REVIEW ARTICLE

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Hemorrhagic Shock

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Hemorrhagic shock is a form of hypovolemic shock in which severe blood loss leads to inadequate oxygen delivery at the cellular level. If hemorrhage continues unchecked, death quickly follows. The causes of hemorrhage resulting in shock vary widely and include trauma, maternal hemorrhage, gastrointestinal hemorrhage, perioperative hemorrhage, and rupture of an aneurysm.[1-4]

Death from hemorrhage represents a substantial global problem, with more than 60,000 deaths per year in the United States and an estimated 1.9 million deaths per year worldwide, 1.5 million of which result from physical trauma.[5] Because trauma affects a disproportionate number of young people, these 1.5 million deaths result in nearly 75 million years of life lost (Table 1). Furthermore, those who survive the initial hemorrhagic insult have poor functional outcomes and significantly increased long-term mortality.[3,8] This article summarizes recent advances in our knowledge of the pathobiology of hemorrhagic shock and details new approaches to treatment for these critically ill patients.

Pathobiology

Understanding the host response to severe hemorrhage has taken more than a century.[9] Early theories that hemorrhagic shock resulted from nervous system dysfunction or a toxin released from ischemic tissues were ultimately disproved, giving way to the accepted view that blood loss causes inadequate oxygen delivery and activates a number of homeostatic mechanisms designed to preserve perfusion to vital organs. Only now is the complexity of these events at the cellular, tissue, and whole-organism levels becoming clear, along with the relative contributions of hemorrhage-induced hypoperfusion and tissue injury from physical trauma (Fig. 1).

At the cellular level, hemorrhagic shock results when oxygen delivery is insufficient to meet oxygen demand for aerobic metabolism.[10] In this delivery-dependent state, cells transition to anaerobic metabolism. Lactic acid, inorganic phosphates, and oxygen radicals start to accumulate as a result of the mounting oxygen debt.[11] Release of damage-associated molecular patterns (known as DAMPs or alarmins), including mitochondrial DNA and formyl peptides, incites a systemic inflammatory response.[12] As ATP supplies dwindle, cellular homeostasis ultimately fails, and cell death ensues through necrosis from membrane rupture, apoptosis, or necroptosis.

At the tissue level, hypovolemia and vasoconstriction cause hypoperfusion and end-organ damage in the kidneys, liver, intestine, and skeletal muscle, which can lead to multiorgan failure in survivors. In extreme hemorrhage with exsanguination, pulselessness results in hypoperfusion of the brain and myocardium, leading to cerebral anoxia and fatal arrhythmias within minutes.[13] Hemorrhage also induces

Table 1. Estimated Hemorrhage-Related Deaths per Year and Years of Life Lost in the United States and Worldwide, According to the Cause of Hemorrhage.

Cause of Hemorrhage	Deaths from Hemorrhage*	U.S. Cases of Hemorrhage		Global Cases of Hemorrhage	
		No. of Deaths per Yr	Yr of Life Lost	No. of Deaths per Yr	Yr of Life Lost
	percent				
Abdominal aortic aneurysm	100	9,988†	65,273‡	191,700§	2,881,760¶
Maternal disorder	23§	138‖	7,572**	69,690‖	4,298,240**
Peptic ulcer disease	60††	1,860‖	38,597**	141,000‖	3,903,600**
Trauma	30‡‡	49,440‖	1,931,786**	1,481,700‖	74,568,000**
Total		61,426	2,043,228	1,884,090	85,651,600

