii. Redistribution of pulmonary flow with nitric oxide was shown to decrease the intrapulmonary shunt fraction after transplantation.

iii. Nitric oxide therapy should be initiated at 10 to 20 ppm for 12 to 24 hours. Toxicity is monitored by methemoglobin levels. Nitric oxide is rapidly inactivated by hemoglobin, producing methemoglobin, which can impair oxygen delivery at high levels.

iv. If oxygenation and pulmonary infiltrates improve, nitric oxide may be weaned over 6 to 12 hours to 5 ppm, after which a slower wean, even over several days, is initiated; more profound hemodynamic consequences of weaning from 5 ppm to 0 ppm than from 20 ppm to 5 ppm have often been observed. Right heart failure, manifested by a rise in CVP and fall in cardiac output, is monitored during nitric oxide weaning.

3. Dysrhythmias (see Section I)

C. Management issues

1. Inotropic and fluid management (see Section I)

2. Respiratory management

a. After ICU admission: anteroposterior chest radiograph; initial ventilator settings: F_{IO_2} of 50%, tidal volume of 10 to 15 mL/kg, assist-control rate of 10 to 14 breaths/minute, and PEEP of 3 to 5 cm H_2O. Initial tidal volumes and flow rates are adjusted to limit peak airway pressures to <40 cm H_2O, to minimize barotrauma and high airway pressures which may compromise bronchial mucosal blood flow.

b. Arterial blood gases 30 minutes after each ventilator setting change to achieve a Pao_2 >75 mm Hg on an FIo_2 of 0.4, a $Paco_2$ between 30 and 40 mm Hg, and a pH between 7.35 and 7.45.

c. Weaning to extubation is initiated after the patient is stable, awake, and alert. Generally, weaning is conducted through successive decrements in the intermittent mandatory ventilation (IMV) rate, followed by a sustained trail of continuous positive airway pressure (CPAP). Extubation is often possible within the first 24 hours' posttransplant.

d. Subsequent pulmonary management comprises diuresis, supplemental oxygen to maintain adequate oxygen saturations, bronchodilators, aggressive pulmonary toilet and incentive spirometry, and frequent interval chest radiographs.

i. Albuterol and ipratropium bromide (Atrovent) inhaled therapy is helpful in cases of bronchospasm in the native lung due to underlying disease and/or in the lung allograft clue to mild ischemia-reperfusion injury.

ii. Owing to pulmonary airway denervation, pulmonary toilet with frequent endotracheal suctioning is necessary to avoid mucous plug and atelectasis development. Care should be taken during deep suctioning to avoid unnecessary trauma to the tracheal or bronchial anastomoses.

3. Coagulopathy (see Section I)

4. Electrolyte and renal dysfunction (see Section I)

5. Perioperative infection prophylaxis (see Section I)

6. Immunosuppression (see Section I)

Suggested Reading

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144 CRITICAL CARE OF HEMATOPOIETIC CELL TRANSPLANT RECIPIENTS

Marco Mielcarek

I. GENERAL PRINCIPLES

A. Definition: Hematopoietic cell transplantation (HCT) is potentially curative treatment for malignant and nonmalignant diseases including leukemia, lymphoma, multiple myeloma, aplastic anemia, hemoglobinopathies, and congenital immune deficiencies. High-dose chemoradiation is typically used to eradicate the underlying disease and is followed by intravenous infusion of the stem cell graft. Among other cells, the graft contains the stem cells that reconstitute the ablated hematopoietic system. Immunosuppressive therapy is required after allogeneic HCT to prevent graft-versus-host disease (GVHD) and graft rejection.

B. Classification: The type of HCT used in an individual patient is a complex decision based on patient's age, diagnosis, donor availability and presence of comorbidities:

1. Stem cell source
- **a.** Bone marrow
- **b.** "Mobilized" peripheral blood: growth factors are frequently used alone (e.g., granulocyte-colony stimulating factor (G-CSF) or in combination with chemotherapy (in autologous HCT) for "mobilization" of hematopoietic stem cells, which are collected by blood leukapheresis
- **c.** Cord blood: collected from the umbilical cord after delivery

2. Donor type
- **a.** Autologous: using one's own stem cells
- **b.** Syngeneic: identical twin (no genetic disparity between donor and recipient)
- **c.** Allogeneic: donor with similar human leukocyte antigen (HLA) type
  - **i.** Sibling donor: statistical likelihood for a fully HLA-matched sibling is 25% per sibling.
  - **ii.** Unrelated donor: HLA-matched volunteer donor is identified through a database search.

3. Intensity of the preparative regimen
- **a.** Myeloablative: the preparative regimen ablates the hematopoietic system of the patients and leads to transient but profound myelosuppression with pancytopenia.
- **b.** Nonmyeloablative: preparative regimen has minimal early toxicity, is frequently outpatient based and mainly aimed at preventing graft rejection. Underlying disease is eliminated through ensuing immunologic graft-versus-tumor effects. Onset of typical post-HCT complications such as GVHD and infections is delayed.

C. Transplant statistics: estimated number of HCTs: 45,000 to 50,000/year worldwide (approximately two thirds autologous and one third allogeneic HCTs).

D. Risk factors for posttransplant complications: likelihood of developing transplant-related complications depends on age, intensity of the preparative regimen, type and stage of underlying disease, presence of comorbidities and HLA-disparity between donor and recipient. Allogeneic HCT recipients have

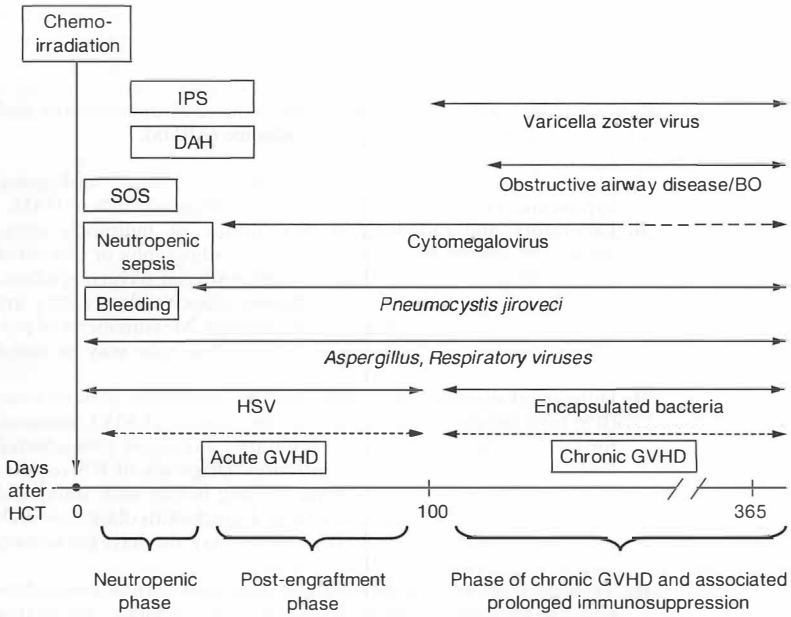

Figure 144-1. Complications after myeloablative allogeneic hematopoietic cell transplantation. IPS, idiopathic pneumonia syndrome; DAH, diffuse alveolar hemorrhage; SOS, sinusoidal obstruction syndrome; BO, bronchiolitis obliterans; HSV, herpes simplex virus; RSV, respiratory syncytial virus; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplant.

greater risk of transplant-related morbidity and mortality than autologous recipients.

E. Prognosis: highly variable and influenced by numerous mortality risk factors related to the transplant procedure and to recurrent malignancy after surviving the transplant.

II. TRANSPLANT-RELATED COMPLICATIONS

A. HCT-related morbidity and mortality can be categorized into four groups (Fig. 144-1).

1. Toxicity of the preparative regimen
2. Infection
3. Bleeding
4. GVHD

III. TOXICITY OF THE PREPARATIVE REGIMEN

A. General principles. Cytotoxic chemotherapy with or without total body irradiation (TBI) may compromise function of many organs. This toxicity occurs predominantly within the first 3 to 4 weeks of HCT and is considerably less severe after nonmyeloablative HCT.

1. Lung

a. Etiology/pathophysiology. Idiopathic pneumonia syndrome (IPS), a noninfectious inflammatory lung process that may be triggered by TBI and chemotherapeutic drugs (e.g., carmustine [BCNU] or busulfan); median onset: 2 to 3 weeks after HCT. Contributing factors include release

of inflammatory cytokines due to alloreactivity and/or sepsis; role of latent infections is controversial. Other common noninfectious pulmonary problems that may occur within 30 days posttransplant include diffuse alveolar hemorrhage (DAH), edema syndromes due to excessive fluid administration or cyclophosphamide-induced cardiomyopathy, and sepsis with adult respiratory distress syndrome (ARDS).

b. Diagnosis:

i. Clinical presentation: fever, nonproductive cough, tachypnea, hypoxemia. Hemoptysis is an infrequent symptom of IPS or DAH.

ii. Laboratory and radiologic studies: diffuse or multifocal intraalveolar or interstitial infiltrates on chest radiography or computed tomography (CT). An increased alveolar-arterial oxygen gradient, a new restrictive pattern or a diffusion capacity abnormality are evidence for abnormal pulmonary physiology. Measurements of pulmonary artery wedge pressure or echocardiography may be useful to rule out cardiogenic pulmonary edema.

iii. Differential diagnosis: it is paramount to distinguish noninfectious (IPS) from infectious causes (e.g., cytomegalovirus [CMV], bacterial, fungal) for diffuse pulmonary infiltrates. Localized parenchymal lung disease is usually due to infection. Diagnosis of IPS requires a negative bronchoalveolar lavage or lung biopsy with stains and cultures for bacteria, fungi, and viruses. Bronchiolitis obliterans (BO) can be related to chronic GVHD. Patients may also have pulmonary relapse of their underlying malignancy.

iv. Treatment: IPS treatment consists of supportive care and secondary infection prevention. Empiric broad spectrum antibiotics and trial of diuretics. Bleeding disorders should be corrected. Although there are no prospective trials to support the use of high-dose corticosteroids, a small percentage of IPS patients do respond to doses of 1 to 2 mg/kg/day. Patients with BO frequently respond to corticosteroid therapy (1 mg/kg/day).

v. Prognosis: mortality of diffuse IPS after myeloablative HCT is 50% to 70%. Approximately 6% of patients who require mechanical ventilation after HCT survive for 30 days after extubation and are discharged; half of these survivors live for >2 years. The presence of either hemodynamic instability or sustained hepatic and renal failure makes survival of ventilated patients with IPS extremely unlikely. Since improvements in supportive care may improve the prognosis, treatment decisions have to be individualized. Therefore, aggressive management, including mechanical ventilation, to identify and treat reversible causes of respiratory failure is a reasonable initial approach for most HCT recipients with diffuse or multifocal pulmonary infiltrates.

2. Gastrointestinal (GI) tract

a. Etiology/pathophysiology: oral mucositis, esophagitis/gastritis and diarrhea are commonly associated with chemoradiation and can be worsened by methotrexate given for GVHD prophylaxis. Mucositis places patients at a high risk for aspiration and facilitates translocation of intestinal bacteria and sepsis.

b. Diagnosis:

i. Clinical presentation: dysphagia, odynophagia, mucosal ulcerations and hemorrhage, oropharyngeal hypersecretion, anorexia, nausea, vomiting, diarrhea, dyspnea, signs of upper airway compromise.

ii. Laboratory and radiologic studies: usually noncontributory.

iii. Differential diagnosis: mucositis may be associated with infection (herpes simplex virus [HSV], CMV, varicella zoster virus [VZV]

or fungal) and GVHD. Anorexia, nausea, vomiting, and diarrhea persisting beyond 3 weeks after allogeneic HCT may be caused by GVHD and/or herpes virus infection, or medications.

c. Treatment. Supportive care, opioid analgesia, institution of parenteral nutrition. Severe oropharyngeal mucositis with impending airway compromise may require intubation for airway protection.

3. Liver

a. Etiology/pathophysiology: jaundice, hepatomegaly, and abnormal liver tests within the first 2 months of HCT may have many causes including toxicity from the preparative regimen. Total bilirubin >4 mg/dL, regardless of etiology, is a powerful predictor for transplant-related mortality. Sinusoidal obstruction syndrome (SOS), also referred to as veno-occlusive disease (VOD), occurs in up to 50% of myeloablated HCT recipients. Cyclophosphamide, TBI, and preexisting chronic liver disease are risk factors for SOS.

b. Diagnosis:

i. Clinical presentation: tender hepatomegaly, renal sodium retention with weight gain, and jaundice following the preparative regimen in the absence of other explanations for these signs and symptoms are suggestive of SOS.

ii. Laboratory and radiologic studies: total serum bilirubin sensitive, but nonspecific. Hepatomegaly, ascites and attenuated hepatic venous flow by ultrasound and venous duplex Doppler imaging are consistent with SOS; biliary dilatation or infiltrative lesions must be excluded. Measurement of the hepatic venous pressure gradient and biopsy may be indicated.

iii. Differential diagnosis: other causes of post-HCT jaundice seldom lead to renal sodium avidity, rapid weight gain, and hepatomegaly before the onset of jaundice. Combinations of illnesses that may mimic SOS are sepsis with renal insufficiency and cholestasis, cholestatic liver disease with hemolysis and congestive heart failure, and GVHD and sepsis syndrome. Hepatic VZV infection may occur in VZV-seropositive patients who are not on prophylactic acyclovir (transaminases typically >1,000 U/mL). Empiric acyclovir should be given until VZV-hepatitis has been ruled out.

c. Treatment. Ursodeoxycholic acid has reduced severity of post-HCT SOS in two randomized trials. As 70% to 85% of patients recover spontaneously, supportive management of sodium and water balance for symptomatic ascites or pulmonary compromise is important. Uncontrolled trials with defibrotide have been promising. Anticoagulation with heparin and thrombolytic therapy may be a consideration in patients with a high estimated mortality.

4. Heart

a. Etiology/pathophysiology: the major dose-limiting toxicity of high-dose cyclophosphamide (doses above 200 mg/kg), a component of many preparative regimens, is cardiac injury with hemorrhagic myocardial necrosis. Patients who did receive a cumulative dose of the anthracylin doxorubicin of >550 mg/m^2 are at increased risk for developing heart failure.

b. Diagnosis:

i. Clinical presentation: congestive heart failure occurring within a few days of receiving cyclophosphamide. Onset of anthracyclin-related cardiomyopathy may be delayed.

ii. Laboratory and radiologic studies: voltage loss on electrocardiogram (ECG); arrhythmia; echocardiogram shows signs of systolic dysfunction. Pericardial effusion/tamponade may be present.

iii. Differential diagnosis. Congestive heart failure from fluid overload, malignant effusion, and infectious perimyocarditis.

c. Treatment. Management of fluid and sodium balance, afterload reduction, inotropes.

5. Kidney

a. Etiology/pathophysiology: drugs that most commonly affect renal function in transplant patients are cyclosporine, tacrolimus, amphotericin, and aminoglycosides. Six percent to 10% of allogeneic HCT recipients develop a thrombotic microangiopathy (TM), which is the result of endothelial injury by chemoradiation, cyclosporine, or tacrolimus. Overall mortality of acute renal failure post-HCT requiring dialysis exceeds 80%.

b. Diagnosis:

i. Clinical presentation: patients with drug-related renal dysfunction are typically asymptomatic. Classical symptoms associated with thrombotic thrombocytopenic purpura (TTP) (thrombocytopenia, fragmentation hemolysis, neurologic abnormalities, and fever) may not be present in HCT patients with TM.

ii. Laboratory studies: serum creatinine elevation. Cyclosporine and amphothericin may lead to renal potassium and magnesium wasting. The hallmark of TM is red blood cell (RBC) fragmentation (schistocytosis) associated with increased RBC turnover (reticulocytosis; elevation of lactate dehydrogenase [LDH] and indirect bilirubin), without evidence for either immune-mediated hemolysis or disseminated intravascular coagulation (DIC).

iii. Differential diagnosis: liver disease (SOS) may cause renal dysfunction (hepatorenal syndrome) with increased sodium avidity. Consider also prerenal mechanisms (heart failure, hypotension, volume depletion), sepsis, and tumor lysis syndrome.

c. Treatment. Discontinuation of the likely offending agent; adjustment of cyclosporine/tacrolimus serum levels; adjustment of volume status. Efficacy of substituting tacrolimus for cyclosporine is controversial. In contrast to classic TTP, TM after HCT is usually not responsive to plasma exchange.

