CHAPTER 58  HEMORRHAGIC SHOCK

MARIANNE E. CINAT • DAVID B. HOYT

The definition of shock describes the final common pathway of many disease states: ineffective tissue perfusion, resulting in severe dysfunction of organs vital to survival. The most commonly used classification system for shock includes four categories based on hemodynamic characteristics (1):

1. **Hypovolemic shock** resulting from a decreased circulating blood volume in relation to the total vascular capacity and characterized by a reduction in diastolic filling pressures and volumes

2. **Cardiogenic shock** related to cardiac pump failure caused by loss of myocardial contractility/functional myocardium or structural/mechanical failure of the cardiac anatomy characterized by elevations of diastolic filling pressures and volumes

3. **Extracardiac obstructive shock** involving obstruction to flow in the cardiovascular circuit and characterized by either impairment of diastolic filling or excessive afterload

4. **Distributive shock** caused by loss of vasomotor control, resulting in arteriolar and venular dilatation and characterized by increased cardiac output and decreased systemic vascular resistance after fluid resuscitation.

Although the hemodynamic characteristics of the various forms of shock may vary, the final common pathway—inadequate cellular perfusion—must be addressed early to prevent long-term sequelae and death (Fig. 58.1).

**Hemorrhagic shock** is a form of hypovolemic shock. It is a common, yet complicated, clinical condition that physicians are frequently called upon to evaluate and treat. Etiologies include trauma, postoperative bleeding, medical conditions, and iatrogenic causes. Diagnosis must be accurate and expedient. Therapy must be direct, efficient, and multifactorial in order to avoid the potential multisystem sequelae.

The purpose of this chapter is to address the immediate concerns for patients with hemorrhagic shock, as well as the etiology and epidemiology of this clinical condition, and to describe the pathophysiology, clinical features, and diagnostic and therapeutic approach to hemorrhagic shock. New and experimental therapies will also be introduced.

**IMMEDIATE CONCERNS**

The key steps in the approach to patients with hemorrhagic shock are listed in Table 58.1.

1. **Early recognition.** Early recognition requires astute clinical acumen to identify early systemic signs of hemorrhage and hypovolemic shock. Signs and symptoms include restlessness, anxiety, altered level of consciousness, shortness of breath, tachypnea, pallor, tachycardia, and oliguria. A decreased pulse pressure may also be observed along with decreased capillary refill due to peripheral vasconstriction. Hypotension indicates significant volume depletion and may be a late clinical manifestation.

2. **Important aspects in the patient history.** An accurate history should be obtained expeditiously. For patients with traumatic injury, a thorough understanding of the mechanism of injury should be obtained, including the magnitude of blunt force trauma and/or the trajectory of the missile or object in penetrating trauma. In postoperative or postprocedural patients, the exact nature of the surgical procedure should be defined and potential sites of hemorrhage identified. In patients without recent surgery, risk factors for nonpostoperative, nontraumatic etiologies should also be sought (gastrointestinal, peptic ulcer disease, atherosclerosis with aneurysmal disease). Significant comorbidities should also be delineated including coagulation disorders (von Willebrand, hemophilia), medical conditions associated with altered coagulation (cirrhosis, renal failure, iatrogenic vitamin K deficiency from parenteral nutrition or antimicrobials), or use of medications such as antiplatelet therapy and anticoagulants (Coumadin, heparin, low-molecular-weight heparin, or antimicrobials).

3. **Initial action and intervention.** The initial action taken in each case of hemorrhagic shock, regardless of etiology, should be directed at restoring circulating volume to ensure adequate tissue perfusion. Once the airway is secured and adequate ventilation is ensured, two peripheral large-bore intravenous catheters should be placed and fluid resuscitation begun. A blood sample should also be sent immediately for type and cross-match per institutional protocol. Initial resuscitation can include crystalloids, but should quickly be changed to blood products if signs of hypovolemia and ongoing hemorrhage persist. If a patient is in extremis and going hemorrhage persist. If a patient is in extremis and cross-matched blood products are not immediately available, type O blood (universal donor) should be immediately requested and transfused. For massive hemorrhage, clotting factors such as fresh frozen plasma, platelets, and cryoprecipitate should be prepared. The value of massive transfusion protocols to include predetermined ratios of clotting factors will be discussed later in this chapter.

4. **Directed physical examination.** Physical examination should be directed at obvious sources of external bleeding such as lacerations, extremity fractures, or surgical incisions. If identified, these should be immediately controlled. Physical signs of underlying liver disease should also be identified such as petechia, jaundice, ascites, angiomas, or testicular atrophy. Previous cardiac or carotid surgical incisions may hint toward concurrent antithrombotic or anticoagulant therapy. Evidence of retroperitoneal bleeding in patients with pancreatitis is marked by flank or periumbilical contusions.
5. **Identify occult source of hemorrhage.** If no obvious source of external bleeding is identified, a rapid evaluation should be performed to identify likely occult sources of bleeding. In the trauma patient, significant internal hemorrhage can occur in four defined regions: the thoracic cavity, the peritoneal cavity, the retroperitoneum, and extremity fractures. These areas can be rapidly assessed by chest radiograph, pelvic radiograph, a focused abdominal sonographic examination for trauma (FAST), and physical examination of extremities along with appropriate radiographs. In nontrauma patients without clear evidence of bleeding, the gastrointestinal tract should be rapidly evaluated via nasogastric tube, rectal examination, and endoscopy where appropriate. Additional diagnostic tests can be obtained based on clinical history, patient background, and condition. Abdominal aortic aneurysms can be identified on physical examination, by ultrasound, or by calcifications on abdominal radiograph. In rare selected instances, angiography may be used to identify and treat sources of hemorrhage not otherwise apparent (pelvic fractures, pancreatitis, lower gastrointestinal bleeding). This should only be instituted when a specific source of hemorrhage is highly likely and therapeutic intervention is sought. Computed tomography should never be sought in hemodynamically unstable patients with hemorrhage.

6. ** Expedite treatment.** Once a source of bleeding is identified, a swift and directed treatment plan should be formulated and implemented without delay. Prolonged untreated hemorrhagic shock can lead to rapid decompensation and death if not appropriately identified and treated. Rapid intervention with surgical, angiographic, or endoscopic control of the hemorrhage is indicated, along with rapid correction of the underlying coagulopathy.

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**EPIDEMIOLOGY AND ETIOLOGY**

Hypovolemic shock can be due to hemorrhagic and nonhemorrhagic sources. Hemorrhage is the most frequent cause of hypovolemic shock and is most commonly due to blood loss after trauma or major surgery (Table 58.2). Following trauma, obvious external signs of injury and hemorrhage should be rapidly identified and controlled. As described above, the thoracic cavity, peritoneal cavity, and retroperitoneum should all be evaluated for occult hemorrhage.
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Early diagnosis of hemorrhagic shock is imperative to avoid delay in treatment. However, clinical signs are relatively insensitive for small amounts of blood loss (2). There is a progressive hemodynamic deterioration with ongoing blood loss. This class- 
sic progression is delineated in Table 58.1. Total blood volume is estimated at approximately 70 mL/kg in the average adult, or nearly 5 L for a 70-kg person.