* This column lists the best estimates of deaths from hemorrhage as a percentage of all deaths from the given diagnosis (e.g., all deaths from abdominal aortic aneurysm are ultimately related to hemorrhage).
† Information is from Leading Causes of Death Reports, 1981–2015, Centers for Disease Control and Prevention, 2017 (https://webappa.cdc.gov/sasweb/ncipc/leadcause.html).
‡ Data are from Years of Potential Life Lost (YPLL) Reports, 1999–2015, Centers for Disease Control and Prevention, 2017 (https://webappa.cdc.gov/sasweb/ncipc/ypll10.html).
§ Data are from Lozano et al.[5]
¶ Data are from Global Health Data Exchange, 2016 (http://ghdx.healthdata.org/gbd-results-tool).
‖ Data are from Global Health Estimates 2015: Global Deaths by Cause, Age, Sex, by Country and by Region, 2000–2015. World Health Organization, 2016 (www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html).
** Data are from Global Health Estimates 2015: Disease Burden by Cause, Age, Sex, by Country and Region, 2000–2015. World Health Organization, 2016 (www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html).
†† Information is from Christensen et al.[6]
‡‡ Information is from Kauvar et al.[7]

profound changes in the vascular endothelium throughout the body.[14] At the site of hemorrhage, the endothelium and blood act synergistically to promote thrombus formation. However, the mounting oxygen debt and the catecholamine surge eventually induce a so-called endotheliopathy through systemic shedding of the protective glycocalyx barrier.[15]

With hemorrhage and shock, both adaptive and maladaptive changes occur in the blood. At the site of hemorrhage, the clotting cascade and platelets are activated, forming a hemostatic plug.[16] Remote from the site of hemorrhage, fibrinolytic activity increases, presumably to prevent microvascular thrombosis.[17] However, excess plasmin activity and autoheparinization from glycocalyx shedding can result in pathologic hyperfibrinolysis and diffuse coagulopathy.[14,17,18] Conversely, nearly half of patients with trauma have a hypercoagulable phenotype of fibrinolysis shutdown.[18] Depleted platelet numbers, decreased platelet margination due to anemia, and reduced platelet activity also contribute to coagulopathy and increased mortality.[19-22]

Iatrogenic factors can further exacerbate coagulopathy in patients with active bleeding.[23] Overzealous resuscitation with crystalloid dilutes the oxygen-carrying capacity and clotting factor concentrations. Infusion of cold fluids exacerbates the heat lost from hemorrhage, depleted energy stores, and environmental exposure and leads to decreased function of the enzymes in the clotting cascade.[24] Finally, overadministration of acidic crystalloid solutions worsens the acidosis caused by hypoperfusion and further impairs the function of clotting factors, resulting in a "bloody vicious cycle" of coagulopathy, hypothermia, and acidosis (Fig. 1).[25]

New insights into the genetic response to severe injury and hemorrhage have been gleaned from the Inflammation and the Host Response to Injury research program.[26] Historically, the prevailing view was that a patient's initial response to severe injury and shock was a robust, innate systemic inflammatory response syndrome (SIRS), which was followed by relative immunosuppression, termed compensatory antiinflammatory response syndrome (CARS), and then eventual recovery. If there were any complications, the cycle would reset with another SIRS,