6. Central nervous system (CNS)

a. Etiology/pathophysiology: neurologic complications after HCT can have infectious, cerebrovascular, metabolic, toxic and immune-mediated causes. Their timing after HCT may aid with the differential diagnosis:

i. During or shortly after conditioning therapy: chemotherapeutic drugs such as high-dose busulfan and BCNU may cause encephalopathy and seizures (importance of prophylactic anticonvulsant treatment). CNS toxicity manifesting as coma has been reported with ifosfamide. High-dose cytarabine may cause cerebellar dysfunction, encephalopathy, and seizures.

ii. Pre-engraftment (during pancytopenia): intracranial hemorrhage is a frequently fatal complication in patients with refractory thrombocytopenia. Subdural hematomas have a more favorable prognosis. Encephalopathy is most often related to gram-negative sepsis, the use of sedative-hypnotic drugs, and hepatic dysfunction due to SOS. Bacterial meningitis is rare. Human herpes virus 6 (HHV-6) encephalitis may be typically encountered during the first 30 days after HCT.

iii. Postengraftment (during GVHD-related immunosuppression): post-HCT immunosuppression increases the risk of opportunistic infections. *Aspergillus* spp. account for 30% to 50% of CNS infections in autopsy series. Given the available prophylaxis with

trimethoprim–sulfamethoxazole and acyclovir, *Toxoplasma gondii*, HSV, and VZV encephalitis are rarely seen in HCT recipients. Cyclosporine causes more neurologic problems in HCT patients than any other drug (seizures, encephalopathy). Corticosteroids may be associated with psychosis, mania, or delirium.

b. Diagnosis:

i. Clinical presentation: focal symptoms are more suggestive of infectious or cerebrovascular etiologies; diffuse symptoms (delirium, coma) may have metabolic causes. CNS infections can present without fever.

ii. Laboratory and radiologic studies: a thorough workup should include magnetic resonance imaging (MRI) or CT, followed by lumbar puncture for CSF analysis (cultures, stains, and viral [HHV-6] polymerase chain reaction [PCR] studies) for suspected infection. Patients with cyclosporine neurotoxicity may have MRI changes, most often in the occipital lobe white matter.

c. Treatment: post-HCT CNS infections have a poor prognosis. Treatment of metabolic encephalopathy should be directed at the underlying problem; discontinue offending drugs. Cyclosporine neurotoxicity: discontinue cyclosporine temporarily, restart at a lower dose.

IV. INFECTION

A. General principles: infections are frequent after autologous and allogeneic HCT. Occurrence pattern determined by several factors including pretransplant history, intensity of the preparative regimen, regimen used for infection prevention, microbiological flora of the patient and the individual transplant unit, and degree of immunosuppression after transplant (GVHD activity). Recovery after HCT can be divided broadly into three phases with typical infection patterns.

1. Pre-engraftment (<30 days posttransplant): characterized by neutropenia and oral/GI mucosal injury. Bacterial and fungal infections most common. Hence, many transplant centers use a prophylactic antibiotic regimen. Viral infections most commonly caused by HSV. With indwelling central venous catheters, the risk for infections caused by gram-positive organisms (e.g., staphylococci and streptococci) increases. Fungal infections during this period may present with skin lesions (*Candida* spp.), sinus involvement (*Aspergillus* spp. and mucor), lung lesions (*Aspergillus* spp.), or hepatitis (*Candida* spp.).

a. Workup and treatment: fever should be treated immediately as a presumptive infection. In addition to careful history and physical examination, blood cultures for bacteria and fungi, urine culture, and a chest x-ray should be obtained. Antibiotics to treat gram-positive and gram-negative infections, including pseudomonas, should be started promptly (e.g., ceftazidime with or without an aminoglycoside). If fever persists for >48 hours or if the central line site is red and tender, additional coverage (e.g., vancomycin) for gram-positive infections should be added. If fever persists for 2 to 4 more days or a fungal infection is suspected clinically, empiric antifungal agents should be considered. *Clostridium difficile* colitis may manifest with diarrhea and can be treated with oral metronidazole.

2. Postengraftment (30 to 100 days' posttransplant). Characterized by skin and mucosal injury, and compromised cellular immunity related to GVHD and its treatment. Viral (CMV) and fungal (*Aspergillus* spp., *Pneumocystis jiroveci)* infections predominate. Gram-negative bacteremias related to GVHD-associated mucosal injury, and gram-positive infections due to indwelling catheters may occur. Other causes of fever of unknown origin

after engraftment include occult sinusitis, hepatosplenic candidiasis, and pulmonary or disseminated *Aspergillus* infection.

a. Workup and treatment: patients with pulmonary infiltrates should undergo bronchoscopy. Serial blood cultures and sinus CT may be indicated. CMV-reactivation and infection typically treated with ganciclovir (myelosuppressive). *P. jiroveci* pneumonia treated with trimethoprim–sulfamethoxazole, dapsone, or pentamidime. Removal of the central venous catheter may be required. *Aspergillus* infections are treated with mold-active triazoles (i.e., voriconazole) or an amphotericin B-derivative.

3. Late phase (>100 days' posttransplant). Patients with chronic GVHD have persistently decreased cellular immunity. They are highly susceptible to recurrent bacterial infections, especially from encapsulated bacteria, including *Streptococcus pneumoniae, Hemophilus influenzae* and *Neisseria meningitidis* (functional asplenia). Nonbacterial infections at this stage are commonly caused by VZV, CMV, *P. jiroveci,* and *Aspergillus* spp.

a. Workup and treatment: patients with chronic GVHD should receive prophylaxis with penicillin and trimethoprim–sulfamethoxazole. Immunoglobulin deficiency should be ruled out and treated. Late sinopulmonary infections can be successfully treated with antibiotics. Herpes zoster is treated with high-dose intravenous acyclovir.

V. BLEEDING

A. Etiology/pathophysiology: bleeding can occur as a result of thrombocytopenia or coagulopathy. Breakdown of mucosal barriers (regimen-related toxicity and/or GVHD) increases likelihood of hemorrhage. CNS hemorrhage can be rapidly fatal. Hemorrhagic cystitis can be caused by high-dose cyclophosphamide and BK-virus infection.

B. Diagnosis: depending on presentation, endoscopic evaluation (colonoscopy, esophagogastroduodenoscopy [EGD], bronchoscopy) or CNS imaging.

C. Treatment: platelet count $<10{,}000/mm^3$ increases the risk for spontaneous bleeding and should be treated prophylactically with platelet transfusion. The decision to transfuse platelets for platelet counts $>10{,}000/mm^3$ should be guided by the clinical situation. All transplant patients should receive either CMV-negative or leukocyte-reduced (leukocytes harbor CMV), and irradiated (to prevent transfusion-associated GVHD) blood products. DAH may manifest with pulmonary infiltrates and bleeding can be seen on bronchoscopy; treatment: high-dose corticosteroids (e.g., methylprednisolone 1 g/day for 3 days).

VI. GVHD

A. General principles: GVHD is a major cause of morbidity and mortality after allogeneic HCT.

B. Etiology/pathophysiology: the GVHD syndrome is caused by donor T cells that are activated by immunologically disparate HLA and non-HLA antigens in the recipient.

C. Diagnosis:

1. Clinical presentation: acute GVHD (occurring before posttransplant day 100) may involve the skin (erythematous rash), GI tract (nausea, vomiting, diarrhea) and liver (hyperbilirubinemia, transaminitis). Chronic GVHD (occurring after posttransplant day 100), typically, has a more insidious onset, and may involve the skin, eyes, joints, and liver; it is reminiscent of autoimmune diseases such as systemic sclerosis and obstructive lung disease (BO) may occur.

2. Laboratory and radiologic studies. Skin punch biopsy and GI endoscopy with biopsy confirm the diagnosis in the appropriate clinical setting.

Cholestatic jaundice is the hallmark of liver involvement and liver biopsy is rarely required. Pulmonary function test and lung biopsy in patients with presumed BO to rule out infectious etiologies.

3. Differential diagnosis. Drug rash, peptic ulceration, and viral or mycotic enteritis should be ruled out. In patients with liver function abnormalities, drug toxicity (e.g., cyclosporine), sepsis (cholangitis lenta), biliary sludge syndrome, viral infections (CMV, Epstein–Barr virus (EBV), hepatitis B) and concurrent hemolysis should be considered.

D. Treatment. Despite prophylaxis (e.g., cyclosporine plus methotrexate), 40% to 80% of allogeneic HCT recipients develop GVHD. Corticosteroids are standard first-line therapy (e.g., prednisone 1 to 2 mg/kg/day; slow taper after 1 to 2 weeks). Prolonged corticosteroid treatment increases susceptibility to infections. Steroid-refractory patients require second-line immunosuppressive therapy and usually have poor prognosis.

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XIV Rheumatologic and Immunologic Problems in the Intensive Care Unit

145 RHEUMATOLOGIC DISORDERS IN THE INTENSIVE CARE UNIT

Donough G. Howard

I. **OVERVIEW.** This chapter reviews the important rheumatic diseases most likely to be encountered in the intensive care unit (ICU). Brief descriptions and treatment options are discussed with a constant emphasis on the ongoing risk of infectious complications that may lead to critical illness.

II. **RHEUMATOID ARTHRITIS**

- **A. General principles.** A chronic inflammatory disorder affecting the synovial lining of joints, tendons, and bursae in addition to a large variety of extra-articular structures. The etiology of rheumatoid arthritis (RA) is unknown. Patients may require ICU admission because of disease complications or complications of therapy, typically infection.
- **B. Treatment.** Table 145-1 details current treatment with disease-modifying antirheumatic drugs (DMARDs). As a general rule immunosuppressive DMARDs should be withheld in critically ill patients.
- **C. System-specific considerations in RA**
  - **1.** Pulmonary
    - **a.** Pleural disease
      - **i.** Pleural inflammation/effusions occur frequently.
      - **ii.** May be asymptomatic or lead to large symptomatic effusions.

TABLE 145-1 Treatment of Rheumatoid Arthritis with Disease-Modifying Antirheumatic Drugs

	Dose/administration	Class	Adverse reactions	Special considerations
Methotrexate	7.5–25 mg q wk PO, SC/IM	Dihydrofolate reductase inhibitor	Hepatotoxicity, bone marrow suppression, interstitial lung disease, decreased resistance to infection	
Leflunomide (Arava)	10–20mg qd PO	Pyrimidine synthesis inhibitor	Diarrhea, alopecia, rash, hepatotoxicity, decreased resistance to infection, increases hepatotoxicity of other drugs	Metabolized through enterohepatic circulation with half-life of >90 d Urgent elimination requires treatment with cholestyramine
Etanercept (enbrel)	50 mg q wk SC in single or divided doses	TNF receptor blocker	Sepsis, reactivation of TB	Caution in CHF; avoid live vaccines; contraindicated in serious infections
Adalimumab (Humira)	40 mg q 2 wk SC	Monoclonal anti-TNF antibody	Sepsis, reactivation of TB	Caution in CHF; avoid live vaccines; contraindicated in serious infections
Infliximab	3–5 mg/kg q 4–8 wk IV infusion	Monoclonal anti-TNF antibody	Sepsis, reactivation of TB, infusion reactions	Caution in CHF; avoid live vaccines; contraindicated in serious infections
Rituximab (Rituxan)	1,000mg IV on d 1 and 15 repeated q 6–18 mo	Monoclonal anti-CD20 antibody	Sepsis, infusion reactions	Patients remain B-cell depleted and immunocompromised for months after treatment; rare cases of progressive multifocal leukoencephalopathy (PML) due to reactivation of JC virus has been reported; not used in combination with other biologic DMARDs
Abatacept (Orencia)	500–1,000 mg IV q 4 wk	Inhibits T cell activation	Sepsis, may exacerbate COPD	Risk of reactivation of TB not fully elucidated, reactivation of Hepatitis B reported; avoid live vaccines; not used in combination with other biologic DMARDs
Anakinra (Kineret)	100 mg qd SC	IL-1 receptor antagonist	Diarrhea, increased risk of infection	Avoid live vaccines; not used in combination with other biologic DMARDs

PO, per oral; mg, milligram; SC, subcutaneous; IM, intramuscular; TNF, tumor necrosis factor; TB, tuberculosis; CHF, congestive heart failure; IV, intravenous; COPD, chronic obstructive pulmonary disease; DMARDs, disease-modifying antirheumatic drugs; IL-1, interleukin 1.

iii. Effusions require aspiration to rule out infection or other causes.
iv. Effusions are exudative with low glucose levels.

b. Parenchymal lung involvement
i. Bronchiolitis obliterans with organizing pneumonia (BOOP) or cryptogenic organizing pneumonia (COP)
ii. Interstitial lung disease (ILD)
iii. Lung toxicity from medications, principally methotrexate-induced pneumonitis
iv. Infection due to immunocompromised state, including tuberculosis
v. Pulmonary rheumatoid nodules

c. Diagnosis
i. Presence of ground glass and reticular changes on high-resolution computed tomography (CT) scanning.
ii. Bronchoscopy and bronchoalveolar lavage (BAL) are useful to rule out opportunistic infection.
iii. Open lung biopsy or video-assisted thoracic surgery (VATS) is reserved for cases where there is diagnostic confusion or in patients who have failed to respond to initial treatment.

d. Treatment
i. BOOP and acute methotrexate toxicity tend to be steroid responsive and usually do not require other immunosuppressive agents.
ii. ILD treatment in RA is controversial. Corticosteroids and cyclophosphamide have been used in rapidly advancing disease.

2. Neurologic involvement
a. Spinal cord compression due to cervical vertebral instability is one of the most common neurologic sequelae of long-standing severe RA.
b. Synovitis damages the transverse ligament leading to subluxation of the odontoid peg of C2, compressing the spinal cord and brainstem. This area is particularly vulnerable during endotracheal intubation or endoscopy
c. Patients with long-standing RA should ideally be screened with flexion and extension imaging of the cervical spine before any intubation.
d. If instability is present or even suspected, endoscopic intubation following neck stabilization should be undertaken.

III. CRYSTAL ARTHROPATHY

A. Gout. Acute attacks represent an inflammatory reaction to the crystalline form of uric acid when it precipitates in joints and/or soft tissues. Attacks may involve one or more joints, typically the first metatarsophalangeal (MTP) joint, ankle, knee, or wrist.

1. Pathogenesis
a. Sudden fluxes in serum uric acid levels facilitate uric acid crystallization in joints.
b. Uric acid levels are sensitive to the use of intravenous (IV) fluids, dietary changes, and the use of a variety of medications.

2. General principles
a. Acute attacks lead to the sudden onset of severe pain and tenderness, with erythema and warmth over the affected joint, which can include nearly any joint.
b. Low-grade fever is common, especially if more than one joint is involved.

3. Diagnosis
a. Diagnosed by demonstrating the presence of intracellular monosodium urate crystals on polarized microscopy of synovial fluid.