Class I

Class I hemorrhage is marked by a less than 750 mL estimated blood loss, or less than 15% of total circulating blood volume. There are minimal physical signs associated with this volume of blood loss. The patient may not have tachycardia, with a heart rate remaining less than 100 beats per minute; the systolic blood pressure and pulse pressure remain normal; the respiratory rate remains at 14 to 20 breaths per minute; and urine output remains adequate (>30 mL/hour). Only subtle physi- 
cal signs such as delayed capillary refill and slight anxiety may exist.

Class II

Class II hemorrhage is marked by an estimated blood loss of 750 to 1,500 mL (or 15% to 30% of the total circulating blood volume). Physical signs begin to manifest during this stage of hemorrhage. Although the systolic blood pressure may be maintained, the patient usually becomes tachycardic (heart rate greater than 100 beats per minute), the pulse pressure be- gins to decrease, and capillary refill is delayed. The respiratory rate begins to increase (20–30 breaths per minute), urine output

Material

TABLE 58.1

<table>
<thead>
<tr>
<th>Steps in the Approach to a Patient with Hemorrhagic Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Early recognition</td>
</tr>
<tr>
<td>a. Signs and symptoms may be subtle.</td>
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<tr>
<td>b. Assure clinical acumen is necessary to identify</td>
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<tr>
<td>hemorrhage prior to hemodynamic collapse.</td>
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<tr>
<td>2. Obtain an accurate patient history</td>
</tr>
<tr>
<td>a. Trauma</td>
</tr>
<tr>
<td>b. Recent surgical procedures</td>
</tr>
<tr>
<td>c. Medical history</td>
</tr>
<tr>
<td>(i) Gastrointestinal disease (peptic ulcer disease,</td>
</tr>
<tr>
<td>varices, etc.)</td>
</tr>
<tr>
<td>(ii) Atherooclerosis (aneurysmal disease)</td>
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<tr>
<td>(iii) Coagulation disorders</td>
</tr>
<tr>
<td>3. Initiate intervention</td>
</tr>
<tr>
<td>a. “ABCs”—airway, breathing, circulation</td>
</tr>
<tr>
<td>b. Initiate resuscitation</td>
</tr>
<tr>
<td>(i) Crystalloid</td>
</tr>
<tr>
<td>(ii) Blood products</td>
</tr>
<tr>
<td>1. Type O uncross-matched blood if in extremis</td>
</tr>
<tr>
<td>2. Cross-matched blood when available</td>
</tr>
<tr>
<td>3. Clotting factors</td>
</tr>
<tr>
<td>4. Directed physical examination</td>
</tr>
<tr>
<td>a. External sources of bleeding</td>
</tr>
<tr>
<td>b. Internal sources of bleeding</td>
</tr>
<tr>
<td>5. Expedite definitive treatment</td>
</tr>
<tr>
<td>a. Surgical control</td>
</tr>
<tr>
<td>b. Endoscopic control</td>
</tr>
<tr>
<td>c. Angiographic control</td>
</tr>
<tr>
<td>6. Correct coagulopathy</td>
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TABLE 58.2

<table>
<thead>
<tr>
<th>Major Etiologies of Hemorrhagic Shock</th>
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<tbody>
<tr>
<td>1. Trauma (blunt or penetrating)</td>
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<tr>
<td>a. Intraocular trauma</td>
</tr>
<tr>
<td>b. Intraperitoneal</td>
</tr>
<tr>
<td>c. Soft tissue or fractures</td>
</tr>
<tr>
<td>2. Gastrointestinal</td>
</tr>
<tr>
<td>a. Upper gastrointestinal tract</td>
</tr>
<tr>
<td>b. Peptic ulcer disease, reflex esophagitis, variceal</td>
</tr>
<tr>
<td>bleeding, erosive gastritis, aortoduodenal fistula</td>
</tr>
<tr>
<td>c. Lower gastrointestinal tract</td>
</tr>
<tr>
<td>d. Hemorrhoids, tumor, arteriovenous malformation,</td>
</tr>
<tr>
<td>diverseritis, ulcerative colitis, Crohn disease, ischemia</td>
</tr>
<tr>
<td>e. Hemobilia</td>
</tr>
<tr>
<td>f. Bilary tumor, iatrogenic injury or manipulation,</td>
</tr>
<tr>
<td>penetrating trauma</td>
</tr>
<tr>
<td>g. Pancreatic</td>
</tr>
<tr>
<td>h. Pancreatitis, iatrogenic injury or manipulation</td>
</tr>
<tr>
<td>i. Abdominal aortic aneurysm</td>
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</tbody>
</table>

Causes of hemorrhagic shock not due to trauma include 
a ruptured abdominal aortic aneurysm and gastrointestinal 
blooding. Gastrointestinal bleeding can be caused by peptic ul-
cer disease, reflux esophagitis, variceal bleeding, erosive gas-
tritis (stress ulcers), or an aortoduodenal fistula after vascular 
surgery. Prior manipulation by endoscopy or sphincterotomy 
can also lead to upper gastrointestinal bleeding. Lower gas-
trointestinal bleeding can result from diverticular disease, car-
cinoma, polyps, arteriovenous malformations, ischemia, or col-
itis. Pulmonary sources of hemorrhage can occur from tumor, 
tuberculosis, fungal infection, bronchectasis, or tracheoin-
nominate fistula following tracheotomy. Hematoma from a 
tumor, trauma, or polycystic kidney disease is rare but can lead 
to hemorrhagic shock.

Nonhemorrhagic sources of hypovolemic shock can also 
occur. Although not the focus of this chapter, these are due 
to external fluid losses such as dehydration, vomiting, di-
arrhea, polyuria, uncontrolled diabetes mellitus leading to 
itis, and acute adrenocortical insufficiency. Disorders that 
leads to interstitial fluid redistribution such as ther-
mal injury, trauma, and anaphylaxis can also lead to hypo-
volmic shock. Finally, disorders that cause increased vascular 
capacitance (venodilation) can lead to a relative hypovolemia 
and include sepsis, anaphylaxis, and the release of toxins/drugs 
leading to vasodilation.
becomes diminished (20–30 mL/hour), and the patient becomes very anxious.

**Class III**

Class III hemorrhage is marked by an estimated blood loss of >1,500 to 2,000 mL (or >30%–40% of total circulating blood volume). During this phase, significant hemodynamic compensation becomes apparent. Heart rate increases to >120 beats per minute, systolic blood pressure decreases, pulse pressure decreases, capillary refill decreases, tachypnea worsens with a respiratory rate of 30 to 40 breaths per minute, urine output drops to 5 to 15 mL/hour, and the patient becomes confused, showing further evidence of decreased perfusion of the central nervous system.