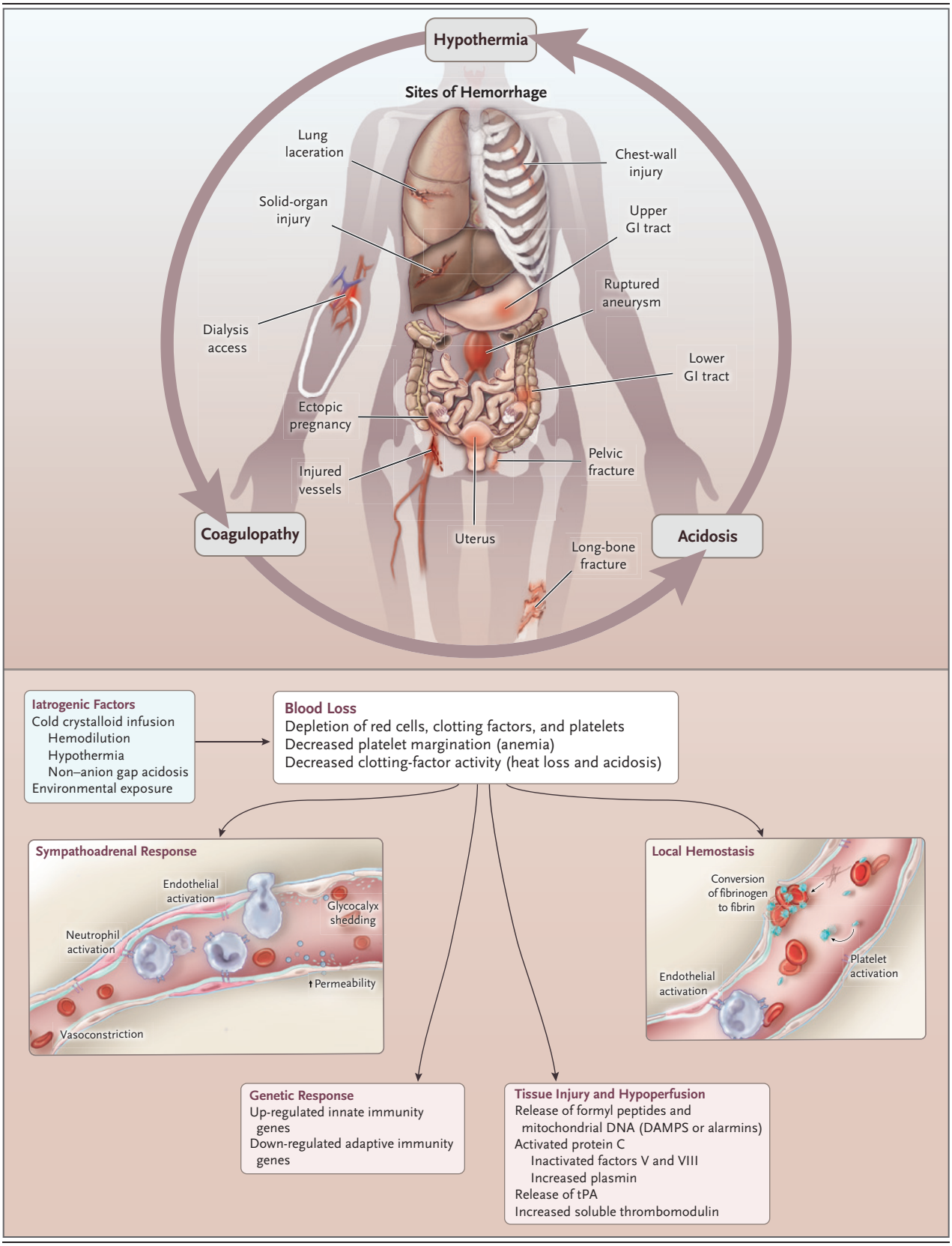

Figure 1 (facing page). Pathobiology of Hemorrhagic Shock.
The combined effects of intravascular volume depletion, loss of red-cell mass and procoagulant elements, simultaneous activation of the hemostatic and fibrinolytic systems, compensatory mechanisms, and iatrogenic factors contribute to the phenotype of coagulopathy, hypothermia, and progressive acidosis, which results in further derangements, ultimately leading to death. In patients with trauma, tissue injury exacerbates the coagulopathy. Shedding of the endothelial glycocalyx at sites remote from the hemorrhage leads to vascular permeability and additional inflammatory and coagulopathic stimulation. DAMPs denotes damage-associated molecular patterns, GI gastrointestinal, and tPA tissue plasminogen activator.

followed by CARS. The Inflammation and the Host Response to Injury studies have revealed, however, that soon after injury, proinflammatory and antiinflammatory innate immunity genes are up-regulated while adaptive immunity genes are simultaneously down-regulated. In patients without complications, these responses quickly return to baseline levels during recovery, whereas patients with complications have exaggerated responses that return to baseline more slowly.