TABLE 145-2 Treatment of Gout

Drug	Dosage	Adverse reaction	Special considerations
Colchicine	0.6 mg tid PO or 0.6 mg hourly for a total of ten doses	GI toxicity (nausea, diarrhea), bone marrow suppression (granulocytopenia)	Dosage needs to be adjusted for renal function; IV dosing is rarely used and is reserved for the experienced prescriber
Corticosteroids—Prednisone	20–40 mg qd PO for 2–3 d, then taper over 1 wk	Immune suppression hyperglycemia	PO route is usually not appropriate in patients in ICU
ACTH	40–80 units IM; may need to be repeated once or twice at 12-hourly intervals		Caution in anticoagulated patients
Intra-articular steroid	Doses varied depending on joint involved Methylprednisolone 15–80 mg Triamcinolone 10–40 mg	If high suspicion of joint infection, wait for Gram stain result	
NSAIDs	Indomethacin is most commonly used; start at maximum daily dose, reduce as symptoms subside and continue for 48 h after symptoms resolve	GI toxicity, renal toxicity, platelet dysfunction	Usually not appropriate for patients in the ICU

PO, per oral; mg, milligram; GI, gastrointestinal; IV, intravenous; IM, intramuscular; ICU, intensive care unit; ACTH, adrenocorticotrophic hormone; NSAIDs, nonsteroidal anti-inflammatory drugs.

b. Synovial fluid white blood cell (WBC) counts may vary from 5,000 to 80,000/mm^3.

4. Treatment (Table 145-2).

B. Pseudogout

1. General

a. Caused by the presence of intra-articular calcium pyrophosphate crystals

b. Typically affects knees or hands

c. Clinical appearance identical to that of gout

2. Diagnosis. Synovial fluid aspiration shows the presence of intracellular weakly positive birefringent rhomboid crystals. Plain radiographs may show chondrocalcinosis indicating chronic calcium pyrophosphate within the joint.

3. **Treatment**
   a. Identical to that for gout.
   b. Joint aspiration may be sufficient to resolve some cases.
   c. Colchicine is less effective compared to gout.

C. **Other crystal arthritides.** Rarer forms of crystal arthropathy include those caused by calcium oxalate and calcium hydroxyapatite, which tend to occur in individuals on dialysis.

IV. SEPTIC ARTHRITIS

A. General principles

1. Bones, joints, and bursae may be infected with a large variety of microorganisms.
2. *Staphylococcus aureus* is the most common cause of musculoskeletal infection.
3. Other microorganisms are increasing in prevalence.
4. Most cases are acute with swelling, pain, surrounding erythema, and loss of joint function.
5. Monoarticular involvement is most common, but several joints may be affected with hematogenous spread.
6. Fever is usually present but is not invariable.

B. Diagnosis

1. Immediate joint aspiration is imperative in any suspected case.
2. Synovial fluid should be sent for:
   a. Gram stain
   b. Cell count and differential cell count
   c. Culture and sensitivity
   d. Polarized microscopy for crystals
3. Cell count may vary but is usually $>50{,}000/mm^3$.
4. The presence of crystals does not out rule the possibility of infection.

C. Treatment

1. Repeated daily aspirations or surgical washout is essential.
2. Empiric antibiotic therapy should be initiated following a stat Gram stain and antibiotics adjusted once cultures become available (Table 145-3).
3. The joint should be rested with physical therapy referral to prevent contractures.
4. Baseline radiographs should be obtained to follow progress.
5. Baseline C-reactive protein (CRP) may be helpful in monitoring longer-term therapeutic response.
6. Fungal joint infection is rare, more indolent in presentation, and occurs usually in immunocompromised patients.
7. Fungal components are normally visible on Gram stain, allowing for early initiation of antifungal therapy.

V. ANTIPHOSPHOLIPID ANTIBODY SYNDROME.

Defined as recurrent arterial or venous thrombosis often associated with fetal losses in the presence of anticardiolipid antibodies or lupus anticoagulant. It may be primary or may be associated with another connective tissue disease.

A. Diagnosis.

Clinical features include:

1. One or more episodes of arterial or venous thrombosis or both
2. Fetal death or recurrent spontaneous abortion
3. Other features include thrombocytopenia, livedo reticularis, cardiac valvular lesions, migraine headaches, chorea, and leg ulcers
4. Presence of either anticardiolipid antibody immunoglobulin M (IgM) or IgG in medium or high titer or lupus anticoagulant on two occasions, at least 6 weeks apart

TABLE 145-3 Antibiotics in Septic Arthritis

Clinical setting	Top three microorganisms	Initial empiric antibiotic choice
Nonimmunocompromised, not sexually active	**1.** Staphylococcus aureus **2.** *Streptococccus* **3.** Gram-negative bacilli	Vancomycin or third-generation cephalosporin depending on results of Gram stain
Nonimmunocompromised, sexually active	**1.** *Neisseria gonorrheae* **2.** *S. aureus* **3.** *Streptococci*	Gram stain negative — third-generation cephalosporin Gram stain shows gram-positive cocci in clusters — vancomycin pending sensitivity
Prosthetic joints	**1.** *Staphylococcus epidermidis* **2.** *S. aureus* **3.** *Enterobacteriaceae*	Vancomycin and third-generation cephalosporin or ciprofloxacin until Gram stain and cultures available; consider addition of aminoglycoside if pseudomonas suspected
Immunocompromised	*Large variety of organisms possible*	Vancomycin and third-generation cephalosporin until cultures available; seek I. D. input early

PO, per oral; mg, milligram; GI, gastrointestinal; IV, intravenous; IM, intramuscular; ICU, intensive care unit; ACTH, adrenocorticotrophic hormone; NSAIDs, nonsteroidal anti-inflammatory drugs.

B. Treatment

1. Anticoagulation with heparin followed by lifelong warfarin is indicated. See recently published guidelines on managing long-term anticoagulation (Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians. Evidence-based clinical practice guidelines (8th edition). *Chest* 2008;133(6):160S-198S).
2. The catastrophic antiphospholipid antibody defines a syndrome involving widespread thrombosis with life-threatening illness. Treatment may include corticosteroids, cyclophosphamide, plasmapheresis, anticoagulation, and possibly rituximab.

VI. IDIOPATHIC INFLAMMATORY MYOSITIS. Polymyositis and dermatomyositis are inflammatory muscle diseases characterized by proximal muscle weakness, elevated muscle enzymes, and characteristic cutaneous features.

A. Diagnosis. Clinical features include:

1. Proximal girdle and shoulder weakness
2. Skin involvement includes Gottron's papules (an erythematous and often scaly eruption typically seen symmetrically over the extensor surfaces of the MCP and to a lesser extent the interphalangeal joints and elbows); erythema of the neck, chest, and forehead; heliotrope rash; and periungual erythema
3. Dysphagia and aspiration pneumonia

4. ILD, especially in patients who are Jo-1 antibody–positive
5. Cardiomyopathy, arrhythmias, and congestive heart failure

B. Treatment

1. High-dose corticosteroids with consideration for an additional agent such as methotrexate.
2. In progressive ILD, high-dose steroids with cyclophosphamide are indicated. Other agents such as mycophenolate, tacrolimus, and azothioprine may be used.

VII. SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

A. General principles. An inflammatory disorder of unknown etiology characterized by antibody production, immune complex deposition, and a wide variety of organ and system involvement. Diagnosis is based on the presence of characteristic clinical features and laboratory findings, including decreased complement levels, cytopenias, and typical autoantibody profiles.

B. Renal involvement. Occurs in 50% of patients. Treatment protocols exist, depending on the histologic classification on renal biopsy, with active nephritis requiring treatment with high-dose corticosteroids and cyclophosphamide or mycophenolate.

C. Pulmonary involvement

1. Pleuritis is the most common pulmonary manifestation of SLE, affecting approximately 50% of SLE patients.
2. Pulmonary hemorrhage is a rare but serious complication of SLE.
   a. Patients, frequently young females, present with severe hypoxia, patchy infiltrates, and hemoptysis.
   b. Treatment is with high-dose corticosteroids and immunosuppressive agents with a potential role for plasmapheresis.

D. Hematologic

1. Autoimmune hemolytic anemias respond well to high-dose steroids; other immunosuppressants, rituximab, and splenectomy are options for unresponsive cases.
2. Idiopathic thrombocytopenic purpura (ITP) can also occur; treatment is with high-dose oral or IV steroids and if needed IV immunoglobulin.

E. Neurologic

1. Neuropsychiatric lupus is the name given to the large variety of neurologic presentations seen in SLE.
2. These include seizure disorders, stroke disease, demyelinating disorders, psychosis, transverse myelopathy, peripheral neuropathy, and headache.

VIII. SCLERODERMA

A. General principles. Multisystem disease characterized by tissue inflammation and fibrosis with vascular involvement leading to episodic vasospasm and tissue ischemia.

B. Interstitial lung disease. Frequent complication and the leading cause of death.

1. High-resolution CT findings range from ground glass opacities to honeycombing.
2. BAL shows an elevated neutrophil and eosinophil count; pulmonary function tests show a restrictive pattern.
3. Treatment including cyclophosphamide combined with corticosteroids although newer therapies are emerging.

C. Pulmonary hypertension

1. Complication of typically long-standing limited scleroderma.
2. Diagnosis is suggested by echocardiography or an otherwise unexplained elevation of the B-type natriuretic peptide (BNP) and confirmed on right heart catheterization.

3. Treatment with IV and inhaled prostacyclins and endothelin antagonists may increase survival.

D. Scleroderma renal crisis

1. Renal crisis is a syndrome of rapidly progressive hypertensive renal failure.
2. Accompanied by microvascular hemolysis.
3. The associated hyperreninemic state drives the process and treatment is therefore with urgent administration of high-dose angiotensin-converting enzyme inhibitors.
4. Rarely, normotensive renal crisis can occur.

E. Gastrointestinal

1. Constipation due to decreased peristalsis.
2. Diarrhea due to bacterial overgrowth.
3. Gastroesophageal reflux disease (GERD) is almost universal
4. Enteral nutrition should be maintained when possible in the ICU setting.

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146 ANAPHYLAXIS

Helen M. Hollingsworth and Nereida A. Parada

I. GENERAL PRINCIPLES

A. Anaphylaxis is a severe and potentially fatal form of immediate hypersensitivity (immunoglobulin E [IgE]-mediated antigen recognition).

B. An *anaphylactoid reaction* differs from anaphylactic reactions in that mast cell/basophil activation is caused by a mechanism other than IgE recognition of antigen.

C. In this chapter, IgE-mediated and non–IgE-mediated reactions are referred to as *anaphylactic reactions.*

II. PATHOPHYSIOLOGY

A. Binding of allergenic antigen (Table 146-1) to adjacent IgE molecules on sensitized mast cells/basophils activates synthesis and secretion of mediators of anaphylaxis, such as histamine, leukotrienes (LTC4, LTD4, and LTE4), and cytokines.

B. Mast cell and basophil activation also occur through a variety of non–IgE-mediated mechanisms (Table 146-2).

III. CLINICAL FEATURES

A. The major clinical features of anaphylaxis are urticaria, angioedema, respiratory obstruction (stridor, wheezing, breathlessness), and vascular collapse (dizziness, loss of consciousness), with urticaria being the most common.

B. Additional clinical manifestations include a sense of impending doom, rhinorrhea, generalized pruritus and swelling, dysphagia, vomiting, and abdominal pain.

C. **Physical examination** of a patient with anaphylactic shock often reveals a rapid, weak, irregular, or unobtainable pulse; tachypnea, respiratory distress, cyanosis, hoarseness, or stridor; diminished breath sounds, wheezes, and hyperinflated lungs; urticaria; angioedema, or conjunctival edema. Only a subset of these may occur in any given patient.

D. **Laboratory findings** include elevation of blood histamine and mature β-tryptase and total tryptase levels, low complement levels, and disseminated intravascular coagulation (DIC). Comparing tryptase levels during an event with baseline levels increases accuracy. A normal tryptase level does not exclude anaphylaxis. No truly diagnostic blood test is currently available.

E. Arrhythmias may occur.

IV. DIAGNOSIS

A. The rapid onset and progression of typical symptoms to a severe and sometimes fatal outcome after exposure to a typical antigen or inciting agent are characteristic of anaphylaxis.

B. Mild systemic reactions often last for several hours, rarely >24 hours.

C. Severe manifestations (e.g., laryngeal edema, bronchoconstriction, hypotension), if not fatal, can persist or recur for several days but sometimes resolve within minutes of treatment.

TABLE 146-1 Causes of IgE-mediated Anaphylaxis

Type	Agent	Example
Proteins	Allergen extracts	Pollen, dust mite, mold
	Enzymes	Chymopapain, streptokinase, L-asparaginase
	Food	Egg white, legumes, milk, nuts, celery, shellfish, psyllium, wheat
	Heterologous serum	Tetanus antitoxin, antithymocyte globulin, snake antivenom
	Hormones	Insulin, ACTH, TSH, progesterone, salmon calcitonin
	Vaccines	Influenza
	Venoms	Hymenoptera
	Others	Heparin, latex, thiobarbiturates, seminal fluid
Haptens	Antibiotics	β-Lactams, ethambutol, nitrofurantoin, sulfonamides, streptomycin, vancomycin
	Disinfectants	Ethylene oxide
	Local anesthetics[a]	Benzocaine, tetracaine, xylocaine, mepivacaine
	Others	Cisplatin, carboplatin

ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone.
[a] Precise mechanism not established.

TABLE 146-2 Causes of Non–IgE-Mediated Anaphylaxis

Complement activation
Blood product transfusion in IgA-deficient patient
Hemodialysis with cuprophane membrane
Direct release of chemical mediators of anaphylaxis
Protamine[a]
Radiographic contrast media
Ketamine
Local anesthetics[a]
Codeine and other opiate narcotics
Highly charged antibiotics, including amphotericin B
Cyclooxygenase inhibition
Indomethacin
Acetylsalicylic acid
Ibuprofen
Naproxen
Sulindac
Zomepirac sodium
Tolmetin sodium
Other
Antineoplastic agents (e.g., paclitaxel[a], etoposide[a])
Sulfiting agents
Exercise
Idiopathic recurrent anaphylaxis

[a] Precise mechanism not established.

V. TREATMENT: GENERAL CARDIOPULMONARY SUPPORTIVE MEASURES

A. Oxygen saturation, blood pressure, cardiac rate, and rhythm should be monitored closely and supplemental oxygen administered.

B. Intubation and assisted ventilation may be necessary for laryngeal edema or severe bronchoconstriction.

C. Occasionally, cricothyroidotomy is necessary.

D. One characteristic of patients with biphasic or protracted anaphylaxis is oral ingestion of the offending antigen. Enteral administration of activated charcoal and sorbitol may reduce absorption and duration of exposure to the antigen.

VI. TREATMENT: PHARMACOLOGIC

(Table 146-3)

A. Adrenergic agents

1. Epinephrine should be given promptly to treat all initial manifestations of anaphylaxis; a delay in administration of epinephrine may be fatal.
2. In adults the dose of epinephrine hydrochloride (1 mg/mL) is 0.3 to 0.5 mL intramuscularly. This may be repeated in 5 to 15 minutes. In children, the dose is 0.1 mg/kg intramuscularly and may be repeated in 5 to 15 minutes.