**Class IV**

Class IV hemorrhage is marked by an estimated blood loss of ≥2,000 mL (or >40% of total circulating blood volume). During this phase, most compensatory cardiovascular mechanisms have been maximized and total hemodynamic collapse is imminent. Signs of class IV hemorrhage include severe tachycardia with a heart rate >140 beats per minute, a decreased systolic blood pressure, a decreased pulse pressure, delayed capillary refill, significant tachypnea with a respiratory rate of >35 breaths per minute, minimal to no urine output, and severely altered mental status as marked by confusion and/or lethargy.

**Potential Pitfalls**

Despite these guidelines, several potential pitfalls exist that can make the diagnosis more difficult. Concurrent medication, such as β-blockers, may attenuate the physiologic response to hemorrhage. In the presence of β-blockade, tachycardia may be blunted or may not occur at all. Prior hydration status and use of diuretics can also alter the rate at which these signs present. Pregnant patients have a significantly increased total blood volume, and thus can lose up to 1,000 mL of blood before presenting with any clinical signs of hemorrhage. Blood is diverted from the placenta via vasoconstriction; the mother's total blood circulation is maintained at the expense of the fetus. Elderly patients may have atrial arrhythmias leading to a high ventricular response, making tachycardia less sensitive in this patient population. Concurrent use of antiplatelet or anticoagulant medication can cause relatively small injuries to bleed excessively, and identification and intervention may be delayed. Although unloading of the baroreceptors and activation of the sympathetic nervous system usually lead to tachycardia, some patients may respond to traumatic hemorrhage with bradycardia as a result of a vagal nerve-mediated transient sympathoinhibition due to acute and sudden blood loss (3–9). Finally, a significant reduction in skin blood flow (i.e., cool, clammy skin) is an early ominous sign of shock in view of selective cutaneous vasoconstriction (10). Intervention and resuscitation must be imminent upon presentation of these signs and symptoms.

**PATHOPHYSIOLOGY**

**Circulatory Changes**

Hemorrhage results in a predictable pattern of events that begins with acute changes in circulating blood volume and culminates in a final common pathway shared by all classifications of shock (Fig. 58.1). Hemodynamically, hypovolemic shock is characterized by a fall in ventricular preload, resulting in decreased ventricular diastolic filling pressures and volumes. This in turn leads to a decrease in cardiac output and stroke volume (3–5,11–13). Following unloading of the cardiac baroreceptors and activation of the sympathetic nervous system, tachycardia ensues in an attempt to compensate for the decrease in cardiac output and stroke volume (12). The sympathetic output also results in vasoconstriction, leading to a decrease in pulse pressure. Greater variations in blood pressure will occur with the respiratory cycle due to an increased sensitivity of the underfilled heart to changes in venous return with varying intrathoracic pressure (16–18). The increased sympathetic tone may prevent a severe drop in arterial blood pressure initially. However, continued blood loss will ultimately result in hypotension and shock (3). Due to compensatory vasoconstriction, systemic vascular resistance rises early after the development of hypovolemic shock, but may fall in later stages, potentially heralding irreversibility and death (3,19,20).

The response to blood loss is a dynamic process that involves competing adaptive (compensatory) and maladaptive

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**TABLE 58.3**

**CLINICAL CLASSES OF HEMORRHAGIC SHOCK**

<table>
<thead>
<tr>
<th></th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss</td>
<td>&lt;750 mL</td>
<td>750–1,500 mL</td>
<td>1,500–2,000 mL</td>
<td>&gt;2,000 mL</td>
</tr>
<tr>
<td>(&lt;15%)</td>
<td>15%–30%</td>
<td>&gt;30%–40%</td>
<td>&gt;40%</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>&lt;100</td>
<td>&gt;100</td>
<td>&gt;120</td>
<td>&gt;140</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>Normal</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Capillary refill</td>
<td>Delayed</td>
<td>Delayed</td>
<td>Delayed</td>
<td>Delayed</td>
</tr>
<tr>
<td>Respiratory rate (breaths per minute)</td>
<td>14–20</td>
<td>20–30</td>
<td>30–40</td>
<td>&gt;35</td>
</tr>
<tr>
<td>Urine output (mL/h)</td>
<td>&gt;30</td>
<td>20–30</td>
<td>5–15</td>
<td>Minimal</td>
</tr>
<tr>
<td>Mental status</td>
<td>Slightly anxious</td>
<td>Anxious</td>
<td>Confused</td>
<td>Confused and lethargic</td>
</tr>
</tbody>
</table>
responses at each stage of development. Although intravascular volume replacement is always a necessary component of resuscitation in hypovolemic shock, the complex bidirectional response to the insult may progress to a point at which such resuscitation is insufficient to reverse the progression of the shock syndrome. For instance, patients who have sustained greater than a 40% loss of blood volume for 2 hours or more may not be able to effectively resuscitated. Severe hemorrhage leads to a series of inflammatory mediator, cardiovascular, and organ responses that supersede the injury itself and ultimately drive recovery or death (3,19–25).

**Oxygen Balance**

Shock is characterized by an oxygen deficit in tissues and cells. The significance of the deficit and the extent of cellular injury can be quantified as a function of both the severity and the duration of the deficit—the greater the severity, the longer the duration, the worse the outcome of shock.

Oxygen delivery to tissues is determined by cardiac output and the oxygen content in arterial blood. Oxygen content refers to the number of milliliters of oxygen contained in 100 mL of blood (ml/dL) and is a function of the hemoglobin concentration, the oxygen saturation of hemoglobin, and the amount of oxygen dissolved in plasma (the calculation is [Hgb × 1.34 × O2 saturation] + [PaO2 × 0.0003]). During hemorrhage, as the cardiac output falls, oxygen delivery to the tissues also falls. Initially, the body will maintain sufficient uptake of oxygen by extracting more from the arterial blood. This will result in an increase in the mixed venous oxygen saturation (SvO2) with an increase in the arteriovenous oxygen content gradient (CaO2 – CvO2). Eventually, this compensatory mechanism also fails, and tissue hypoxia with lactate acidosis ensues. Cerebral and cardiac functions are maintained by diversion of blood flow from other organs (skin, muscle, and kidneys) (26). However, when these compensatory mechanisms are maximalized, cardiac function and tissue oxygen delivery deteriorates further, and irreversible shock may develop (27).

Critical oxygen delivery is a function of cellular needs for oxygen and the ability of cells to extract oxygen from the arterial blood. Many factors contribute to this equation. During hemorrhage, tissue oxygen needs may increase due to increased respiratory muscle activity and increased catecholamine circulation (28). However, some evidence suggests that catecholamines down-regulate the metabolic needs of cells during hypovolemic shock (4,28–30). Regional blood flow is modified during hypovolemic shock in an attempt to maintain oxygen delivery to critical tissues (26,31). In addition, the individual needs of various tissues may vary during hemorrhagic shock. For instance, the oxygen needs of the kidney may decline during hemorrhage because a fall in renal perfusion leads to a fall in glomerular filtration and a decrease in energy-consuming tubular absorption (26). In contrast, the gut may experience an increased oxygen debt early due to the high oxygen need of the mucosa, along with redistribution of blood away from the gut to more critical tissues. This is the physiologic basis for gastric tonometry as a means of measuring the adequacy of resuscitation early following hemorrhage (32,33).