DIAGNOSIS AND MANAGEMENT

Early recognition of hemorrhagic shock and prompt action to stop the bleeding are lifesaving, since the median time from onset to death is 2 hours.[27] Rapidly controlling the source of hemorrhage and restoring the patient's intravascular volume and oxygen-carrying capacity serve both to limit the depth and duration of the shock state and to repay the accumulated oxygen debt, in the hope that the debt is repaid before shock becomes irreversible.[10]

PREHOSPITAL CARE

As with other time-sensitive conditions, such as myocardial infarction and stroke, the chain of survival for patients with severe bleeding starts in the prehospital setting (Fig. 2).[28] With limited options for resuscitation and definitive hemostasis, priorities for prehospital care include minimizing further blood loss, providing limited fluid resuscitation through large-bore peripheral vascular access, and rapidly transporting the patient to a facility that can provide definitive care.

New evidence indicates that tourniquet application proximal to sites of hemorrhage in the extremities saves lives without risking amputation or extremity dysfunction, if the patient is rapidly transported to a hospital where definitive care can be provided.[29,30] On the basis of this evidence, a public education program has been initiated by the American College of Surgeons and several partner organizations to train bystanders on tourniquet application and other hemorrhage-control measures.[31] Guidelines for providing first aid[32] and prehospital care[33] now endorse tourniquet application when direct pressure is ineffective or impractical. For large bleeding wounds in junctional locations where a tourniquet cannot be applied (e.g., axilla or groin [Fig. 2]), a number of new hemostatic dressings have shown some benefit.[34]

Numerous studies have evaluated prehospital resuscitation, particularly in the case of patients with severe injuries from trauma. Delaying resuscitation (i.e., withholding intravenous fluid until the moment of definitive hemostasis), a concept first espoused by Walter B. Cannon, improves survival among patients with penetrating trauma to the torso who receive care in an urban trauma center,[35] probably because this approach averts dilutional coagulopathy. The Resuscitation Outcomes Consortium found no benefit of either hypertonic saline or hypertonic dextran as compared with normal saline for prehospital resuscitation in a mixed population of patients with blunt or penetrating trauma.[36] Likewise, albumin offers no benefit over crystalloid solutions.[37] Prehospital transfusion of red cells, plasma, or both was shown to provide a significant survival benefit in a recent retrospective analysis of matched cohorts of patients with combat-related trauma,[38] and several ongoing clinical trials are evaluating the usefulness of this approach in civilians. Currently, however, most prehospital providers use a small volume of crystalloid as needed to maintain mentation and a palpable radial pulse in patients with severe bleeding.[39]

Rapid transport to a hospital capable of providing care for critically ill patients is essential for ensuring definitive hemostasis before hemorrhagic shock becomes irreversible. Systems-level education and policy changes have recently shortened transport times and improved survival for combat casualties.[40] In some urban centers, the ultrarapid "scoop and run concept" has been extended to allow police transport for patients with penetrating trauma,[41] ideally with tourniquets