TABLE 146-3 Treatment of Anaphylaxis in Adults

Mandatory and Immediate

General measures
- Administer aqueous epinephrine (1:1,000), 0.3–0.5 mL intramuscularly (IM), up to 3 doses at 1- to 5-min intervals
- Apply a tourniquet proximal to antigen injection or sting site
- Infiltrate aqueous epinephrine (1:1,000), 0.1–0.3 mL into antigen injection or sting site
- Administer supplemental oxygen

For laryngeal obstruction or respiratory arrest
- Establish airway using endotracheal intubation, cricothyroidotomy, or tracheotomy
- Initiate mechanical ventilation

After clinical appraisal

General measures
- Diphenhydramine, 1.25 mg/kg to maximum of 50 mg, intravenously (IV) or IM
- Aqueous hydrocortisone, 200 mg; dexamethasone, 10 mg; or methylprednisolone, 50 mg; IV every 6 h for 24–48 h
- Cimetidine, 300 mg, or ranitidine 50 mg, IV over 3–5 min

For hypotension
- Aqueous epinephrine (1:1,000), 1 mL in 500 mL of saline at 0.5–2.0 mL/min, or 1–4 μg/min, through central venous line
- Volume expansion with normal saline
- Norepinephrine 4 mg in 1,000 mL of D5W at 2–12 μg/min IV
- Glucagon (if patient is receiving β-blocker therapy) 1 mg/mL IV bolus or infusion or 1 mg/L of D5W at a rate of 5–15 mL/min

For bronchoconstriction
- Supplemental oxygen
- Albuterol (0.5%), 0.5 mL in 2.5 mL of saline, by nebulizer; once intubated, use albuterol metered dose inhaler (MDI) 10–20 puffs, endotracheally, every 20 min, as needed

D5W, dextrose 5% in water.

3. Epinephrine delays antigen absorption when infiltrated locally into an injection or sting site.

B. Antihistamines

1. H_1 receptor—blocking antihistamines reverse histamine-induced vasodilatation, tachycardia, and bronchoconstriction, as well as cutaneous manifestations, but are insufficient to treat anaphylaxis in the absence of epinephrine.
2. H_2 receptor blocking antihistamines are often prescribed although evidence for benefit is limited.

C. Glucocorticoids

1. Systemic glucocorticoids increase tissue responses to β-adrenergic agonists and inhibit generation of LTC4, LTD4, and LTE4.
2. Despite the general sense that glucocorticoids prevent late recurrences of anaphylaxis, biphasic anaphylaxis may occur in 20% of anaphylactic reactions despite glucocorticoid therapy.

VII. PREVENTION OF ANAPHYLACTIC REACTIONS

A. Obtaining and recording a careful history identifying possible precipitants of anaphylaxis at the time of presentation is crucial.

B. Patients should be encouraged to wear a MedicAlert (MedicAlert Foundation, 2323 Colorado Ave., Turlock, CA 95382 or www.medicalert.org) or similar identifying bracelet.

C. Patients should carry two epinephrine devices for intramuscular injection (e.g., EpiPen or EpiPen, Jr.).

D. β-Blocking medication may increase the risk of anaphylaxis and make it more refractory to treatment; so β-blocking medication should be avoided, if possible, in patients at risk for recurrent anaphylaxis.

VIII. MANAGEMENT OF ANAPHYLAXIS TO SPECIFIC PRECIPITANTS

A. β-Lactam antibiotic anaphylaxis

1. Approximately 10% of allergic reactions to β-lactams are life threatening: of these, 2% to 10% are fatal.
2. Skin testing that includes both major and minor antigenic determinants detects IgE-mediated sensitivity but is not currently commercially available.
3. Skin testing does not evaluate other types of sensitivity, such as serum sickness reactions, morbilliform rashes, and interstitial nephritis.
4. Cross-reactivity occurs infrequently between penicillin and cephalosporins (5.4% to 16.5%) but frequently between penicillins and carbapenems (e.g., imipenem).
5. Monobactams (e.g., aztreonam) do not show cross-reactivity with penicillins but do cross-react with the cephalosporins.
6. For less severe reactions and when no alternative agent is available, desensitization may be attempted in the intensive care unit (ICU) setting. Five to six 10-fold dilutions of the target concentration are administered in sequence, starting with the most dilute and progressing to the next stronger concentration every 15 to 20 minutes, as tolerated.

B. Stinging insect venom anaphylaxis

1. After initial treatment, patients should be referred to an allergist for skin testing and possible desensitization.
2. Specific venom desensitization provides >95% protection against anaphylaxis on subsequent stings.

C. Food anaphylaxis

1. Eggs, milk, peanuts, soy, tree nuts, wheat, fish, and shellfish are the foods that most commonly cause severe reactions.

2. Fatal anaphylaxis from food occurs most commonly in patients with asthma, in a public setting rather than at home, and when administration of epinephrine is delayed.
3. Strict avoidance of implicated foods is essential.

D. Radiographic contrast media anaphylaxis

1. In patients with a history of a previous radiocontrast media anaphylactic reaction, the repeat reaction rate is reported to be 35% to 60%.
2. Patients with a general history of allergies, whether to inhalant allergens, foods, or medications, have an increased reaction rate compared with nonallergic individuals.
3. Low ionic contrast or alternative radiographic studies (e.g., computed tomography with gadolinium, magnetic resonance imaging, or ultrasound) should be considered.
4. Pretreatment with glucocorticoids (50 mg prednisone, 13 hours, 7 hours, and 1 hour before administration) and diphenhydramine (50 mg orally or intramuscularly 1 hour before administration) with or without ephedrine (25 mg orally 1 hour before administration) may reduce the reaction rate.
5. For an emergent procedure, hydrocortisone (200 mg) can be given intravenously (IV) immediately and repeated every 4 hours until the procedure in addition to diphenhydramine (50 mg IV) immediately before the procedure.

E. Latex-induced anaphylaxis

1. Health care workers and patients with spina bifida or a history of multiple latex is found in a wide spectrum of medical products.
2. Serum radioallergosorbent testing (CAP-Pharmacia) is helpful in diagnosis but may have false-negative results (50% to 60% sensitivity).
3. Standardized skin testing is not commercially available.
4. Patients with latex allergy should be cared for in latex-free operating rooms, ICUs, and hospital rooms.

F. Angiotensin-converting enzyme (ACE) inhibitor anaphylaxis

1. Severe, potentially life-threatening facial and oropharyngeal angioedema can occur in individuals with sensitivity to ACE inhibitors and angiotensin receptor blockers (ARBs).
2. Onset of angioedema usually starts within the first several hours or up to a week of beginning therapy but may be delayed for months to years.
3. Cross-reactivity does occur among the different ACE inhibitors but usually not between ACE inhibitors and ARBs.
4. Epinephrine is not always helpful: endotracheal intubation or cricothyroidotomy may be necessary to maintain an airway. Angioedema may take 1 to 3 days to resolve.

G. Hereditary angioedema

1. Individuals with absent or inactive C1 esterase inhibitor can develop life-threatening angioedema of the upper respiratory tract.
2. Urticaria is generally not present, but a history of recurrent abdominal pain from intestinal angioedema may be elicited.
3. Acutely, complement C2 and C4 levels are low; C1q is normal in the hereditary form and low in the acquired form.
4. C1 esterase inhibitor is either low or nonfunctional.
5. Angioedema is frequently refractory to epinephrine, necessitating intubation or cricothyroidotomy.
6. Fresh frozen plasma may be given 2 units every 4 to 6 hours until symptoms improve.
7. Stanazol 4 mg orally every 4 hours for four doses may shorten the duration of symptoms.

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147 VASCULITIS IN THE INTENSIVE CARE UNIT

Paul F. Dellaripa

I. **OVERVIEW.** A group of disorders in which inflammation and necrosis of blood vessels leads to organ dysfunction due to the development of thrombosis or hemorrhage. Mimics of vasculitis include subacute bacterial endocarditis, atrial myxoma, antiphospholipid syndrome, and cholesterol embolism.

II. WEGENER'S GRANULOMATOSIS

A. General principles

1. Characterized by granulomatous inflammation of the upper and lower respiratory tract, segmental necrotizing glomerulonephritis, and small vessel inflammation of other organs systems.
2. Reasons for intensive care unit (ICU) admission for Wegener's granulomatosis (WG) and all of the vasculitidies include respiratory failure due to alveolar hemorrhage, rapidly progressive renal failure, and infections due to immunosuppressive treatment of disease. Stridor due to subglottic stenosis is rare in WG.

B. Pathogenesis

1. There is no known etiologic agent for WG.
2. Antineutrophilic cytoplasmic antibodies (ANCA) are present in >90% of cases of WG. C-ANCA (with specificity to PR3 antigen) seen in 90% and P-ANCA (with specificity to myeloperoxidase [MPO]) seen in a minority of cases.

C. Diagnosis

1. Clinical presentation typically includes sinusitis, rhinitis, epistaxis, otitis media, and hearing loss.
2. Lower respiratory tract is involved frequently, with cough, dyspnea, hemoptysis, and progressive respiratory failure due to alveolar hemorrhage. Pulmonary infiltrates or nodules may be diffuse or cavitary. Lung biopsy may be necessary to confirm diagnosis and eliminate the possibility of mycobacterial or fungal disease.
3. Renal involvement may be rapidly progressive leading to dialysis. Rarely, ANCA-associated vasculitis coexists with antiglomerular basement antibodies (anti-GBM). Diagnosis is confirmed based on clinical findings, presence of ANCA, and tissue biopsy of affected organs including kidney, lung, eye, nerve, or skin. In some cases, tissue biopsy may not be necessary when the clinical suspicion for disease is high and the ANCA pattern unequivocally supports the diagnosis.

D. Treatment

1. In the setting of respiratory failure, alveolar hemorrhage, and progressive renal failure, therapy should include cyclophosphamide (CYC) and high-dose corticosteroids. Intravenous (IV) methylprednisolone in doses of 1,000 mg/day for 3 days may be considered.
2. Oral dosing of CYC is 2 mg/kg, but in renal failure it is as follows: 1.5 mg/kg/day if creatinine clearance (CrCl) is 50 to 99; 1.2 mg/kg/day if CrCl is 25 to 49; 1.0 mg/kg/day if CrCl is 15 to 24; and 0.8 mg/kg/day if CrCl is <15 or dialysis.

3. In the setting of critical illness and potential variability of gastrointestinal (GI) absorption, IV CYC (0.5 g/m^2 to 1 g/m^2) is indicated. Appropriate IV hydration pre- and post-CYC infusion is important.
4. Pneumocystis pneumonia (PCP) prophylaxis should be offered.
5. Plasmapheresis and IV immunoglobulin (Ig) may be useful in severe or refractory WG and severe alveolar hemorrhage with or without anti-GBM antibodies.
6. The presence of worsening pulmonary infiltrates in those treated with CYC and steroids raises the suspicion of fungal infections and PCP, warranting early bronchoscopy or biopsy and early consideration for antifungal and PCP therapy.
7. Other agents such as mycophenolate mofetil, azathioprine, and rituximab may be used in less severe cases or in refractory cases.

III. MICROSCOPIC POLYANGIITIS

A. General principles:

1. Small and medium vessel necrotizing vasculitis presenting with pauci-immune segmental necrotizing glomerulonephritis and pulmonary capillaritis with alveolar hemorrhage.
2. ANCA (P-ANCA with MPO specificity) is positive in 70% of cases.
3. Clinical presentation can overlap with WG, though pathologically there is lack of granulomas.

B. Diagnosis. Biopsy of appropriate tissue, typically kidney, lung, or nerve in conjunction with ANCA positivity

C. Treatment. Treatment similar to that for WG

IV. CHURG-STRAUSS SYNDROME (CSS)

A. General principles:

1. Characterized by eosinophilic infiltrates and granulomas in the respiratory tract in the setting of a history of asthma and eosinophilia.
2. Peripheral neuropathy, mesenteric ischemia, cardiac, and central nervous system (CNS) involvement may occur. Renal involvement and alveolar hemorrhage are rare.

B. Diagnosis. ANCA is positive in 60% of patients, mostly MPO pattern. Biopsy of suspected organs show granulomas and fibrinoid necrosis.

C. Treatment

1. Corticosteroids in milder presentation, with CYC or other immunosuppressant agent in more severe disease.
2. Five-factor score (proteinuria >1g/day, azotemia, GI or CNS dysfunction, cardiomyopathy) helps to determine prognosis and level of treatment.

V. POLYARTERITIS NODOSA (PAN)

A. General principles. Systemic necrotizing vasculitis involving small and medium muscular arteries.

B. Etiology. The etiology of PAN is unknown, though rarely the presence of circulating hepatitis B surface antigen in vessel walls is noted.

C. Diagnosis

1. Presents with a prodrome of malaise, fatigue, fever, and weight loss.
2. Vasculitic lesions may result in mononeurtis multiplex, cutaneous lesions, intestinal ischemia, myocardial infarction, and congestive heart failure.
3. Laboratory findings include anemia and elevated sedimentation rate. ANCA is absent.
4. Diagnosis is confirmed by tissue biopsy or evidence of microaneurysms on mesenteric angiogram.

D. Treatment

1. High-dose corticosteroid therapy orally or intravenously with pulse methylprednisolone at 1 g/day for 3 days; CYC used in severe cases.
2. In cases associated with hepatitis B, antiviral therapy may be used in early conjunction with corticosteroids and plasmapheresis.

VI. CRYOGLOBULINEMIC VASCULITIS

A. General principles. Cryoglobulins are immunoglobulins that precipitate in the cold. There are three types, with types II and III closely, though not exclusively, associated with hepatitis C infection.

B. Diagnosis

1. Findings include palpable purpura, peripheral neuropathy, and infrequently life-threatening renal, GI, and pulmonary involvement including pulmonary hemorrhage.
2. Laboratory values include low complement levels (C4), abnormal liver enzymes, and positive rheumatoid factor.

C. Treatment

1. Treatment consists of high-dose corticosteroid and adding CYC in cases of renal failure or mononeuritis multiplex.
2. Plasmapheresis or cryofiltration may be beneficial in severe cases.

VII. PULMONARY CAPILLARITIS

A. General principles

1. Pathologically, pulmonary capillaritis is due to alveolar wall inflammation that leads to disruption of the integrity of the alveolar-capillary basement membrane, presenting clinically as diffuse alveolar hemorrhage (DAH).
   a. It is most often associated with immune-mediated processes such as WG, microscopic polyangiitis, the antiphospholipid antibody syndrome, systemic lupus erythematosus (SLE), Henoch Schönlein purpura, IgA nephropathy and drug-induced vasculitis such as propylthiouracil.
2. Clinically, pulmonary capillaritis may be an isolated phenomenon or can be seen in concert with other systemic manifestations, including glomerulonephritis, known as the so-called pulmonary renal syndrome.

B. Diagnosis

1. In patients with evidence of either isolated alveolar hemorrhage or pulmonary renal syndrome, assessment of ANCA, antinuclear antibody (ANA), anti-GBM, and antiphophospholipid antibodies is appropriate.
2. Biopsy of lung or kidney may be useful though may be difficult to accomplish in the setting of critical illness.

C. Treatment

1. Treatment consists of empiric high dose steroids 1 g/day IV for 3 days, cytotoxic therapy, and consideration for plasmapheresis if respiratory or renal failure is severe. In established cases of vasculitis in patients already on immunosuppression, DAH should also raise suspicion for infections such as *Aspergillus*.

VIII. VASCULITIS OF THE CENTRAL NERVOUS SYSTEM

A. General principles. Heterogeneous group of neurologic disorders divided into primary (granulomatous and nongranulomatous) CNS vasculitis and secondary forms related to rheumatic syndromes such as SLE, rheumatoid arthritis (RA), sarcoidosis, Sjögrens and Behcet's syndrome amongst others. The focus of this chapter is on primary forms of CNS vasculitis.