Oxygen extraction in tissues is influenced by the position of the oxyhemoglobin dissociation curve (34–37). Factors that improve the ability of tissues to extract oxygen from hemoglobin (i.e., shift the curve to the right) include acidosis, hypercarbia, hyperthermia, and decreased blood viscosity. However, in any extreme, each of these factors can be overcome by inadequate oxygen delivery and cardiovascular collapse. Interestingly, the oxyhemoglobin curve has been shown to shift to the left in critically ill patients (38). The presence of 2,3-diphosphoglycerate (2DP) in transfused blood has also been associated with a left shift of the oxyhemoglobin dissociation curve (39). Thus, although transfusions may increase the hemoglobin level, theoretically improving oxygen delivery, they may negatively affect the ability of tissues to extract oxygen from the hemoglobin.

The severity of oxygen debt during hypovolemic shock has been shown to be a major determinant of survival in animals and in patients following trauma, hemorrhage, and major surgery (20,27,40,41). A large oxygen debt has been associated with the development of acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS) (33,40–44). Conversely, a high oxygen delivery and uptake during resuscitation has been associated with improved survival (27,41–46). Whether increasing oxygen delivery to supranormal levels ultimately improves survival during resuscitation in critical illness remains controversial, and the medical literature has produced mixed results (27,33,43,44,47–50).

**Cellular Response**

During hypovolemic shock, the oxygen deficit in the tissues causes a fall in the mitochondrial production and concentration of high-energy phosphates. In the presence of sufficient oxygen, aerobic combustion of 1 mol of glucose yields 38 mol of energy-rich ATP. However, in the absence of sufficient oxygen, glucose taken up by the cells cannot be combusted because of insufficient uptake of pyruvate into the mitochondrial tricarboxylic acid cycle. Pyruvate is then converted to lactate within the cytoplasm. Anaerobic glycolysis yields only 2 mol of ATP, which is then hydrolyzed into hydrogen ion, ultimately leading to intracellular and extracellular metabolic acidosis (51,52,56–62) (Fig. 58.2). This process is ultimately a function of the severity and duration of regional microperfusion relative to oxygen demand and is more pronounced in some tissues (diaphragm, liver, kidney, gut) than in others (heart, skeletal muscle). Ultimately, a significant fall in the high-energy phosphates for a prolonged duration will lead to irreversible cellular injury and death.

The sequelae of low ATP production are profound. About 60% of the energy produced by respiring cellular mitochondria is needed to fuel the sodium-potassium (Na+–K+) pump of the cell. This pump controls the gradient in electrolyte concentrations and electric potential over the cell membrane. In the absence of sufficient ATP, the Na+–K+ pump is inhibited, resulting in an influx of sodium into the cell and efflux of potassium out of the cell. This in turn leads to cellular fluid uptake (51,53,63–66). Hyperkalemia may result due to potassium exchange between cells, the intravascular fluid, and vascular space. Independent of the Na+–K+ pump, there may be a selective increase in cell membrane permeability for ions during hemorrhagic shock. Hypovolemic shock has been shown to lead to a
rapid decrease in the transmembrane potential (with a less negative inner membrane potential), resulting in rapid electrolyte and fluid shifts across the membrane. Circulating heat shock proteins may also contribute to these changes independent of energy deficit (66–71).

Finally, calcium (Ca\(^{2+}\)) influx into cells and their mitochondria inhibits cellular respiration and ultimately contributes to cellular damage and swelling. Plasma levels of free Ca\(^{2+}\) may also fall. This may have profound consequences on the function of several organs during shock including the liver, kidney, heart, and vascular smooth muscle (64,65,72–82). Intracellular lysosomes lose their integrity, and proteolytic enzymes are released and contribute to cellular dysfunction and cell death. The sum of the intracellular changes and alterations in signaling transduction pathways described above ultimately leads to the development of cellular dysfunction and multiple organ dysfunction syndrome, which may be irreversible (82). Laboratory investigations are aimed at novel resuscitation techniques involving substances that attenuate abnormalcytologic alterations (82). Intracellular lysosomes lose their integrity, and proteolytic enzymes are released and contribute to cellular dysfunction and cell death.

The sum of the intracellular changes and alterations in signaling transduction pathways described above ultimately leads to the development of cellular dysfunction and multiple organ dysfunction syndrome, which may be irreversible (82). Laboratory investigations are aimed at novel resuscitation techniques involving substances that attenuate abnormalcytologic alterations (82).

**Microcirculation**

One of the most important determinants of tissue perfusion during shock is the response and function of the microvasculature, which is defined as vessels less than 100 to 150 μm in diameter. Although arteries and medium-sized arterioles are constricted in response to the extrinsic control mechanisms described above, terminal arterioles, venules, and capillaries remain unaffected and are more controlled by local metabolic factors.

**Neurohumoral Response**

In response to hemorrhage and hypovolemia, a complex neurohumoral response is initiated in an attempt to maintain blood pressure and retain fluid. Decreased intravascular volume stimulates baroreceptors in the carotid body and aortic arch, along with mechanoreceptors in the right atrium. This stimulation leads to several neurohumoral responses (Fig. 58.3). Circulating catecholamines are liberated by activation of the sympathetic nervous system and the adrenal medulla. Direct sympathetic stimulation of the vessel wall leads to vasoconstriction. Angiotensin II is liberated via the renin-angiotensin-aldosterone system. Vasopressin (antidiuretic hormone [ADH]) is released by the pituitary in hypovolemic shock and leads to vasoconstriction. Finally, decreased cardiac filling pressures reduce cardiac secretion of atrial natriuretic peptide (ANP), thereby reducing the vasodilatory and diuretic effects of ANP.

**Macrocirculation**

During loss of circulating blood volume, mechanisms are initiated to counteract the fall in cardiac output and oxygen delivery by facilitating a redistribution of peripheral blood flow (26). Regional autoregulation takes place via a delicate balance of endogenous vasodilators and vasoconstrictors. Endothelial cells produce potent vasodilators such as endothelium-derived relaxing factor (nitric oxide [NO]), heme oxygenation-derived carbon monoxide (CO), and metabolic byproducts in tissues, including carbon dioxide (CO\(_2\)), potassium, and adenosine (25,83–89). Some authors describe that inhibition of NO early following hemorrhage ameliorates early hypotension and improves mortality (90–94). Conversely, other authors describe endothelial dysfunction in organs with diminished NO production (95–96). Endothelin is a potent endothelial cell–derived vasoconstrictor that is released upon catecholamine stimulation or hypoxia (97). The overall increase in systemic peripheral vascular resistance is distributed differently among various organs in the body (31). Vasocostriction also occurs in the venous vasculature, increasing return of available blood to the heart (14,98). The complex interplay of these mechanisms for vasodilation and vasoconstriction ultimately determines the regional redistribution of blood flow to organs following hemorrhagic shock. The redistribution of blood flow results in a greater share of oxygen delivery to organs with high obligatory metabolic demands (heart and brain), and a lesser share to those with fewer demands including the skin, skeletal muscle, kidney, intestine, and pancreas (5,31,86,99–101).