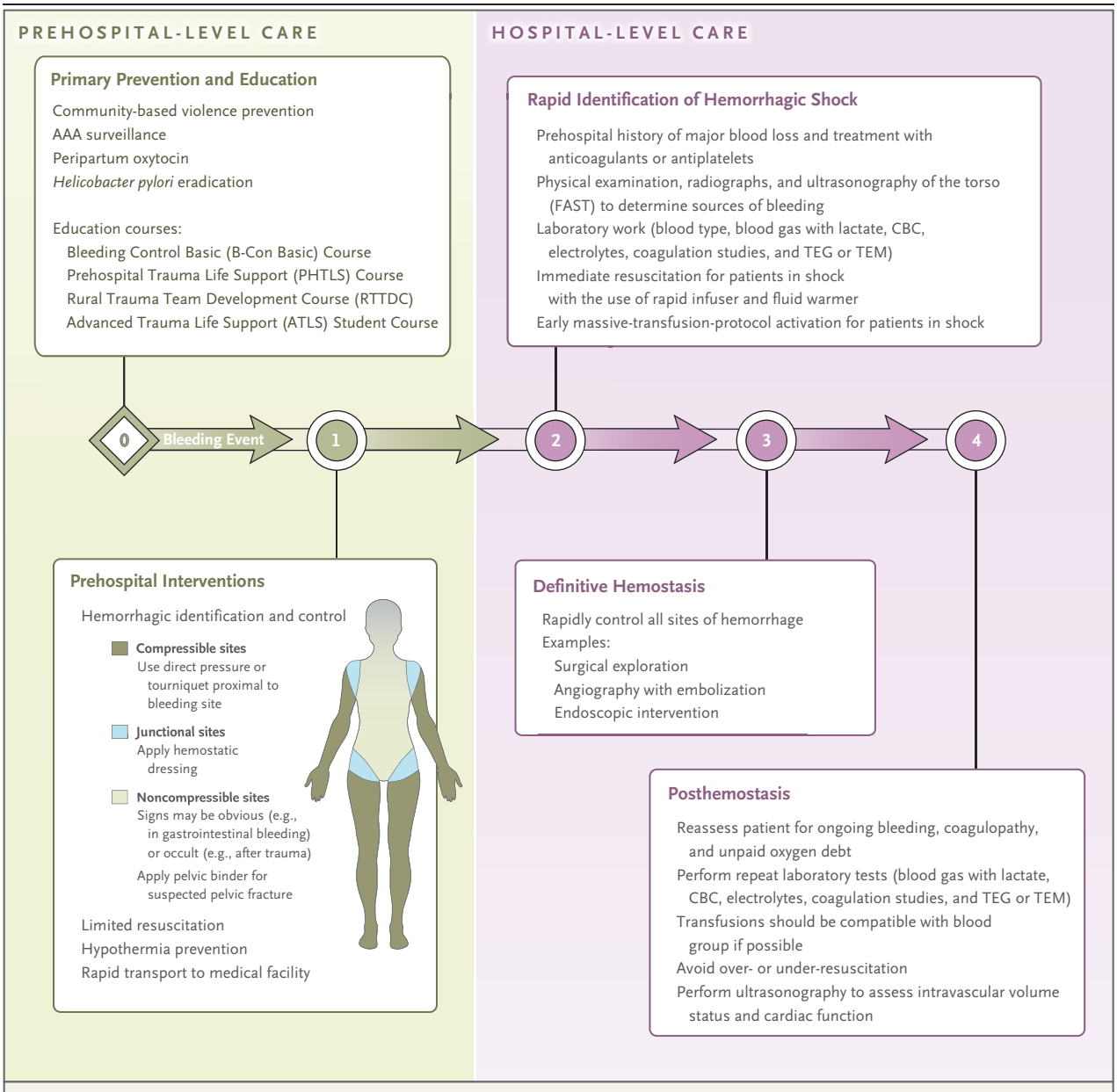

Figure 2. Chain of Survival for Patients with Severe Hemorrhage.

The chain starts with primary prevention and prehospital interventions. Once the patient arrives at the hospital, early recognition and resuscitation, achievement of definitive hemostasis, and subsequent actions all factor into the outcome. AAA denotes abdominal aortic aneurysm, CBC complete blood count, FAST focused assessment with sonography for trauma, TEG thromboelastography, and TEM thromboelastometry.

applied proximal to any bleeding wounds in the extremities.

EVALUATION OF PATIENTS WITH SEVERE HEMORRHAGE

Signs and symptoms of hemorrhagic shock, especially from occult sources of bleeding, are often subtle. In most patients, robust compensatory mechanisms render hypotension an insensitive indicator of shock until more than 30% of the patient's blood volume has been lost (Table 2). More subtle clinical cues indicative of shock include anxiety, tachypnea, a weak peripheral pulse, and cool extremities with pale or mottled skin.

Table 2. Classification of Hemorrhagic Shock.*

Shock Class	Blood Loss†	Heart Rate	Blood Pressure	Pulse Pressure	Respiratory Rate	Mental Status
	ml (%)	*beats/min*			*breaths/min*	
I	<750 (15)	<100	Normal	Normal	14–20	Slightly anxious
II	750–1500 (15–30)	100–120	Normal	Narrowed	20–30	Mildly anxious
III	1500–2000 (30–40)	120–140	Decreased	Narrowed	30–40	Anxious, confused
IV	>2000 (>40)	>140	Decreased	Narrowed	>35	Confused, lethargic

* Data are from the American College of Surgeons Committee on Trauma.[42]
† Blood-loss volume and percentage of total blood volume are for a male patient with a body weight of 70 kg.