B. Diagnosis

1. Granulomatous angiitis of the central nervous system (GACNS): usually a slow, progressive process characterized by headache, focal deficits, and changes in higher cortical function.
   a. Lumbar puncture reveals mononuclear pleocytosis and elevated protein.
   b. **Magnetic resonance imaging**(MRI) shows abnormal multifocal vascular lesions and leptomeningeal enhancement.
   c. Angiography is nonspecific or normal in up to 60% of cases.
   d. Biopsy of the cortex and leptominges showing granulomas and giant cells is diagnostic procedure of choice.
2. Nongranulomatous angiitis of the CNS may share clinical features with GACNS or may present with a more rapid course and variable, and sometimes normal, spinal fluid.

C. Treatment. CNS vasculitis is treated with corticosteroids and CYC.

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XV Psychiatric Issues in Intensive Care

148 DIAGNOSIS AND TREATMENT OF AGITATION AND DELIRIUM IN THE INTENSIVE CARE UNIT PATIENT

Jason P. Caplan

I. GENERAL PRINCIPLES

A. Definition

1. Agitation is a frequent behavioral aberration in severely ill patients, which significantly risks the safety of patient and staff alike.

2. Agitation may be a symptom of delirium (a neuropsychiatric manifestation of a systemic disturbance), the most common cause of agitation in the intensive care unit (ICU). Delirium presents with alterations in consciousness, attention, and cognition that develop over hours to days and wax and wane throughout the day. The hallmark of delirium is inattention, which can be gauged by simple bedside testing (e.g., attention to conversation, serial subtraction of 7 from 100, recitation of the months of the year backward).

B. Epidemiology

1. Delirium occurs in >30% of all patients in the ICU and in >80% of patients in the ICU who are intubated.

C. Risk factors

1. Acute physiologic risk factors include metabolic disturbances, infection, shock, hypoxia, renal failure, hepatic failure, and intracranial processes.

2. Chronic physiologic risk factors include advanced age; malnutrition; alcohol or drug abuse; and prior diagnoses of depression, dementia,

stroke, seizure, congestive heart failure, or human immunodeficiency virus infection.

3. Iatrogenic risk factors include medication side effects (most commonly those of anticholinergics, benzodiazepines, opiates, antihistamines, and steroids) and indwelling catheters.

II. ETIOLOGY AND PATHOGENESIS

A. The mnemonics "WWHHHHIMPS" and "I WATCH DEATH" aid recall of life-threatening and common causes of delirium, respectively (see Tables 148-1 and 148-2).

B. The current leading hypothesis of the neural mechanism of delirium implicates hypocholinergic and hyperdopaminergic states.

C. Acetylcholine is the primary neurotransmitter of the reticular activating system, a network vital to both alertness and attention. Therefore, a relative cholinergic deficit is likely to disrupt these functions.

D. Impaired oxidative metabolism increases the release and disrupts the reuptake and extracellular metabolism of dopamine. Excess dopamine is associated with hallucinations, delusions, and other psychotic symptoms, and may facilitate the excitatory effects of glutamate, thereby producing agitation.

III. DIFFERENTIAL DIAGNOSIS

A. Delirious patients may present with a hypoactive subtype, which is commonly mistaken for **depression**. Hypoactive delirium is distressing to the patient, may progress to the agitated form, and requires appropriate treatment.

B. Patients with **dementia** are at risk of agitation and delirium in the ICU as a result of being in unfamiliar surroundings. Behavioral measures should be employed to help these patients maintain orientation to their milieu.

C. Patients with **schizophrenia** may also have difficulty adapting to ICU restrictions. Measures should be taken to make the ICU as familiar and comfortable as possible. Table 148-3 compares and contrasts diagnostic features of these different causes of agitation.

D. **Alcohol or sedative-hypnotic withdrawal** is a prominent cause of delirium in the ICU. This syndrome results from decreased activity of γ-aminobutyric acid (GABA) and unopposed noradrenergic, glutamatergic, and dopaminergic activation when the intake of alcohol or sedative-hypnotic agents is ceased suddenly. Confusion, agitation, diaphoresis, tremor, and autonomic

TABLE 148-1 WWHHHHIMPS, A Mnemonic for Life-Threatening Causes of Delirium

Withdrawal
Wernicke's encephalopathy
Hypoxia or hypoperfusion of the brain
Hypertensive crisis
Hypoglycemia
Hyper- or hypothermia
Intracranial mass or hemorrhage
Meningitis or encephalitis
Poisons (including medications)
Status epilepticus

(Adapted from Wise MG, Trzepacz PT. Delirium (confusional states). In: Rundell JR, Wise MD, eds. *The American Psychiatric Press textbook of consultation-liaison psychiatry*. Washington, DC: American Psychiatric Press, 1996:258–274.)

TABLE 148-2 I WATCH DEATH, a Mnemonic for Common Causes of Delirium

Infectious	Pneumonia, urinary tract infection, encephalitis, meningitis, syphilis
Withdrawal	Alcohol, sedative-hypnotic agents
Acute metabolic	Acidosis, alkalosis, electrolyte disturbances, and hepatic or renal failure
Trauma	Heat stroke, burns, postoperative state
Central nervous system pathology	Abscess, hemorrhage, seizure, stroke, tumor, vasculitis, normal pressure hydrocephalus
Hypoxia	Hypotension, pulmonary embolus, pulmonary or cardiac failure, anemia, carbon monoxide poisoning
Deficiencies	Vitamin B_{12}, niacin, thiamine
Endocrinopathies	Hyper- or hypoglycemia, hyper- or hypoadrenalism, hyper- or hypothyroidism, hyper- or hypoparathyroidism
Acute vascular	Hypertensive encephalopathy, shock
Toxins or drugs	Medications, drugs of abuse, pesticides, solvents
Heavy metals	Lead, manganese, mercury

(Adapted from Wise MG, Trzepacz PT. Delirium (confusional states). In: Rundell JR, Wise MD, eds. *The American Psychiatric Press textbook of consultation-liaison psychiatry*. Washington, DC: American Psychiatric Press, 1996:258–274.)

instability (collectively known as *delirium tremens*) may progress to seizure and death.

E. Inadequately controlled pain, overwhelming anxiety, or hopelessness resulting from depression may also result in agitation.

IV. TREATMENT

A. Definitive treatment of delirium requires identification and treatment of the underlying causes.

B. Agitation and other symptoms of delirium may be managed adjunctively with neuroleptics due to their antagonism of the dopamine receptor.

C. The "gold standard" of this adjunctive treatment is intravenous (IV) haloperidol. IV administration, although "off label," is the standard of care and is preferable to other routes due to better absorption, less discomfort, and reduced extrapyramidal side effects (EPS).

1. Treatment with IV haloperidol is usually initiated with a dose ranging from 0.5 mg (in the elderly) to 10 mg (for severe agitation). Subsequent doses can be doubled at 30-minute intervals until optimal tranquilization is achieved.
2. Complete absence of agitation should be the goal, after which haloperidol can be given 2 or 3 times daily with additional doses provided as needed.
3. Over time, the total dose can be gradually decreased; it is usually wise to wean the evening dose last.

D. Data on the efficacy and safety of the atypical or second-generation neuroleptic agents (e.g., risperidone, olanzapine, quetiapine, and ziprasidone) in the delirious patient are limited.

E. Quetiapine may have a niche role in the treatment of delirium in patients with Parkinson's disease or Lewy body dementia as it is less likely than haloperidol to exacerbate these disorders.

F. The anticholinesterase inhibitor physostigmine has been shown to reverse delirium resulting from multiple etiologies. Owing to its brief duration of

TABLE 148-3 Differential Diagnosis of Causes of Agitation

	Delirium	Dementia	Depression	Schizophrenia
Onset	Acute	Insidious[a]	Variable	Variable
Course	Fluctuating	Progressive[b]	Variable	Variable
Reversibility	Usually	Not usually	Usually	No
Level of consciousness	Impaired	Clear until late stages	Unimpaired	Unimpaired[c]
Attention/ memory	Inattention, poor memory	Poor memory without marked inattention	Attention usually intact, memory intact	Poor attention, memory intact
Hallucinations	Usually visual; can be auditory, tactile, gustatory, olfactory	Can be visual or auditory	Usually auditory	Usually auditory
Delusions	Fleeting, fragmented, usually persecutory	Paranoid, often fixed	Complex, mood-congruent	Frequent, complex, systematized, often paranoid

[a]Except for dementia due to stroke.
[b]Lewy body dementia often presents with a waxing and waning course imposed on an overall progressive decline.
[c]Except when complicated by catatonia.
(Adapted from Trzepacz PT, Meagher DJ. Delirium. In: Levenson JL, ed. *The American Psychiatric Publishing textbook of psychosomatic medicine*. Washington, DC: American Psychiatric Publishing, 2005:91–130.)

efficacy and narrow therapeutic window, its use is limited to delirium thought due to anticholinergic toxicity.

G. Treatment of alcohol or sedative-hypnotic withdrawal typically requires administration of a benzodiazepine (e.g., lorazepam). Great care should be taken in the diagnosis of alcohol or sedative-hypnotic withdrawal in the agitated patient since the prescribed treatment (i.e., a benzodiazepine) is almost certain to exacerbate delirium due to another etiology.

V. COMPLICATIONS

A. Delirium has been associated with prolonged hospital stay and increased morbidity and mortality. Fiscally, delirium predicts heightened costs in the ICU and in overall hospital care.

B. Neuroleptic administration may contribute to progressive widening of the QT interval, resulting in increased risk for *torsades des pointes* (TDP) and possible death.

1. Although the incidence of fatal TDP is relatively low, cardiac rhythm should be carefully monitored with close attention paid to serum levels of potassium, magnesium, and calcium.
2. Prolongation of the corrected QT interval (QTc) >25% from baseline or a QTc >500 ms may warrant telemetry, cardiologic consultation, and reduction or discontinuation of haloperidol.
3. Other potentially QTc-prolonging agents (e.g., fluoroquinolone antibiotics, calcium channel blockers) may need to be discontinued.

Suggested Reading

American Psychiatric Association. Practice guideline for the treatment of patients with delirium. *Am J Psychiatry* 1999;156 (5 Suppl):1–20.
The American Psychiatric Association consensus statement on the appropriate work-up and management of delirium.

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Menza MA, Murray GB, Holmes VF, et al. Decreased extrapyramidal symptoms with intravenous haloperidol. *J Clin Psychiatry* 1987;48:278–280.
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Roden DM. Drug-induced prolongation of the QT-interval. *N Engl J Med* 2004;350: 1013–1022.
A useful review of the mechanisms of QT-interval prolongation and drugs that may precipitate it.

Tesar GE, Murray GB, Cassem NH. Use of high-dose intravenous haloperidol in the treatment of agitated cardiac patients. *J Clin Psychopharmacol* 1985;5:344–347.
A case series by the pioneers of the use of intravenous haloperidol in the treatment of agitation in the critically ill that reports safety and efficacy of the drug at high doses.

SUICIDE

149

Saori A. Murakami

I. GENERAL PRINCIPLES

A. Description

1. The treatment of a suicidal patient in the intensive care unit (ICU) includes evaluation, management, and safeguarding of the patient's safety.
2. Evaluation and management of the suicidal patient requires an understanding of risk factors, protective factors, the interplay among these elements, and the relationship between the staff and the patient.
3. Psychiatric care is essential during and after the stabilization of medical problems. It is helpful to initiate psychiatric involvement from the beginning of the admission, even if the patient is intubated and heavily sedated. In these circumstances, the consulting psychiatrist can obtain collateral information, assess the severity and lethality of the attempt, establish the chronology of symptoms leading to the presentation, and conduct serial safety assessments.

B. Risk and protective factors

1. Suicide is the 11th leading cause of death in the United States (8th in men, 17th in women).
2. It is not possible to make absolute predictions of suicidal behavior.
3. Risk factors for suicide include sociodemographic factors, past and current psychiatric and medical illnesses, family history, and psychosocial stressors (Table 149-1).
4. Protective factors include the absence of these risk factors and the presence of supports.
5. The assessment of risk and protective factors must be conducted on a case-by-case basis.

II. TREATMENT

A. Nonpharmacologic interventions

1. Suicidal thinking can be expressed in various ways, including explicit declaration or implicit action (e.g., refusal to eat or to cooperate with care). All forms of suicidal thinking require immediate attention.
2. Monitoring is essential and can be accomplished through 1:1 observation or frequent checking on the patient. In some situations, physical restraints may be necessary.
3. The ICU staff should be aware of potential means by which the patient may harm himself or herself, including personal belongings and items brought in by visitors.
4. Safety assessments should be made at least daily.
5. The primary team should identify and address negative feelings that may be induced by some suicidal patients, particularly those who have made multiple attempts or who clamor for the attention of the ICU staff.

B. Medications

1. Consideration should be given to discontinuing or decreasing the dose of medications that may heighten impulsivity or disinhibition (e.g., benzodiazepines and anticholinergic agents).

TABLE 149-1 Risk Factors for Suicide

Sociodemographic factors

- Age: late adolescence to young adulthood, older than 65 yr
- Gender: men are more likely to complete suicide, women more likely to attempt
- Race: white
- Marital status: divorced or widowed > single > married

Psychiatric history and present psychiatric illness

- Psychiatric disorders
- Substance abuse
- History of suicide attempts and other self-injurious behavior
- History of homicidal or assaultive behavior
- Impulsivity
- History of physical or emotional trauma
- History of noncompliance with treatment
- Poor tolerance of emotions
- Poor coping skills

Medical history and present medical illness

- Neurologic disorders
- Head trauma
- Cognitive deficits
- Malignancies
- Human immunodeficiency virus infection
- Peptic ulcer disease
- Chronic inflammatory disease
- Chronic renal failure
- Heart disease
- Chronic pulmonary disease

Family history

- Psychiatric illness or substance abuse
- History of completed suicide

Psychosocial stressors

- Family life
- Work life
- Relationships
- Finances
- Recent real or perceived loss
- Few supports

(Adapted from the American Psychiatric Association. *Practice guideline for the assessment and treatment of patients with suicidal behaviors*. Arlington: American Psychiatric Association, 2003. Available at www.psych.org.)

2. Establishing an accurate psychiatric diagnosis will guide the decision to start or restart psychiatric medications following a suicide attempt. Outpatient medications should not be resumed reflexively.
   a. The patient's physical condition, sensorium, and risk for seizures and arrhythmias, as well as medication side effects, should also be considered.

3. Anxiety should be treated, as it is a potent risk factor for suicide. Potential treatment includes benzodiazepines or neuroleptic medications, the latter particularly when anxiety expands into outright fear.

C. Psychiatric consultation

1. Psychiatric consultation is strongly recommended whenever a patient's safety is questionable.
   a. This is particularly important in cases of implicit action or when there are overwhelming risk factors even without an explicit declaration.
   b. Elderly patients often do not reportthoughts of suicide to their caretakers.
2. The primary team should provide the consultant with as many details of the suicide attempt as possible. When an explicit declaration has been made, the team should inform the consultant of the exact words used and the context of the statement.
3. Clear documentation is important.
4. Consultation can also be helpful in understanding and processing the psychological dynamics between patient and staff.

D. Disposition

1. The two options for discharge include home or psychiatric facility.
2. This decision is usually made with the help of the psychiatric consultant, who will assist with placement, insurance authorization, and legal matters (e.g., involuntary commitment if the patient is unwilling to be hospitalized psychiatrically).

Suggested Reading

American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*, 4th ed. Washington: American Psychiatric Association, 1994.
The "bible" of psychiatric diagnosis.

American Psychiatric Association. *Practice guideline for the assessment and treatment of patients with suicidal behaviors.* Arlington: American Psychiatric Association, 2003. Available at www.psych.org.
This practice guideline from the American Psychiatric Association provides a comprehensive review of the evaluation and management of suicidality and also addresses risk management and documentation.

Bryan CJ, Rudd DM. Advances in the assessment of suicide risk. *J Clin Psychol* 2006; 62:185–200.
This recent review discusses the assessment and management of suicidality.

Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS). 2005. Available at: www.cdc.gov/ncipc/wisqars.
This CDC website provides the most recent statistics on fatal and nonfatal suicidal thoughts and behavior.

Roy A. Suicide. In: Sadock BJ, Sadock VA, eds. *Kaplan & Sadock's comprehensive textbook of psychiatry.* 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2000: 2031–2040.
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Stern TA, Perlis RH, Lagomasino IT. Suicidal patients. In: Stern TA, Fricchione GL, Cassem NH, et al., eds. *Massachusetts general hospital handbook of general hospital psychiatry*, 5th ed. St Louis: Mosby, 2004:93–104.
This comprehensive reference for the psychiatric management of medically ill, hospitalized patients summarizes the epidemiology, risk factors, evaluation, and management of suicidality.

150 DIAGNOSIS AND TREATMENT OF DEPRESSION IN THE INTENSIVE CARE UNIT PATIENT

John Querques, Theodore A. Stern, and Edith S. Geringer

I. GENERAL PRINCIPLES

A. Major depressive disorder is a psychiatric condition that affects mood and neurovegetative functions (e.g., sleep, appetite, concentration).

1. While experiencing a depressed mood transiently can be a normal and expected part of life, the full constellation of a clinical major depressive disorder is never a normal or appropriate reaction to a stressful situation.

2. Left untreated, major depression decreases survival in general and increases morbidity and mortality from cardiac conditions.

B. Definition

1. Major depressive disorder is a syndrome characterized by five of the symptoms listed in Table 150-1 for 2 weeks or more.

2. One of the five symptoms must be either depressed mood or anhedonia (i.e., a decrease in one's interests or drives in life).

3. The mnemonic SIG: E CAPS (i.e., label: energy capsules) is a helpful guide to remember these defining criteria (Table 150-1).

II. DIAGNOSIS

A. Clinical features. The manifestations of depression include affective, behavioral, and cognitive abnormalities (i.e., the ABCs of depression) (Table 150-2). The delirious patient will have a reduced level of wakefulness, alertness, and/or attentiveness; that is, the sensorium will be clouded. Though a depressed patient may be psychomotorically slowed and have scant facial expression, his or her sensorium will be intact. The hypomanic or manic patient will have an elevated, expansive, or irritable mood rather than a dysphoric one.

B. Differential diagnosis. Depression in the intensive care unit (ICU) can occur as a primary affective disorder (e.g., major depressive disorder), a mood disorder associated with a specific medical condition or its treatment, or a psychological reaction to an acute medical illness.

1. Medical causes. Various medical conditions (Table 150-3) and medications (Table 150-4) can cause depression. Laboratory testing should be guided by results of a comprehensive history and physical examination.

2. Psychological reaction. Critical illness often threatens a patient's sense of physical integrity, autonomy, and control and can remind some patients of either personal or family histories of similar life-threatening circumstances.

III. TREATMENT

A. Management of depression includes pharmacologic treatment, psychological interventions, and electroconvulsive therapy (ECT).

B. Pharmacologic treatment. In the ICU, medications are used most frequently (Table 150-5). An antidepressant medication is selected based on side effect profile and rapidity of onset of action.

TABLE 150-1 Mnemonic for the Diagnostic Criteria for a Depressive Episode – SIG: E CAPS

Depressed mood
Sleep (increased or decreased)
Interest (decreased)
Guilt (or worthlessness)
Energy (decreased)
Concentration (decreased)
Appetite disturbed (increased or decreased) or weight gain or loss
Psychomotor agitation or retardation
Suicidal thinking or thoughts of death

(Adapted from American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington, DC, American Psychiatric Association, 1994.)

TABLE 150-2 Affective, Behavioral, and Cognitive Features of Depression – the ABCs

Affective symptoms
Depressed mood
Hopelessness
Crying
Irritability
Anger
Decreased interest
Behavioral symptoms
Insomnia
Anorexia
Apathy
Increased sleep
Increased appetite
Decreased energy
Psychomotor agitation
Psychomotor retardation
Noncompliance
Deliberate self-harm
Impulsivity
Poor eye contact
Increased or intractable pain
Cognitive symptoms
Guilty rumination
Decreased concentration
Suicidal thinking or thoughts of death
Confusion
Dementia-like symptoms
Somatic preoccupation

(Adapted from Geringer ES, Kolodziej M, Burns T, et al. Diagnosis and treatment of depression in the intensive care unit patient. In: Irwin RS, Rippe JM, eds. *Intensive care medicine*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2008:2304–2319.)

TABLE 150-3 Selected Medical Conditions Associated with Depression

Cardiovascular
Congestive heart failure
Hypertensive encephalopathy
Collagen-vascular
Systemic lupus erythematosus
Endocrine
Diabetes mellitus
Hypo- and hyperadrenalism
Hypo- and hyperparathyroidism
Hypo- and hyperthyroidism
Infectious
Hepatitis
Human immunodeficiency virus infection
Mononucleosis
Metabolic
Acid–base disorders
Hypokalemia
Hypo- and hypernatremia
Renal failure
Neoplastic
Carcinoid syndrome
Pancreatic carcinoma
Paraneoplastic syndromes
Neurologic
Brain tumor
Multiple sclerosis
Parkinson disease
Complex partial seizures
Stroke
Subcortical dementia
Nutritional
Vitamin B_{12} deficiency (pernicious anemia)
Thiamine deficiency (Wernicke encephalopathy)

(Adapted from Geringer ES, Kolodziej M, Burns T, et al. Diagnosis and treatment of depression in the intensive care unit patient. In: Irwin RS, Rippe JM, eds. *Intensive care medicine*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2008:2304–2319.)

1. Psychostimulants
   a. Dextroamphetamine and methylphenidate work within hours to days.
   b. Can cause or contribute to tachycardia, hypertension, arrhythmias, and coronary spasm, but rarely at the low doses (5 to 20 mg daily) usually used
   c. Bupropion and modafanil can also be used for their stimulant-like effects and usually have some effect within a few days to a week, certainly earlier than the selective serotonin reuptake inhibitors (SSRIs).
2. Selective serotonin reuptake inhibitors
   a. Exert their therapeutic effect within 4 weeks
   b. Can cause agitation, irritability, insomnia, tremulousness, diaphoresis, anorexia, nausea, vomiting, diarrhea, and sexual dysfunction

TABLE 150-4 Selected Medications Associated with Depression

Acyclovir (especially at high doses)
Anabolic steroids
Anticonvulsants (at high doses or plasma levels): carbamazepine, phenytoin, primidone
Antihypertensives: reserpine, methyldopa, thiazides, clonidine, nifedipine, prazosin
Asparaginase
Baclofen
Barbiturates
Benzodiazepines
β-Blockers
Bromocriptine
Contraceptives
Corticosteroids
Cycloserine
Dapsone
Digitalis (at high doses or in elderly patients)
Diltiazem
Disopyramide
Halothane (postoperatively)
Histamine-2 receptor antagonists
Interferon-α
Isoniazid
Levodopa (especially in elderly patients)
Mefloquine
Metoclopramide
Metrizamide
Nalidixic acid
Narcotics
Nonsteroidal anti-inflammatory drugs
Phenylephrine
Phenylpropanolamine (withdrawal)
Procaine derivatives: penicillin G procaine, lidocaine, procainamide
Thyroid hormone
Trimethoprim–sulfamethoxazole

(Adapted from Geringer ES, Kolodziej M, Burns T, et al. Diagnosis and treatment of depression in the intensive care unit patient. In: Irwin RS, Rippe JM, eds. *Intensive care medicine*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2008:2304–2319.)

c. SSRIs, when given in combination with other serotonergic drugs (rarely when used alone), can cause serotonin syndrome, an uncommon but potentially fatal condition of serotonergic hyperstimulation characterized by confusion, agitation, incoordination, tremor, myoclonus, diaphoresis, shivering, diarrhea, hyperthermia, and hyperreflexia. Treatment is largely supportive and includes discontinuation of the offending agents.

d. Have fewer cardiovascular effects than tricyclic antidepressants (TCAs) and do not commonly cause orthostatic hypotension

e. Are extensively metabolized by the hepatic cytochrome P-450 system

f. All of them, except citalopram and escitalopram, inhibit this enzymatic pathway and raise serum levels of coadministered drugs (Table 150-6).

TABLE 150-5 Usual Starting Doses of Antidepressant Agents in Critically Ill Patients

Agent	Usual starting dose (mg/d)
Selective serotonin reuptake inhibitors	
Citalopram	5–10
Escitalopram	5–10
Fluoxetine	5–10
Paroxetine	5–10
Sertraline	25–50
Serotonin-norepinephrine reuptake inhibitors	
Duloxetine	30–60
Venlafaxine	37.5–75
Others	
Bupropion	50–100
Dextroamphetamine	2.5–5
Methylphenidate	5
Mirtazapine	7.5–15

TABLE 150-6 Selected Substrates and Inhibitors of Cytochrome P-450 Isoenzymes

	1A2	2C	2D6	3A3/4
Substrates	Acetaminophen	Barbiturates	Codeine	Amiodarone
	Aminophylline	Diazepam	Encainide	Calcium channel blockers
	Haloperidol	Omeprazole	Flecainide	Diazepam
	TCAs	Phenytoin	Haloperidol	Disopyramide
	Theophylline	Propranolol	Hydrocodone	Lidocaine
		TCAs	Metoprolol	Macrolide antibiotics
			Propranolol	Omeprazole
			TCAs	Quinidine
			Timolol	Steroids
				TCAs
Inhibitors	Fluoxetine	Fluoxetine[a]	Fluoxetine[a]	Fluoxetine
	Paroxetine	Sertraline	Paroxetine[a]	Nefazodone[a]
			Sertraline	Sertraline

[a]Strong inhibitor.
TCA, tricyclic antidepressant.
(Adapted from Geringer ES, Kolodziej M, Burns T, et al. Diagnosis and treatment of depression in the intensive care unit patient. In: Irwin RS, Rippe JM, eds. *Intensive care medicine*, 6th ed. Philadelphia: Lippincott Williams& Wilkins, 2008:2304–2319.)

3. Serotonin-norepinephrine reuptake inhibitors (SNRIs)
   a. Venlafaxine
      i. Exerts its therapeutic effect within 4 weeks, similar to SSRIs
      ii. Can cause a dose-dependent increase in supine diastolic blood pressure
      iii. Does not inhibit the P-450 system
   b. Duloxetine
      i. Exerts its therapeutic effect within 4 weeks, similar to SSRIs
      ii. Is also U.S. Food and Drug Administration (FDA)-approved for diabetic neuropathy
4. α_2 Adrenergic receptor antagonist
   a. Mirtazapine
      i. Enhances presynaptic release of norepinephrine and serotonin
      ii. Improves sleep and appetite within a few days, while a full antidepressant effect usually develops within 4 weeks
      iii. Is available in an orally disintegrating formulation that is useful in patients who cannot swallow pills
5. TCAs
   a. Exert their therapeutic effect within 4 weeks
   b. Can cause sedation, confusion, blurred vision, dry mouth, constipation, orthostatic hypotension, and disturbances of cardiac conduction and rhythm
   c. Should be used with great caution in patients
      i. With preexisting conduction delays
      ii. With a corrected QT interval (QTc) of >440 ms
      iii. Who are taking other drugs that also have type I antiarrhythmic effects
6. Monoamine oxidase inhibitors
   a. They exert their therapeutic effect within 4 weeks.
   b. Phenelzine and tranylcypromine are not recommended in the ICU because of the profound hypertensive crises that might result when these agents are combined with pressors.

C. Psychological. Patients often benefit from information, clarification, reassurance, and support. Asking about patients' families, work, hobbies, and interests helps restore their sense of identity.

D. ECT. ECT is reserved for patients with severe or delusional depression and for those who cannot tolerate, or have failed to respond to, pharmacologic and talking therapies.

Suggested Reading

Cassem NH, Papakostas GI, Fava M, et al.Mood-disordered patients. In: Stern TA, Fricchione GL, Cassem NH, et al., eds. *Massachusetts general hospital handbook of general hospital psychiatry*, 5th ed. Philadelphia: Mosby, 2004: 69–92.
A comprehensive review of the characteristics of depressive disorders, their differential diagnosis, and their treatment in the context of comorbid medical illness.

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A randomized, double-blind, placebo-controlled trial of 369 patients with major depressive disorder and either acute MI or unstable angina, which showed that sertraline is a safe and effective treatment for recurrent depression in patients with unstable ischemic cardiac disease—the first published evidence that antidepressant drugs are safe and efficacious in this population.

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Moral, Ethical, Legal Issues, and Public Policy in the Intensive Care Unit

XVI

ETHICAL AND LEGAL ISSUES IN INTENSIVE CARE

151

John S. J. Paris, Gregory Webster, Robert Burke, and Michael Patrick Moore

I. BACKGROUND

- **A.** Medial ethics applies moral principles to choices made in a medical context
- **B.** Major principles in bioethics are
  - **1.** Autonomy
    - **a.** The dignity of every human allows the competent individual to make personal choices regarding medical treatment.
    - **b.** An individual without decision-making capacity also has the right of choice with regard to medical decisions.
      - **i.** Exercised by a surrogate or designated proxy.
      - **ii.** Decisions are to be based on the patient's personal values. If these are not known, decision is made in the best interest of the patient.
  - **2.** Beneficence: The physician has a fiduciary duty to act for the patient's well-being.
  - **3.** Nonmaleficence Physician must seek to avoid harm to the patient. The guiding principle of physician's interaction with the patient is "First, do no harm."
  - **4.** Justice
    - **a.** Individual justice Provide each person with what is due to individual within the circumstances of the situation.

- **b.** Social justice Concerned with the impact of individual decisions on the community as a whole. The common good as well as individual benefit must be considered.
- **5.** Truth telling Requires the physician to be open and honest with the patient.
- **6.** Promise keeping Physician owes a duty of loyalty to the patient.
- **7.** Confidentiality
  - **a.** The physician keeps secret those things revealed by the patient in the physician–patient relationship.
  - **b.** Two exceptions
    - **i.** There is a "duty to warn" if there is a danger of significant harm to a third party. (Gunshot wounds and suspected child abuse have mandatory reporting requirements.)
    - **ii.** Communicable diseases such as tuberculosis or smallpox must be reported to the public health authorities.

II. DECISION-MAKING PROCESS

- **A.** Age of physician paternalism—"The doctor knows best"—is over.
- **B.** Good medical decision making is not one-dimensional. At a minimum, it must consider three factors: physician, patient, and society.
  - **1.** Physician
    - **a.** Diagnosis: Determination of the patient's medical condition.
    - **b.** Prognosis: Assessment of implications of the diagnosis based on medical training and experience.
    - **c.** Recommendation: Physician has a positive duty to propose a treatment regime to the patient.
    - **d.** Action: Physician has a duty to carry out agreed-upon treatments or to update the patient on changing circumstances that prevent the agreed-upon treatment from proceeding.
  - **2.** Patient Assesses the physician's recommendation based on individual psychosocial values. Entire range of factors such as cost, burden, pain, anticipated outcome, dislocation, family structure, and personal plans are to be considered. Patient (or proxy) then decides to
    - **a.** Accept proposed treatment.
    - **b.** Negotiate with the physician for a different course.
      - **i.** Different, but equivalent, medical treatment
      - **ii.** Selective utilization of conventional medicine
      - **iii.** Supplemental, herbal, or nonconventional medicine
    - **c.** Request consultation for second opinion
    - **d.** Reject the proposed treatment
      - **i.** Seeks alternative or nonconventional modalities in the absence of conventional medicine.
    - **e.** Omits any treatment.
  - **3.** Society
    - **a.** Protects individual from undertreatment or neglect.
    - **b.** Intervenes to prevent over treatment.
      - **i.** Unwanted by the patient—Court rulings from Quinlan (1976) to Cruzan (1990) establish that both competent and noncompetent patients have a right to refuse unwanted medical interventions.
    - **c.** Treatment wanted by patient (or proxy) but believed by physician to be
      - **i.** Overly burdensome
      - **ii.** Medically unwarranted—Texas, Virginia, Maryland and California have statutes authorizing a physician to discontinue requested treatment if no other facility can be located willing to treat the

patient as the patient or proxy demand. In other jurisdictions such patient-physician conflicts continue to be legally unresolved.

d. Treatment wanted by the patient and offers benefit, but believed to be overly expensive by
  i. Insurance plan
  ii. Health Maintenance Organization (HMO)
  iii. Medicare/medicaid
  iv. Other rationing-by-price model Insurance plans place restrictions on high cost procedures by "denial of benefit," high deductions, tiered co-payments or other "consumer directed" control mechanisms.

e. What is society's action here? Treatment that is not considered life-saving or life-preserving.
  i. Insurance plans may place some procedures in a "non-covered" category. The decision to purchase the procedure out of pocket is up to the patient.