**Anaerobic Glycolysis**

In anaerobic conditions, pyruvic acid cannot enter the citric acid cycle within the mitochondria and is instead shunted to the production of lactate. This process produces only two molecules of adenosine triphosphate (ATP), as opposed to the 36 molecules of ATP produced from glucose in the mitochondria during aerobic glycolysis. Hydrolysis of ATP molecules in anaerobic conditions results in the production of hydrogen ions that cannot be cleared, leading to intracellular acidosis. (Adapted from Mizock BA, Falk JL. Lactic acidosis in critical illness. Crit Care Med. 1992;20(1):80.)

**Aerobic Glycolysis**

ATP produced from glucose in the mitochondria during aerobic glycolysis. Hydrolysis of ATP molecules in anaerobic conditions results in the production of hydrogen ions that cannot be cleared, leading to intracellular acidosis. (Adapted from Mizock BA, Falk JL. Lactic acidosis in critical illness. Crit Care Med. 1992;20(1):80.)
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Hemorrhage (decreased intravascular volume)

↑ Baroreceptor activity
  - Aorta, carotid, splenic
  - Right atrium, pulmonary artery

↑ Mechanoreceptor activity
  - Carotid, aorta, adrenal medulla

↑ Chemoreceptors
  - Aorta, carotid, splanchic
  - Right atrium, pulmonary artery
  - Carotid, aorta, adrenal medulla

↓ Renal Perfusion
  - Flow by renal juxtaglomerular apparatus

CNS Response

Sympathetic Response

Pituitary Response

Hormonal Response

Neural Response

Hormonal
- Epinephrine
- Norepinephrine
- Renin/angiotensin
- Aldosterone

↑ Cardiac contractility

↑ Νa/H+O retention

Flow redistribution

Hormonal
- ACTH release
- ADH release

↑ Cortisol release

Aldosterone secretion

↑ Na/H+O retention

Maintain cardiovascular responsiveness

FIGURE 58.3. Neurohormonal response to hemorrhage. Hemorrhage results in a decrease in the circulating intravascular volume, which initiates a complex cascade of compensatory events. CNS, central nervous system; ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone.

Alterations in microvascular function and flow are affected through precapillary and postcapillary sphincters, which are sensitive to both extrinsic and intrinsic control mechanisms. Exchange of metabolites and compartmental regulation of fluids occurs at the capillary level. Therefore, alteration of tone of the pre- and postcapillary sphincters can have significant effects on microcirculatory function (102–104). Failure to dilate sphincters supplying metabolically active tissues may result in ischemia and anaerobic metabolism with lactate production. Increased precapillary tone, as seen with sympathetic stimulation, results in increased blood pressure systemically and decreased hydrostatic pressure locally. In fact, the microvascular arterioles may even dilate in response to the above vasoconstriction due to release of metabolic byproducts of underperfusion (carbon dioxide, hydrogen ion, etc.). The decrease in hydrostatic pressure locally then leads to redistribution of fluid from the interstitium to the circulation. Conversely, increased postcapillary tone (relative to precapillary tone) results in vascular pooling of blood and loss of fluid to the interstitium (as a result of increased hydrostatic pressure). This increased hydrostatic pressure may become accentuated in response to crystalloid resuscitation, leading to interstitial edema (104). Finally, hemorrhage and shock have also been shown to induce increased permeability of capillaries, leading to interstitial fluid leak during resuscitation (105,106).

Hypovolemic shock and hemorrhage also induce the expression of endothelial adhesion molecules on neutrophils and endothelium (63,107). This results in neutrophil adherence and "rolling" of cells within the capillary bed (108–113). Capillary flow then diminishes and may also impair red blood cell flow. While this decrease in transit time may augment the ability of tissue to extract oxygen, it may also lead to microvascular thrombosis and further tissue ischemia (114,115).

Metabolic and Hormonal Response

The early hyperglycemic response to trauma or hemorrhage is the combined result of enhanced glycogenolysis, caused by the hormonal response to stress including elevated epinephrine, cortisol, and glucagon levels; increased gluconeogenesis in the liver, partly mediated by glucagon; and peripheral resistance to the action of insulin (51,116). Increased gluconeogenesis in the liver, and to a lesser extent in the kidneys, follows increased efflux of amino acids, such as alanine and glutamine from the muscle to the liver, due to a breakdown of muscle protein. The
latter is evidenced by increased urinary losses of nitrogen and a negative nitrogen balance. Lactate produced in muscle can also be catabolized in the liver to glucose (117). Increased epinephrine levels also result in skeletal muscle insulin resistance, sparing glucose for use by glucol-deendent organs such as the heart and brain. Later in shock, hypoglycemia may ensue, possibly because of glycogen depletion or hepatic ischemia (51,117,118). Fatty acids are increased early in shock, but later levels fall (116). Without energy for glycolysis, the cell depends on lipolysis and the autodigestion of intracellular protein for energy. Initially, ketone bodies and the branched-chain amino acids are used as alternative fuel sources. Without oxygen, these sources become inefficient, leading to hypertriglyceridemia, increased β-hydroxybutyric acid and acetoacetate levels, and changes in the amino acid concentration pattern. As these metabolic changes occur, the cell, in motion by cellular hypoxia and promoted by systemic hormonal changes, experiences changes occurring within individual cells (119).

### ORGAN PERFUSION AND FUNCTION DURING HEMORRHAGE

#### Heart

The heart is a critical organ in the pathophysiology of shock. At baseline, myocardial oxygen extraction is almost maximal; therefore, increased cardiac work must occur to meet increased coronary blood flow. When coronary perfusion is compromised, as it is during systemic hypotension, cardiac function suffers. In the presence of sympathetic stimulation, blood flow from the endocardium is redistributed toward the epicardium, impairing cardiac performance (120). Underlying coronary artery disease, arrhythmias, hypoxemia, and acidosis can add to cardiac dysfunction. In the absence of coronary stenosis, myocardial necrosis/infarction is unusual in hypovolemic shock. Rather, the heart plays a participatory role in which it is unable to compensate fully for arterial hypotension caused by hypovolemia, vasodilation, and other factors. Under basal aerobic conditions, 60% of energy comes from fat (free fatty acids and triglycerides), 35% from carbohydrates, and 5% from amino acids and ketone bodies. However, during anoxic conditions imposed by hypoxemia or ischemia, the myocardium shifts to anaerobic glycolysis. Anaerobic glycolysis, however, is insufficient to meet cardiac work demands for any length of time because the myocardial glycogen stores, as an alternative fuel source, are minimal and rapidly depleted.