Promising technologies that may help clinicians more quickly identify patients in shock include the compensatory reserve index[43] and portable incident dark-field microscopy to assess microvascular beds in real time.[44]

During the initial evaluation, potential sources of hemorrhage should be identified. Examples include hematemesis or hematochezia, copious vaginal bleeding, and a known history of an abdominal aortic aneurysm. In patients with trauma, bleeding from sources in the extremities is obvious before the onset of shock, but these sites may no longer be bleeding after severe hemorrhage. Also, the proximal thighs and the retroperitoneum can hold a large volume of blood that may not be readily apparent on the initial assessment. Intracavitary sources of bleeding in patients with trauma include the chest, abdomen, and pelvis. Rapid evaluation of these cavities with chest and pelvic radiographs and focused assessment with sonography for trauma (FAST) can indicate potential sites of bleeding.[45] Ultrasonography can also be used in patients without trauma to identify occult sources of bleeding such as a ruptured abdominal aortic aneurysm, uterine bleeding, or a ruptured ectopic pregnancy, and echocardiography can be used to assess cardiac filling and contractility.[46]

Laboratory measures of cellular hypoperfusion include base deficit and lactate values obtained from blood gas analysis. Other useful laboratory values in a patient with severe bleeding include hemoglobin and the international normalized ratio, which can be used to predict the need for a massive transfusion.[47] The platelet count and fibrinogen levels should be measured and normalized. Electrolytes, including potassium and calcium, should be measured early and often during the course of blood-product resuscitation, since they can fluctuate wildly.[24,48] Finally, coagulopathy should be identified and ongoing blood-product resuscitation should be guided by measuring clot-formation kinetics with the use of viscoelastic testing such as thromboelastography or rotational thromboelastometry.[49] Taken together, these laboratory measures will indicate the severity of shock, the need for mobilizing blood bank resources, and the presence and type of coagulopathy.

Although computed tomographic (CT) imaging is now ubiquitous in the emergency evaluation of critically ill patients, it should be performed only if the source of bleeding remains uncertain and the patient's condition has been stabilized with initial resuscitation. Often, in cases of severe hemorrhage, the patient is better served by rapid interventions that are both diagnostic and therapeutic, such as operative exploration, angiography with embolization, or gastrointestinal endoscopy.

RESUSCITATION

Successful resuscitation requires aggressive measures to prevent the accumulation of further oxygen debt and to repay the existing oxygen debt by stanching all sources of hemorrhage and restoring the intravascular volume as quickly as possible.[10] In patients with trauma, the companion concepts of damage-control surgery[50] and damage-control resuscitation[51,52] achieve these objectives. Similarly, patients with severe hemorrhage from causes other than trauma benefit from rapid localization and control of hemorrhage paired with blood-product resuscitation.

When the patient arrives at the hospital, the priorities for management of bleeding include restoration of intravascular volume and rapid control of hemorrhage as part of the damage-control resuscitation paradigm (Table 3). Strate-

Table 3. Principles of Damage-Control Resuscitation.

Avoid or correct hypothermia
Apply direct pressure or a tourniquet proximal to sites of hemorrhage in the extremities; pack junctional wounds with hemostatic dressings
Delay fluid administration until the time of definitive hemostasis in selected patients (those with penetrating trauma to the torso and short prehospital transport times)
Minimize crystalloid infusions (<3 liters in the first 6 hr)
Use a massive-transfusion protocol to ensure that sufficient blood products are rapidly available
Avoid delays in definitive surgical, endoscopic, or angiographic hemostasis
Minimize imbalances in plasma, platelet, and red-cell transfusions in order to optimize hemostasis
Obtain functional laboratory measures of coagulation (e.g., by means of thromboelastography or rotational thromboelastometry) to guide the transition from empirical transfusions to targeted therapy
Selectively administer pharmacologic adjuncts to reverse any anticoagulant medications and to address persistent coagulopathy

gies for intravascular volume restoration have come full circle over the past several decades, returning to a resuscitation approach that emphasizes use of plasma, platelets, and red cells or even whole blood.[53]