4. Courts should be the place of last resort to resolve utterly irreconcilable clashes.
  a. Costly
  b. Cumbersome
  c. Adversarial
  d. Unpredictable
    i. Always support requests for life-sustaining treatment.
    ii. Set standards which then govern medical practices.

III. RESPONSIBILITY FOR DECISION. Judgments concerning burden and benefit of a recommended treatment for the patient are moral choices.

A. Belong to patient or those responsible for the welfare of an incompetent patient.

B. Disputes between physician and patient (or proxy).

1. Best resolved by negotiation between physician and patient or involvement of an ethics committee.

a. Prevailing standards of both the ethics and the law dictate that the physician should not substitute physician assessment for patient values.
  i. Patient preferences with regard to recommended treatment should prevail.
  ii. Patient (or proxy) may request, but *cannot compel*, treatment not recommended by physician.
  iii. In cases where it is thought that the proxy may not be acting in the best interests of the patient, early involvement of the hospital ethics committee is essential.

b. Physicians considering withholding or withdrawing life-sustaining treatment over the patient or family objections should not act unilaterally.
  i. American Medical Association (AMA) Guidelines recommend a procedural rather than a substantive approach for resolving physician–patient (or proxy) disputes. Decision should be:
    (a) Made in consultation with specialists.
    (b) Reviewed in light of relevant medical literature.
    (c) Approved by an ethics committee.
    (d) Patient (or proxy) given opportunity for outside second opinion.
    (e) Patient (or proxy) given opportunity of a transfer.
  ii. Once these steps are taken, AMA Guidelines indicate that the treating physician has no further obligation to follow family

demands. Documentation of the above in the medical chart is imperative.

IV. DO-NOT-RESUSCITATE (DNR) ORDERS. Despite strong agreement in ethical literature and judicial rulings that patient preferences on forgoing aggressive medical interventions should be respected, the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) reveals that physicians are reluctant to honor such requests. This is particularly true of DNR orders.

- **A.** One third of patients preferred cardiopulmonary resuscitation (CPR) be withheld.
  1. Only 47% of physicians accurately reported that preference.
  2. 49% of those patients did not have a written "DNR order."
- **B.** Blackhall notes, "Physicians have no obligation to provide, and patients and families no right to demand medical treatment that is of no demonstrable benefit."
  1. In cases where CPR will not have demonstrable benefit, the patient or family desire for CPR is irrelevant.
  2. Assessment of anticipated medical benefit is a decision entirely made within the physician's technical expertise. The physician's duty is to explain to the family that if the patient's physical condition is such that no intervention will reverse the dying process, then when cardiac arrest occurs during the final phase of the dying process, CPR will not be attempted.
- **C.** The appropriateness of CPR when attempts at resuscitation are likely to be successful is a decision to be made by the patient or family based on assessment of the patient's present or future quality of life. That subjective choice belongs to the patient.
- **D.** Decision making on CPR for the elderly dying patient with no family or friends should be made as it customarily has been done in hospitals—by the attending physician with the concurrence of another physician or an institutionally designated patient advocate. Such a decision is well within the scope of common medical practice. Are there differences in state laws in this that one needs to be aware of?
  1. It should not be elevated to the role of moral dilemma.
  2. It should not be perceived as a judicial problem.
  3. Patients should not be subjected to aggressive attempts at resuscitation without a reasonable expectation of successful outcome.

V. BRAIN DEATH. Although philosophical debate continues on the meaning of death, as a practical matter every jurisdiction recognizes medically determined cessation of electrical activity in the brain as death. We find it useful when talking to residents that the definition of brain death involves the whole brain (brain stem and cortex). Do you agree?

- **A.** The brain dead patient is dead.
- **B.** Other than for potential organ donation, there is no legal or medical rationale to oxygenate the cadaver.
- **C.** No family permission is required to cease ventilation of the corpse; none should be requested.
  1. Physician should inform the family that the patient is dead.
  2. Physician should request organ donation.
  3. If the family declines organ donation, the physician should inform—*not ask*—the family that all medical interventions will be withdrawn.

VI. WITHHOLDING AND WITHDRAWAL OF MEDICAL INTERVENTIONS. Once it is agreed that a particular intervention is not appropriate—because patient refuses it or it proves ineffective—it may be withdrawn.

- **A.** The same justification that applies to withholding a treatment, that is never starting treatment applies to withdrawal (removing the intervention).
  - **1.** No legal difference between withholding and withdrawal.
  - **2.** No ethical difference between withholding and withdrawal.
  - **3.** It is psychologically easier not to start than to stop.
- **B.** The moral issue in withholding/withdrawal of an intervention is to ensure patient comfort.
  - **1.** Too rapid a withdrawal of ventilatory support produces air hunger, gagging, gasping, and struggle in patient.
    - **a.** Premedicate patient
      - **i.** Morphine to alleviate dyspnea
      - **ii.** Benzodiazepine for anxiety
      - **iii.** Titrate to patient's comfort
    - **b.** Do not institute neuromuscular blocking agents at the time of disconnecting ventilator.
      - **i.** Blurs difference of allowing to die and actively causing patient's death.
      - **ii.** Have no analgesic or sedative properties.
    - **c.** If neuromuscular agents are already in use
      - **i.** Attempt to reverse paralysis.
      - **ii.** If effect cannot be expeditiously reversed, do not compel the patient and family to wait days or weeks until paralysis is reversed before withdrawal of ventilator.
        - **(a)** Write a clear note in chart on rationale for withdrawal despite presence of paralytic agent
        - **(b)** Provide explanation that withdrawal is not a means of achieving euthanasia.

VII. ADVANCE DIRECTIVES. The federal Patient Self-Determination Act of 1990 mandates that all medical facilities should notify patient of right to decline unwanted medical interventions.

- **A.** Living will
  - **1.** Written statement of patient's wishes regarding utilization of medical therapies should patient lose decision-making capacity.
  - **2.** Tend to be written in broad terms. Unless very specific, these are not very helpful in making nuanced or difficult decisions for the patient.
- **B.** "Durable power of attorney" designates a health care agent who is authorized to make medical decisions for the incompetent patient.
  - **1.** The agent has the same decision-making role as the patient.
    - **a.** Acts on known values of patient.
    - **b.** Is able to adjust decisions to changing clinical situation.
  - **2.** Existence of a proxy does not absolve medical staff of responsibility to assure decisions are made in the patient's best interests.

VIII. MYTHS AND MISCONCEPTIONS ON LEGAL BARRIERS TO END-OF-LIFE CARE. The American College of Physicians Consensus Panel on End-of-Life Care identified the following as *commonly held myths*:

- **A.** *Forgoing life-sustaining treatments for patients without decision-making capacity requires evidence that this was the patient's actual wish.* [THE REALITY: A surrogate may speak to the known values of a patient lacking decision-making capacity.]

B. *Withholding or withdrawing artificial fluids and nutrition from terminally ill or permanently unconscious patients is illegal.* [THE REALITY: Artificial nutrition and fluids are medical treatments to be assessed as any other medical intervention, i.e., on the basis of the proportionate benefit and burden to the patient.]

C. *Risk management must be consulted before life-sustaining medical treatment may be terminated.* [THE REALITY: Be aware that the goal of risk management is to minimize exposure of potential liability rather than determining the ethically or clinically appropriate treatment for an individual or providing "an objective legal analysis" of a particular situation.]

D. *Advance directives must comply with specific forms, are not transferable between states, and govern all future treatment decisions; oral advance directives are not enforceable.* [THE REALITY: No specific form is required for an advance directive. Patients may express their wishes and may do so either in writing or orally.]

E. *Administration of high doses of narcotics to relieve pain in terminally ill patients which might hasten death are subject to criminal prosecution.* [THE REALITY: The Supreme Court in *Cruzan* noted that patients are to be provided with the level of analgesic necessary for pain relief even if that medication might foreshorten the patient's life.]

1. The evidence required for surrogate decision making for incompetent patients varies by states. Physicians should seek guidance from legal counsel if unsure of a requirement in a particular state.
2. Oregon is the only state that allows physician-assisted suicide, that is the physician may write a prescription for a lethal dose of medication which the patient self-administers to end his or her life.
3. In all states, including Oregon, active euthanasia, that is physician-administered measures to end life, is illegal. Such action, even if requested by the patient, is subject to criminal prosecution.

Suggested Reading

American Thoracic Society. Withholding and withdrawal of life-sustaining therapy. *Am Rev Respir Dis* 1991;144:726–731.
Official guidelines on end-of-life care by the professional association of physicians who treat patients with respiratory diseases.

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Blackhall L. Must we always use CPR? *N Engl J Med* 1987;317:1281.
A landmark article on limits for use of cardiopulmonary resuscitation.

Curtis JR, Rubenfeld GD. *Managing death in the intensive care unit: the transition from cure to comfort*. New York: Oxford University Press, 2001.
A comprehensive review of ICU care at the end-of-life. Has specific recommendations on transition from attempts at cure to provision of comfort care only.

D'Alessandro AM, Peltier JW, Phelps JE. Understanding the antecedent of the acceptance of donation after cardiac death by health care professionals. *Crit Care Med* 2008;36:1075–1081.
A thorough review of the barriers and concerns among both families and professionals on donation after cardiac death (DCD) organ transplantation.

Fetters MD, Churchill L, Denis M. Conflict resolution at the end of life. *Crit Care Med* 2001;29:921–925.
Discussion of the way physicians handle requests for treatment deemed non-beneficial by either the physician or family.

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This article demonstrates considerable variability in following American Academy of Neurology guidelines on determination of brain death among leading neurologic hospitals in the United States.

Luce JM. Physicians do not have a responsibility to provide futile or unreasonable care if a patient or family insists. *Crit Care Med* 1995;23:760.
A forceful statement by one of the nation's leading physician's on the limits of a patient's right to demand medical interventions.

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A thorough review of legal myths and mythic fears that frequently hinder physicians from providing appropriate end-of-life care.

Nyman DJ, Sprung CL. End-of-life decision making in the intensive care unit. *Intensive Care Med* 2000;26:1414–1420.
Excellent review of issues confronting physicians in ICUs.

Paris JJ, Crone RK, Reardon FE. Physician refusal of requested treatment: the case of Baby L. *N Engl J Med* 1990;322:1012.
First reported case of physician refusal to provide a life-sustaining intervention.

Paris JJ, Schreiber MD, Statter M, et al. Beyond autonomy: physician refusal of life-prolonging ECMO. *N Engl J Med* 1991;325:511.
First reported case of physician refusal to continue life-prolonging technology.

The Society of Critical Care Medicine Ethics Committee. Attitudes of critical care medicine professionals concerning distribution of intensive are resources. *Crit Care Med* 1994;22:358.
A survey of attitudes of critical care providers on distribution or resources.

Spring CL, Cohen SL, Sjokvist P, et al. End-of-life practices in European intensive care units: the Ethics study. *JAMA* 2003;290:790–797.
A review of practice patterns in 37 ICUs across 17 European countries reveals that physician biases as well as medical status influence end-of-life decisions.

The SUPPORT Principal Investigators. A controlled trial to improve care for seriously ill hospitalized patients: the study to understand prognosis and preferences for outcomes and risks of treatments (SUPPORT). *JAMA* 1995;274:1591.
A landmark study of physician behavior in critical care medicine.

Thurow L. Learning to say "no." *N Engl J Med* 1984;311:1569.
A superb essay by an economist that in the absence of agreed-on societal values the marketplace will determine what medicine will be provided.

Treece P, Engelberg RA, Crowley L, et al. Evaluation of a standardized order form for withdrawal of life support in the intensive care unit. *Crit Care Med* 2004;32:1141–1148.
A helpful mechanism for consistent application of appropriate sedation without hastening death in ICU.

Truog RD, Burns JP, Mitchell C, et al. Pharmacologic paralysis and withdrawal of mechanical ventilation at the end of life. *N Engl J Med* 2000;342:508–511.
A careful analysis of appropriate medication to accompany withdrawal of ventilatory support.

Truog RD, Campbell ML, Curtis JR, et al. Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American Academy of Critical Care Medicine. *Crit Care Med* 2008;36:953–963.
The most up to date guidelines from American Academy of Critical Care Medicine on end-of-life care in the ICU.

Veatch RM, Spicer CM. Medically futile care: the role of the physician in setting limits. *Am J Law Med* 1992;18:15.
The best statement of the position that patient autonomy is the overriding principle in medical ethics.
Weil MH, Dellinger RP. In-hospital cardiac arrest. *Crit Care Med* 2005;33: 2825–2830.
A fine concise review of indications for the use of CPR in a hospital setting.
Wenrich MD, Curtis JR, Shannon S, et al. Communicating with dying patients within the spectrum of medical care from terminal diagnosis to death. *Arch Inter Med* 2001;161:868–874.
A sensitive and thoughtful exploration of communication skills in delivering bad news.
Whetstine LM. Advance directives and treatment decisions in the intensive care unit. *Crit Care Med* 2007;11:150–152.
A good review of the limited usefulness of "living wills" as a guide to decision making in the ICU. More valuable is the designation of a health care proxy to make treatment decisions on behalf of an incapacitated patient.
White DR, Curtis JR, Lo B, et al. Decisions to limit life-sustaining treatment for critically ill patients who lack both decision-making capacity and surrogate decision-makers. *Crit Care Med* 2006;34:2053–2059.
A practical guide for decision making on dying incapacitated patients who lack a surrogate.

Legal Cases

1. *In re Quinlan*, 355 A.2 d 647 (1976)
   The New Jersey Supreme Court's landmark decision in the nation's first "right to die" case.
2. *Superintendent of Belchertown State School v. Saikewitz*, 370 N.E.2 d 417 (1977)
   The Massachusetts Supreme Judicial Court ruling that formulated the "substituted judgment" standard for resolving treatment decisions for noncompetent patients. The case is an excellent summary of the ethical norms on end-of-life decision making.
3. *In re Cruzan, Cruzan v. Director*, Missouri Department of Public Health, 497 V.l. 261 (1990)
   The United States Supreme Court opinion that recognized the constitutional right of competent patients to decline any and all unwanted medical interventions including potentially life-prolonging treatments. The same right applies to incompetent patients. The evidentiary standard required for proxy decision making may be set by the various states. It is important to know what, if any, requirements prevail in a particular state.