#### Brain

Like the heart, the brain almost exclusively depends on perfusion, rather than changes in extraction, to meet its oxidative metabolic needs. Protective mechanisms, collectively referred to as autoregulation, have evolved to guard perfusion. Pressure autoregulation refers to the ability of the brain to maintain total and regional cerebral blood flow (CBF) nearly constant despite large changes in systemic arterial blood pressure (Fig. 58.4) (121). Cerebral function seems to be maintained until the mean arterial pressure drops below 50 to 60 mm Hg (122). The factors that control cerebral autoregulation are not completely understood, but seem to include local carbon dioxide and oxygen tension, and the so-called Bayliss effect (i.e., contraction or dilation of arterioloml smooth muscle in the presence of increased or decreased intravascular pressure).

In the presence of neurotrauma, autoregulation is impaired and the brain is exquisitely sensitive to secondary insults, such as hypoxia and hypotension. Hemorrhagic shock and resuscitation may also impair autoregulation because of endothelial cell dysfunction and diminished NO-dependent vasodilator reactivity, so that the brain may experience an oxygen deficit along with metabolic and functional deterioration (52,87). However, the vulnerability of the brain to anoxic injury is uncertain and appears variable. The adequacy and the method of resuscitation can critically influence postischemic recovery. These observations have motivated investigation of specific brain resuscitation regimens (123–126). However, there are no conclusive data that one modality provides improved outcomes.

#### Lungs

Hypovolemic shock is associated with a rise in ventilation marked by tachypnea, hyperventilation, and a fall in arterial PCO₂ (28,30,127–130). These changes are usually due to a decrease in pulmonary perfusion, leading to an increase in dead space ventilation. Thus, a higher minute ventilation is necessary for a given CO₂ production (28,30,127). In addition, minute ventilation may need to increase further in order to compensate for a metabolic acidosis following accumulation of lactic acid in the blood. The imbalance between the increased demands of the diaphragm and reduced blood flow in shock may finally lead to respiratory muscle fatigue and respiratory failure, requiring intubation (28). Therefore, early airway control is imperative in patients with severe hemorrhagic shock. Hemorrhagic shock requiring massive transfusion also increases the risk of acute respiratory distress syndrome (129,130–132). Contributing factors include release of...
proinflammatory mediators; activation of neutrophils in the lungs and other organs after reperfusion; contusion and/or ischemia/reperfusion of the lung; pulmonary microemboli of neutrophils, platelets, and fat particles from long bone fractures; and induction of transfusion-related acute lung injury (TRALI), which is discussed later in this chapter.

Kidney

Oliguria, as defined by a urinary output of less than 0.5 mL/kg/hour, is a cardinal manifestation of shock. However, the pathogenesis of shock-related oliguria is more complex than mere renal hypoperfusion (133–135). Blood flow to the kidney is rarely reduced below 40% to 50% of normal levels, even in the face of more severe reductions in overall cardiac output. Thus, the decreased glomerular filtration rate results from additional mechanisms. Sympathetic stimulation, circulating catecholamines, angiotensin, and locally produced prostaglandins contribute to afferent arteriolar vasoconstriction. These compounds promote the redistribution of blood flow away from cortical glomeruli toward the renal medulla (63). Vasodilation of the efferent arteriole may amplify these changes. The net effect is a decreased glomerular filtration rate and a decrease in the energy needs of the kidney. Additional fluid (and salt) conservation is promoted by the effects of aldosterone and antidiuretic hormone.

If renal hypoperfusion persists, the cortical kidney will become ischemic. Three pathologic changes are observed: (a) tubular necrosis with back-diffusion of glomerular infiltrate, (b) tubular obstruction by casts or other cellular debris, and (c) tubular epithelial damage with consequent interstitial edema and tubular collapse. Following hypovolemia and renal ischemia, these pathologic changes may be secondary events (i.e., reperfusion injury) that can amplify but rarely initiate acute renal failure. The presence of these pathologic changes partially explains why restoration of normal hemodynamic function does not often lead to an immediate improvement in renal function. Although irreversible renal failure from shock alone is rare, fluid and electrolyte balance are often supported by dialysis although normal perfusion has been restored.

Intestine

During hypovolemic shock, blood flow from intestine is redistributed to other organs. The decrease in blood flow to the gut is relatively greater than the decrease in cardiac output due to the local vasocstriction caused by catecholamines, vasopressin, and angiotensin II (4,5,26,136–139). Ischemic injury to the gut is manifested primarily by interstitial fluid sequestration and hemorrhage or necrosis of the mucosal lining, and is most prominent in the stomach (139). Ulcer formation (140) with exangunating hemorrhage can occur several days after normal hemodynamic function has been restored (141). Breakdown of the gut epithelium creates a port of entry for translocation of bacteria or deleterious bacterial products (endotoxin) (142,143). These factors may be important in the pathogenesis of reversible shock (144) by releasing mediators to the systemic circulation. The determination of mucosal pH via tonometry has been described as a potential indicator of the therapeutic response and a marker of MODS (145,146).

Liver

Hepatic perfusion declines during hypovolemic shock because of diminished portal and hepatic arterial blood flow, roughly in proportion to the fall in cardiac output (57,61,109,147–150). Clinical manifestations of ischemic liver injury are not usually apparent in the early stages of hemorrhagic shock, as the organ participates in the release of acute-phase reactants. As hepatic cells die, they release characteristic enzymes (i.e., aspartate aminotransferase, alanine aminotransferase) (151). Occasionally, an obstructive picture with elevated bilirubin and alkaline phosphatase predominates. Later, the synthesis of coagulation factors, albumin, and prealbumin may deteriorate (152,153). Less clinically obvious is the impairment in the reticuloendothelial system function. Impaired hepatic clearance functions and reticuloendothelial system failure contribute to continued circulation of vasoactive substances that can perpetuate shock. Hepatic ischemia may result in a diminished capacity for metabolism of drugs and for gluconeogenesis from lactate and amino acids, contributing to hypoglycemia in the late stages of hypovolemic shock. The capacity to clear gut-derived endotoxin and lactate may also decrease, and the ischemic liver produces lactate (154). The appearance of “shock liver” with massive hepatocellular necrosis is unusual and presents mainly in patients with pre-existing liver conditions (155).

Spleen

The spleen contracts during hypovolemic shock, probably due to an increased sympathetic tone, which results in the release of red blood cells into the circulation (5.26). Changes in hematocrit during the early phase of bleeding probably underestimate the severity of plasma losses. The spleen also releases stored platelets.

Pancreas

The importance of the pancreas in the clinical picture in hemorrhagic shock has not been fully established. Older studies have demonstrated that the pancreas becomes severely ischemic during hypovolemic shock (156). Recently, much work has been done to better elucidate the role of the pancreas following hemorrhage and reperfusion. Preliminary data suggest that following hemorrhage, the mucosal barrier of the intestine becomes ischemic and therefore has increased permeability to pancreatic enzymes. These digestive enzymes then gain access to the wall of the intestine, initiating self-digestion of submucosal extracellular matrix proteins and interstitial cells. This initiates the generation and release of a host of strong inflammatory mediators, which may contribute to the multiorgan dysfunction syndrome. Recent investigations are focusing on protease inhibition in the intestinal lumen as a means of attenuating the inflammatory response following hemorrhage (157–163).