Massive-transfusion protocols mobilize universal donor blood products (e.g., packed red cells, plasma, platelets, and cryoprecipitate) to the patient's bedside in prespecified ratios, along with pharmaceutical adjuncts such as calcium and tranexamic acid. These protocols provide a survival benefit for patients with acute bleeding[52]; any delay in activating the protocol is associated with an increase in mortality.[54] Multiple scoring systems have been designed to assist treatment teams in identifying patients who may need a massive transfusion (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

The ratio of red cells, plasma, and platelets that is clinically beneficial has not been conclusively defined. However, two prospective studies[55,56] and a systematic review[52] indicate that a ratio of plasma to platelets to red cells that is close to 1:1:1 (i.e., 6 units of plasma and 1 unit of apheresis platelets [equivalent to approximately 6 units of pooled platelets] for every 6 units of red cells) is safe and reduces short-term mortality from hemorrhage due to trauma. For patients with hemorrhage from causes other than trauma, a recent retrospective study showed that a ratio of platelets to red cells of more than 1:2 reduced mortality in the first 48 hours, but no benefit could be identified for a plasma-to-red cells ratio of this magnitude.[57]

All these blood products contain the anticoagulant citrate, which the liver rapidly metabolizes in healthy persons. However, in patients with hemorrhagic shock who are receiving a large volume of blood products, citrate may become toxic, with life-threatening hypocalcemia and progressive coagulopathy.[48,58] Thus, empirical calcium dosing during large-volume transfusions (e.g., 1 g of intravenous calcium chloride after transfusion of the first 4 units of any blood product) should be paired with frequent measurements of electrolyte levels.

Isotonic crystalloid resuscitation has been used for decades in the early management of bleeding. However, these solutions have no intrinsic therapeutic benefit except to transiently expand the intravascular volume. When isotonic crystalloid is administered in large volumes, the risk of complications, including respiratory failure, compartment syndromes (both abdominal and extremity), and coagulopathy, increases. Thus, limiting crystalloid infusions to 3 liters in the first 6 hours after arrival at the hospital is now recommended as part of a bundle of care for patients with acute bleeding from trauma.[59] This limit does not include blood products. As with prehospital resuscitation, described above, no benefit has been identified for the use of colloids, dextran, or hypertonic saline for the early in-hospital management of severe bleeding.

Procoagulant hemostatic adjuncts can be used to promote clot formation in patients with bleeding. Examples include activated recombinant factor VII, tranexamic acid, prothrombin complex concentrate, and fibrinogen concentrate.[60] Use of these agents is considered off-label except in patients taking warfarin, for whom prothrombin complex concentrate is indicated, and patients with hemophilia, for whom activated recombinant factor VII or tranexamic acid is indicated. Potential benefits include a reduced need for massive transfusion and even reduced mortality. However, these benefits must be balanced against the potential for thrombotic complications, paradoxical hemorrhage, and multiorgan failure. Thus, use of these medications in patients with trauma should be based on careful interpretation of the original studies and current guidelines.[52] Ongoing studies should clarify the

appropriate use of these medications in patients with acute bleeding. At present, my hemostatic adjunct of choice is tranexamic acid, administered when the massive-transfusion protocol is activated. Vasopressin supplementation is another therapy that may reduce blood-product and fluid requirements in patients with hemorrhagic shock.[61]