Calculations Commonly Used in Critical Care

Mark M. Wilson

APP

A. FAHRENHEIT AND CELSIUS TEMPERATURE CONVERSIONS

°C	°F
45	113.0
44	111.2
43	109.4
42	107.6
41	105.8
40	104.0
39	102.2
38	100.4
37	98.6
36	96.8
35	95.0
34	93.2
33	91.4
32	89.6
31	87.8
30	86.0
29	84.2
28	82.4
27	80.6
26	78.8
25	77.0

°C to °F: $°F = (°C \times 9/5) + 32$
°F to °C: $°C = (°F - 32) \times 5/9$

B. DOSAGE AND ACTION OF COMMON INTRAVENOUS VASOACTIVE DRUGS

	Dosage	α	β_1	β_2
Dopamine	1–2 μg/kg/min	+	+	0
	2–10 μg/kg/min	++	+++	0
	10–30 μg/kg/min	+++	++	0
Dobutamine	2–30 μg/kg/min	+	+++	++
Norepinephrine	0.05–1 mg/kg/min, titrate to effect	+++	++	+
Epinephrine	0.1–1.0 mg/kg/min	++	+++	+++
Isoproterenol	2–10 μg/min	0	+++	+++
Phenylephrine	0.1–0.5 mg/kg/min	+++	0	0
Vasopression	0.04 units/min	0	0	0

Degree of receptor stimulation: 0, none; +, weak; ++, moderate; +++, strong.

C. HEMODYNAMIC CALCULATIONS

MEAN ARTERIAL BLOOD PRESSURE (mm Hg)
= MAP
= (systolic BP + [2 × diastolic BP])/3
= diastolic BP + 1/3 (systolic BP − diastolic BP)
Normal range: 85–95 mm Hg

FICK EQUATION FOR CARDIAC INDEX (L/min/m^2)
= CI
= CO/BSA
= oxygen consumption/(arterial O_2 content − venous O_2 content)
= (10 × V.O_2[mL/min/m^2])/(Hgb [g/dL] × 1.39
×[arterial % saturation − venous % saturation])
Normal range: 2.5–4.2L/min/m^2

SYSTEMIC VASCULAR RESISTANCE (dyne/sec/cm^5)
= SVR
= (80 × [MAP − right atrial mean BP])/CO [L/min]
Normal range: 770–1,500 dyne/sec/cm^5

PULMONARY VASCULAR RESISTANCE (dyne/sec/cm^5)
= PVR
= (80 × [pulmonary artery mean BP
−pulmonary capillary wedge pressure])/CO [L/min]
Normal range: 20–120 dyne/sec/cm^5

D. PULMONARY CALCULATIONS

ALVEOLAR GAS EQUATION (mm Hg)
$PA_{O_2} = PI_{O_2} - (Pa_{CO_2}/R)$
$= [F_{IO_2} \times (P_{atm} - P_{H_2O})] - (Pa_{CO_2}/R)$
$= 150 - (Pa_{CO_2}/R)$(on room air, at sea level)
Normal value: ~100 mm Hg (on room air, at sea level)

ALVEOLAR − ARTERIOLE OXYGEN TENSION GRADIENT (mm Hg)
= A − a gradient
$= PA_{O_2} - Pa_{O_2}$
Normal values (upright): 2.5 + (0.21 × age)

ARTERIAL BLOOD OXYGEN CONTENT (mL/dL)
$= Ca_{O_2}$
= Oxygen dissolved in blood + oxygen carried by hemoglobin
= (0.003[mL O_2/dL] × Pa_{O_2}) + (1.39 × Hgb[g/dL] × %Hgb saturated with O_2)
Normal range: 17.5–23.5 mL/dL

COMPLIANCE (mL/cm H_2O)
= ΔVolume/ΔPressure
On Mechanical Ventilation:
Static respiratory system compliance = C_{st} = Tidal volume/($P_{plateau} - P_{endexp}$)
Dynamic effective compliance = C_{dyn} = Tidal volume/($P_{peak} - P_{end\,exp}$)

E. ELECTROLYTE AND RENAL CALCULATIONS

ANION GAP (mEq/L)
$= [Na^+] - ([Cl^-] + [HCO_3^-])$
Normal range: 9–13 mEq/L

EXPECTED ANION GAP IN HYPOALBUMINEMIA
$= 3 \times$ [(albumin ([g/dL)])

CALCULATED SERUM OSMOLALITY (mOsm/kg)
$= (2 \times [Na^+]) + ([glucose]/18) + ([BUN]/2.8)$
Normal range: 275–290 mOsm/kg

OSMOLAR GAP (mOsm/kg)
= Measured serum osmolality – Calculated serum osmolality
Normal range: 0–5 mOsm/kg

Na^+ CORRECTION FOR HYPERGLYCEMIA
Increase $[Na^+]$ by 1.6 mEq/L for each 100 mg/dL increase in (glucose) above 100 mg/dL

Ca^{2+} CORRECTION FOR HYPOALBUMINEMIA
Increase $[Ca^{2+}]$ by 0.8 mg/dL for each 1.0 gm/dL decrease in (albumin) from 4 g/dL

WATER DEFICIT IN HYPERNATREMIA (L)
$= [(0.6 \times$ body weight ([kg])] $\times \{([Na^+]/140) - 1\}$

Na^+ DEFICIT IN HYPONATREMIA (mEq)
$= (0.6 \times$ body weight [kg]) $\times$ (desired plasma $[Na^+] - 140)$

FRACTIONAL EXCRETION OF SODIUM (%)
$= F_ENa$
$= \{$(excreted $[Na^+]$)/(filtered $[Na^+]$)$\} \times 100$
$= \{$(urine $[Na^+]$)/(serum $[Na^+]$)$\}/\{$(urine [Creat])/(serum [Creat])$\} \times 100$

CREATININE CLEARANCE (mL/min)
= (urine [Creat]) $\times$ (urine volume over 24 h)
= (urine [Creat (g/dL)])
$\times \{$(urine volume [mL/d])/1440 [min/d])$\}$/serum [Creat](mg/dL)
Estimated for males
$= \{(140 -$ age) $\times$ [lean body weight (kg)]$\}/\{$serum [Creat](mg/dL) $\times 72\}$
Estimated for females = 0.85 $\times$ (estimate for males)
Normal range: 74–160 mL/min
ANION GAP (mEq/L)
$= [Na^+] - ([Cl^-] + [HCo_3^-])$ Normal range: 9–13 mEq/L

EXPECTED ANION GAP IN HYPOALBUMINEMIA
$= 3 \times$ [albumin (g/dL)]

CALCULATED SERUM OSMOLALITY (mOsm/kg)
$= (2 \times [Na^+]) + ([glucose]/18) + ([BUN]/2.8)$
Normal range: 275–290 mOsm/kg

OSMOLAR GAP (mOsm/kg)
= Measured serum osmolality–Calculated serum osmolality

Normal range: 0–5 mOsm/kg

Na^+ CORRECTION FOR HYPERGLYCEMIA
Increase $[Na^+]$ by 1.6 mEq/L for each 100 mg/dL increase in [glucose] above 100 mg/dL

Ca^{2+} CORRECTION FOR HYPOALBUMINEMIA
Increase $[Ca^{2+}]$ by 0.8 mg/dL for each 1.0 gm/dL decrease in [albumin] from 4 g/dL

WATER DEFICIT IN HYPERNATREMIA (L)
$= [0.6 \times \text{body weight (kg)}] \times \{([Na^+]/140) - 1\}$

Na^+ DEFICIT IN HYPONATREMIA (mEq)
$= [0.6 \times \text{body weight (kg)}] \times (\text{desired plasma } [Na^+] - 140)$

FRACTIONAL EXCRETION OF SODIUM (%)
$= F_ENa$
$= \{(\text{excreted } [Na^+])/(\text{filtered } [Na^+])\} \times 100$
$= \{(\text{urine } [Na^+])/(\text{serum } [Na^+])\}/\{(\text{urine [Creat]})/(\text{serum [Creat]})\} \times 100$

CREATININE CLEARANCE (mL/min)
= (urine [Creat]) × (urine volume over 24 h)
$= \{(\text{urine [Creat (g/dL)]})\}$
$\times \{[\text{urine volume (mL/d)}]/1440 \text{ (min/d)}]\}/\text{serum [Creat] (mg/dL)}$
Estimated for males
$= \{(140 - \text{age}) \times [\text{lean body weight (kg)}]\}/\{\text{serum [Creat] (mg/dL)} \times 72\}$
Estimated for females = 0.85 × (estimate for males)
Normal range: 74–160 mL/min

F. ACID–BASE FORMULAS

HENDERSON'S EQUATION FOR $[H^+]$
$[H^+](nm/L) = 24 \times \{Paco_2/[HCO_3^-]\}$
Normal values: $[H^+]$ is 40 nm/L at pH of 7.40 and each 0.01 unit change in pH corresponds to an approximate opposite deviation of $[H^+]$ of 1 nm/L (over the pH range of 7.10–7.50)

METABOLIC ACIDOSIS
Bicarbonate deficit (mEq/L) $= 0.5 \times \text{body weight (kg)} \times (24 - [HCO_3^-])$
Expected $Paco_2$ compensation $= (1.5 \times [HCO_3^-]) + 8 \pm 2$

RESPIRATORY ACIDOSIS
Acute $= \Delta[H^+]/\Delta Paco_2 = 0.8$
Chronic $= \Delta[H^+]/\Delta Paco_2 = 0.3$

RESPIRATORY ALKALOSIS
Acute $= \Delta[H^+]/\Delta Paco_2 = 0.8$
Chronic $= \Delta[H^+]/\Delta Paco_2 = 0.17$

G. NEUROLOGIC CALCULATIONS

GLASGOW COMA SCALE
= eye score(1 – 4) + motor score(1 – 6) + verbal score(1 – 5)

Specific Components of the Glasgow Coma Scale:

Component	Score
Eye opening	
spontaneous	4
to speech	3
to pain	2
none	1
Motor response	
obeys commands	6
localizes	5
withdraws	4
exhibits abnormal flexion	3
exhibits abnormal extension	2
none	1
Verbal response	
oriented	5
confused, conversant	4
uses inappropriate words	3
incomprehensible sounds	2
none	1
Normal total value: 15 (range 3–15)	

GLASGOW COMA SCALE

H. PHARMACOLOGIC CALCULATIONS

DRUG ELIMINATION CONSTANT
= Ke
= fractional elimination of drug per unit time
= {ln ([peak]/[trough])/($t_{peak} - t_{trough}$)}

DRUG HALF-LIFE
= $t^{1/2}$
= 0.693/Ke

VOLUME OF DISTRIBUTION (L/kg)
= Vd
= [(dose) × (fraction of active drug in circulation)]/[(area under single dose curve) × Ke]

DRUG CLEARANCE
= Vd × Ke

DRUG LOADING DOSE
= Vd × [target peak]

DRUG DOSING INTERVAL
= {$-Ke^{-1}$ × ln ([desired trough]/[desired peak])} + infusion time (h)

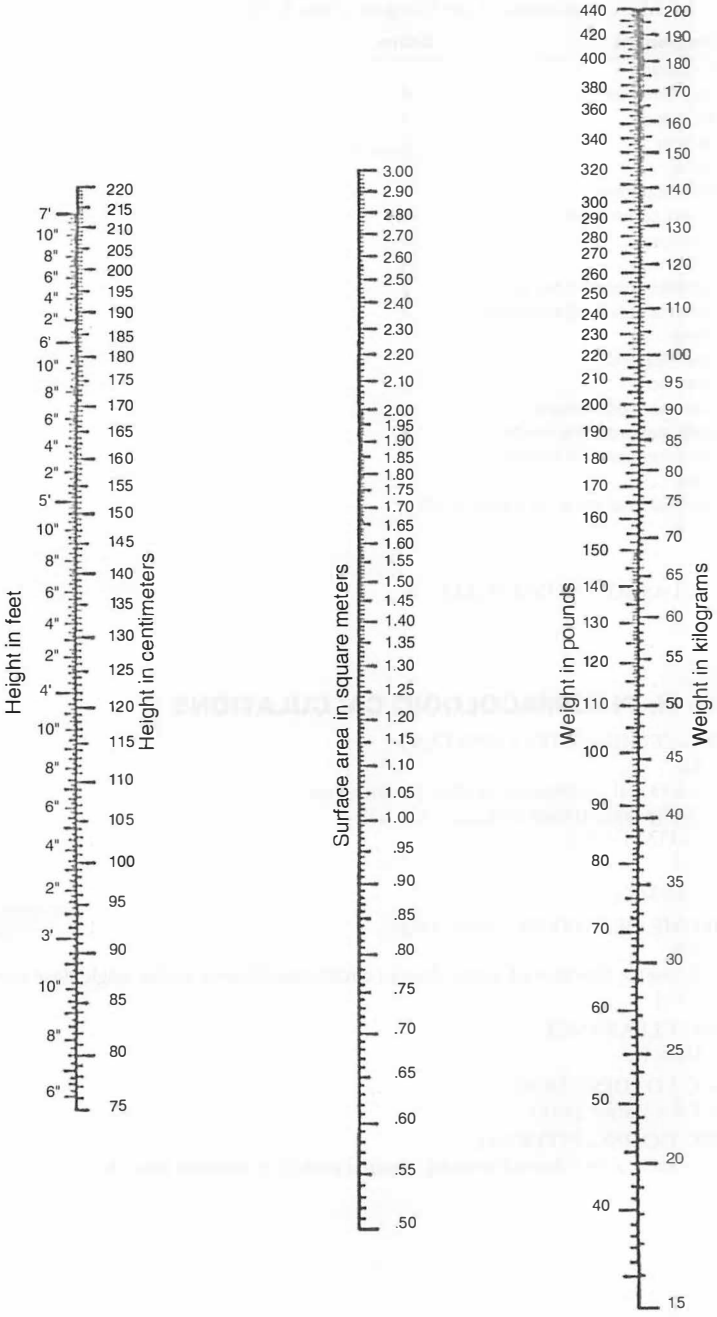
Height in feet
Height in centimeters
7' 10" 8" 6" 4" 2" 6' 10" 8" 6" 4" 2" 5' 10" 8" 6" 4" 2" 4' 10" 8" 6" 4" 2" 3' 10" 8" 6"
220 215 210 205 200 195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75
Surface area in square meters
3.00 2.90 2.80 2.70 2.60 2.50 2.40 2.30 2.20 2.10 2.00 1.95 1.90 1.85 1.80 1.75 1.70 1.65 1.60 1.55 1.50 1.45 1.40 1.35 1.30 1.25 1.20 1.15 1.10 1.05 1.00 .95 .90 .85 .80 .75 .70 .65 .60 .55 .50
Weight in pounds
Weight in kilograms
440 420 400 380 360 340 320 300 290 280 270 260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40
200 190 180 170 160 150 140 130 120 110 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15

Figure A-1.

I. NUTRITIONAL CALCULATIONS

BODY MASS INDEX
= BMI
= weight (kg)/[height (cm)]^2
RESPIRATORY QUOTIENT
= R
= CO_2 production (mL/min)/O_2 consumption (mL/min)
Normal value: 0.8

HARRIS-BENEDICT EQUATION OF RESTING ENERGY EXPENDITURE (kcal/d)
Males = 66 + (13.7 × weight [kg]) + (5 × height [cm]) − (6.8 × age)
Females = 655 + (9.6 × weight [kg]) + (1.8 × height [cm]) − (4.7 × age)

J. BODY SURFACE AREA FORMULA AND NOMOGRAM (ADULT)

BODY SURFACE AREA
= *BSA*
= (height [cm])$^{0.718}$ × (weight [kg])$^{0.427}$ × 74.49
To use the adult nomogram (Fig. A-1), place a straightedge connecting the persons' weight in the right column with their height in the left column. The point where the straightedge crosses the center column denotes that persons' body surface area in square meters.

INDEX

Note: Page numbers followed by f *indicate a figure;* t *following a page number indicates tabular material*

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