INFLAMMATORY RESPONSE AND TISSUE INJURY

A detailed discussion of the inflammatory and immune response to trauma and hemorrhage is beyond the scope of this
chapter. However, several general concepts can be introduced. Following hemorrhage and resuscitation, macrophages, including lung macrophages and Kupffer cells in the liver, may release proinflammatory cytokines including tumor necrosis factor (TNF)-α and interleukin (IL)-1, -6, and -8. During reperfusion, cytokines may induce and amplify the inflammatory response to ischemia and may further induce local and remote organ damage (148,164–174). The reperfused gut, for example, may, together with the liver, be a source of systemically circulating cytokines, and possibly endothelin. Release of mediators into the mesenteric lymph, portal, or systemic circulations during reperfusion may have deleterious effects on remote organs, such as the lungs, due to neutrophil activation and adherence, leading to pulmonary vascular injury with increased permeability (163,168,169). Circulating levels of proinflammatory cytokines may thus be of predictive value for remote organ damage, including ARDS, after trauma and hemorrhage in patients (167,170).

Arachidonic acid makes up 20% of cell membranes and is released from these membranes in response to a multitude of stimuli that activate phospholipase A2 and cyclooxygenase. The cyclooxygenase pathway results in the production of thromboxanes and prostaglandins, while the lipoxygenase pathway produces leukotrienes. Thromboxane has potent vasoconstricting properties on both the pulmonary and splanchnic circulation, promotes aggregation of thrombocytes and neutrophils, causes bronchoconstriction, and can lead to increased vascular permeability. The prostaglandins have varied effects. Prostacyclin (prostaglandin I2 [PGI2]) has potent vasodilating properties and inhibits thromboxane and neutrophil aggregation (175). PGE2 and PGD2 also have vasodilating properties, while other prostaglandins (PGF2α) are potent vasoconstrictors. Leukotrienes, which are produced by the lipoxygenase pathway, cause vasoconstriction and increased capillary permeability and attract neutrophils (175). Thromboxanes, prostaglandins, and leukotrienes interact with other mediators in a complex fashion (175–179). Vasoconstricting prostaglandins may be involved in the tissue damage during ischemia-reperfusion. Vasodilating prostaglandins may be involved in the vasodilated state of terminal hypovolemic shock (3,175–179).

Platelet-activating factor (PAF) is a nonprotein phospholipid, which is secreted by many cells including platelets, endothelial cells, and inflammatory cells. It is a major mediator of the pulmonary and hemodynamic effects of endotoxin. The major systemic effects of PAF are vasodilatation, cardiac depression, and enhancement of capillary leak. Its complex interactions with other mediators are still poorly understood (180).

Antigen–antibody complexes activate the complement cascade, and complement fragments thus generated can interact with other cytokines to promote the inflammatory response. Complement activation can yield potent vasodilating and leukotaxant substances (175,177,181,182).

Oxygen radicals, such as hydrogen peroxide and superoxide anion, are released by activated neutrophils in response to a variety of stimuli. They are also released when xanthine oxidase is activated after reperfusion in ischemia-reperfusion models. These highly reactive products lead to cell membrane dysfunction, increased vascular permeability, and release of eicosanoids (183–186).

This inflammatory process results in the local accumulation of activated inflammatory cells, which release various local toxins such as oxygen radicals, proteases, eicosanoids, platelet-activating factor, and other substances. When unregulated, such accumulations can cause tissue injury. The initial attachment of neutrophils to the vascular endothelium at an inflammatory site is facilitated by the interaction of adherence molecules on the neutrophil and endothelial cell surfaces (108,187–192).

**IMMUNE FUNCTION FOLLOWING HEMORRHAGE AND RESUSCITATION**

Despite the initiation of the inflammatory cascade, hypovolemic shock and resuscitation depress the immune system by suppressing the function of lymphocytes, macrophages, and neutrophils, depressing both humoral and cellular immune responses, decreasing antigen presentation and delayed hypersensitivity to skin-test antigens, and increasing susceptibility to sepsis (63,166,193–198). The immune consequences of hemorrhage and resuscitation differ among cell populations, however, with some cells expressing enhanced (199–201) and others diminished inflammatory responses (202,203). Hormone may also influence immune response (204,205). The immunosuppression after hypovolemic shock may also be potentiated by the release of anti-inflammatory cytokines (IL-10) (206–208) and soluble cytokine receptors (receptor antagonists) for the proinflammatory cytokines (203,209,210).

**MANAGEMENT OF HEMORRHAGIC SHOCK**

Trauma is by far the most common etiology for hemorrhagic shock. While other causes do exist, management priorities are similar regardless of the source of bleeding. Diagnosis, evaluation, and management must often occur simultaneously. A methodical approach is necessary to optimize outcome. Unique to hemorrhagic shock, as opposed to other forms of shock, is that definitive management frequently requires surgical or procedural intervention to cease bleeding. The diagnostic pathway and interventions pursued become part of the resuscitation pathway. What follows is a summary of the interventions, diagnostic studies, monitoring strategies, and resuscitation techniques for hemorrhagic shock.

**Immediate Management**

**Airway and Breathing**

When approaching any patient in shock, the sequence of events should be to address the issues of airway, breathing, and circulation—also known as the “ABCs” (211). Most patients with fully developed shock require tracheal intubation and mechanical ventilation, even if acute respiratory failure has not yet developed. Studies have shown that during shock, the respiratory muscles require a disproportionate percent of the cardiac output (28). Failure to mount a hyperventilatory response to a metabolic acidosis is a significant predictor of the need for...
subsequent intubation in trauma patients (212). Mechanical ventilation allows flow to be redistributed, lessens the work of breathing, may help reverse lactic acidosis, and supports the patient's airway until other therapeutic measures can be effective. Tracheal intubation is also required if there is evidence of mental status changes, such as airway protection is questionable. Evidence of hypoxemia and/or hypventilation is also an absolute requirement for early intubation.

Perhaps most complex is the patient with evidence of compensated hemorrhagic shock whose mental status is still intact. In this type of patient, clinical acumen is imperative. If the initial response to resuscitation is sustained (i.e., "a responder"—see below), then close observation of the airway may be appropriate while additional workup and treatment are pursued. However, in a patient who is not responsive or has a transient response (see below) to fluid resuscitation, control of the airway early is necessary prior to respiratory collapse (212). In addition, if diagnostic and therapeutic interventions, such as angiography and embolization, are required during resuscitation to control hemorrhage, early airway control should be obtained.

Once the airway is secured, it is important to closely monitor techniques of ventilation. Studies have shown that there is a tendency of rescue and medical personnel to hyperventilate patients during trauma (213,214). Hyperventilation has been shown to have an increased mortality when compared to nonhyperventilated patients in the setting of severe traumatic brain injury (214). Animal studies have supported this information, showing that cardiac output increases with hyperventilation and decreases with hypventilation and positive end-expiratory pressure (PEEP). Thus, adequate appropriate ventilator strategies are imperative early in hemorrhagic shock to optimize tissue perfusion and outcome.