ACHIEVING DEFINITIVE HEMOSTASIS

All patients with severe bleeding require timely, definitive hemostasis to ensure survival (Fig. 2). A prolonged time to hemostasis has been linked to increased blood-transfusion requirements, increased mortality, or both for patients with pelvic fractures,[62] ruptured abdominal aortic aneurysm,[63] or gastrointestinal bleeding.[64] Patients with acute torso hemorrhage due to trauma should remain in the emergency department less than 10 minutes for initial diagnosis and resuscitation in order to mitigate the risk of death.[65] Patients with hemorrhage in an extremity and a confirmed need for tourniquet application should be quickly moved to the operating room for vascular exploration. For patients with multicavity torso hemorrhage, it is important to identify the cavity with the most severe bleeding at the outset, since initial surgical exploration of a body cavity with less severe bleeding increases the risk of death.[66] Diagnostic adjuncts such as tube thoracostomy and FAST help ensure proper operative sequencing for such patients, whose condition is too unstable for CT. Patients with purely abdominal or pelvic bleeding from any source may benefit from endovascular occlusion of the aorta as a temporizing measure to slow hemorrhage.[67] This approach, termed resuscitative endovascular balloon occlusion of the aorta (REBOA), lowers the perfusion pressure to distal sites of severe hemorrhage, increases afterload, and redistributes the remaining blood volume preferentially to the heart and brain. REBOA reduces intraoperative mortality among patients with ruptured abdominal aortic aneurysm[68] and is being evaluated in two prospective studies for patients with trauma (Aortic Occlusion for Resuscitation in Trauma and Acute Care Surgery [www.aast.org/Research/MultiInstitutionalStudies.aspx] and the Effectiveness and Cost-Effectiveness of REBOA for Trauma [Current Controlled Trials number, ISRCTN16184981]).[69] REBOA has also been used for severe gastrointestinal bleeding and peripartum hemorrhage.[67] For patients with acute gastrointestinal bleeding, endoscopy should be performed within 24 hours after presentation; adherence to this recommendation may, at least in part, explain the decreasing mortality associated with gastrointestinal bleeding in recent years.[70,71]

RESUSCITATION END POINTS

After the initial course of resuscitation and definitive hemostasis, the patient should be assessed for evidence of ongoing hemorrhage, unpaid oxygen debt, anemia, coagulopathy, electrolyte derangements, and other sequelae of over- or under-resuscitation (Fig. 2).[72] Bedside echocardiography can be used by critical care physicians to assess intravascular volume and cardiac function. Thromboelastography or rotational thromboelastography can be used to identify coagulation abnormalities that require further correction.[49] Symptomatic anemia should also be corrected to normalize intravascular volume and to repay any residual oxygen debt. Values approaching the normal range for lactate and base excess indicate that the patient is being resuscitated appropriately and that ongoing bleeding is unlikely.

FUTURE DIRECTIONS

A systematic and comprehensive focus on hemorrhage and injury research by the Department of Defense has led to many of the advances detailed above[28,73]; however, gaps in both knowledge and capability remain.[74] Efforts to reduce the number of potentially preventable deaths from hemorrhage must combine preventive measures[75] with an all-out, multidisciplinary focus on early control of hemorrhage[33] and a reduced time to definitive hemostasis.[76] New approaches to early hemorrhage control are in development, including partial REBOA, which extends the safe occlusion time while reducing the risk of distal ischemia.[77] Both type O whole blood and freeze-dried plasma are also being investigated for early resuscitation of patients with bleeding from trauma.[78,79]

CONCLUSIONS

Hemorrhagic shock is a major cause of death and disability both in the United States and globally. Through an improved understanding of the pathobiology of hemorrhage and an emphasis

on rapid achievement of definitive hemostasis, starting with prehospital care, survival of patients with massive bleeding and recovery from hemorrhagic shock are now possible. However, much work remains to be done in the areas of primary prevention, early recognition, resuscitation options, and rapid hemostasis to increase the likelihood of recovery and reduce the burden of hemorrhagic shock to zero.

The opinions expressed in this document are solely those of the author and do not represent an endorsement by or the views of the U.S. Air Force, the Department of Defense, or the U.S. government.

Dr. Cannon reports receiving simulation equipment from Prytime Medical. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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