**Circulation**

The management steps to restore adequate circulation are threefold:

1. Secure access to the bloodstream in order to initiate infusion of fluids and blood products.
2. Control obvious sources of hemorrhage and prevent ongoing hemorrhage.
3. Assess extent of shock and hemorrhage.

**Intravenous Access.** Access to the bloodstream should be obtained expeditiously. Two peripheral large-bore intravenous catheters (18 gauge or larger) are necessary. If cannulation of a peripheral vein is difficult due to collapse, then central venous access should be secured. In the presence of trauma to the torso, venous access above and below the diaphragm is preferable. When obtaining intravenous access, it is important to note that the maximal rate of infusion via a catheter is directly proportional to the diameter of the catheter and indirectly proportional to the length. Therefore, a 9 French peripheral intravenous catheter will also infuse fluids more rapidly than a 7 French triple-lumen catheter. A large-bore peripheral intravenous catheter will also infuse fluids more rapidly than a 7 French triple-lumen catheter due to a shorter length and less resistance. In pediatric patients, an intravenous access may be necessary. This is only recommended for children under the age of 6 and should only be used until an alternative source of venous access is obtained.

Control Obvious Hemorrhage Immediately. Resuscitation of the bleeding patient requires early identification of potential bleeding sources followed by prompt action to minimize blood loss, restore tissue perfusion, and achieve hemodynamic stability. This is particularly important in the trauma patient where multiple sources may be involved. Wound compression is the initial maneuver to control an exsanguinating wound. For massive soft tissue injuries, placing a tourniquet proximally may decrease hemorrhage and allow resuscitation prior to definitive control. Fractures should be splinted or placed in traction. Evidence of pelvic instability or hemorrhage may be temporized by a sheet, a pelvic binder, an external fixator, or a pelvic C-clamp (217–220). In the presence of massive trauma, patients may present with coagulopathy in the emergency department and this should be preemptively addressed. The same principles should be applied to nontraumatic hemorrhagic shock, such as gastrointestinal bleeding and ruptured aortic aneurysms: rapidly identify and attenuate the obvious sources of hemorrhage.

Initiate Resuscitation and Assess Extent of Bleeding: Responders and Nonresponders. The traditional classification of hemorrhagic shock was discussed earlier (Table 58.3). While this is a useful guideline for determining the extent of blood loss for a given patient, perhaps more important in determining an appropriate treatment algorithm is the patient's response to resuscitation. Following hemorrhage, resuscitation should be initiated with 2 L of lactated Ringer solution or isotonic crystalloid solution. The response to this initial fluid bolus will provide critical insight as to the presence of ongoing hemorrhage and need for surgical intervention (Table 58.4) (221).

**Transient responders** become hemodynamically normal and remain this way following the initial fluid bolus. This group of patients has likely lost <20% of their total circulating blood volume, and ongoing aggressive resuscitation is not necessary. Intravenous fluids can be lowered to maintenance rates while additional workup proceeds. Blood should still be sent for type and cross-match and should be made available. Retrospective studies have shown that patients with field hypotension who become normotensive on arrival to the emergency department have increased morbidity, mortality, need for operation, and admission rate to the intensive care unit (ICU) (222–224). Approximately 15% of these patients will need transfusion, with 37% requiring therapeutic surgery (224). Hence, even a brief episode of hypotension can be a marker for significant underlying injury.

**Transient responders** represent a group of patients who initially respond to a 2-L bolus of crystalloid, but then begin to show signs of deterioration when intravenous fluid infusion is lowered to maintenance levels. These patients have likely lost 20% to 40% of their circulating blood volume, and either have ongoing blood loss or inadequate resuscitation. Continued fluid resuscitation and initiation of blood transfusion are indicated. A transient response to blood infusion indicates ongoing hemorrhage. Rapid surgical intervention or angiembolization (225–228) to control hemorrhage is immediately indicated.

**Nonresponders** represent patients who fail to respond to crystalloid and blood administration in the emergency department. These patients have likely lost >40% of their circulating blood volume and have ongoing hemorrhage. Immediate control of hemorrhage is necessary via surgical intervention.
Patients sustaining witnessed penetrating trauma with >7th ed. American College of Surgeons Shock States

Hemorrhage—intrathoracic, intra-abdominal, extremity, Cardiac tamponade

Air embolism

Historical teachings have been that tilt-...the use of emergency room thoracotomy in nontrauma infra-

Emergency Department Resuscitative Thoracotomy. Resuscitative thoracotomy is occasionally indicated for exsanguinating hemorrhage. In trauma, indications for resuscitative thoracotomy include (a) patients with penetrating thoracic injuries who arrive pulseless, but with myocardial electrical activity, and (b) blunt trauma patients who have vital signs on arrival but then sustain a witnessed arrest or onset of pulseless electrical activity. Specific recommendations are listed in Table 58.5. Therapeutic maneuvers that can be attained with a resuscitative thoracotomy include (a) evacuation of pericardial blood causing tamponade, (b) direct control of exsanguinating thoracic or cardiac hemorrhage, (c) open cardiac massage, and (d) cross-clamping of the descending aorta to slow blood loss below the diaphragm and improve perfusion to the heart and brain. Depending on the cause of injury, the overall mortality rate is extremely high (229–231). The highest survival rates are found in patients with isolated cardiac injury without loss of vital signs (approximately 35%). Some reports of thoracic aortic cross-clamping for exsanguinating intra-abdominal hemorrhage have reported survival rates of nearly one third (231,232), but this is mainly in the setting of penetrating abdominal trauma. Survival rates following resuscitative thoracotomy in blunt trauma are dismal, ranging from 0% to 5%. Aortic cross-clamping should be viewed as an adjunct to other initial hemorrhage control measures. It has not been established whether thoracic aortic clamping should be performed before or after the abdominal incision, or whether thoracic or intra-abdominal aortic cross-clamping is more effective (233). However, when aortic cross-clamping is deemed necessary for continuous bleeding or low blood pressure, the prognosis is generally poor (234). No clinical data exist for the use of emergency room thoracotomy in nontrauma infra-diaphragmatic bleeding.

Adjunctive Measures. Historical teachings have been that tilting a patient into head-down position (i.e., Trendelenburg) diverts blood volume into the central circulation and improves venous return, thereby improving stroke volume and cardiac output in hypovolemic shock. However, recent studies do not show any significant redistribution of blood volume centrally (235). In fact, the head-down position can worsen gas exchange and cardiac function. Therefore, the Trendelenburg position is no longer recommended as a resuscitative technique. If this type of measure is deemed desirable, raising the legs above the level of the heart should be adequate (13).

<table>
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<tr>
<th>INDICATIONS AND CONTRAINDICATIONS FOR EMERGENCY DEPARTMENT RESUSCITATIVE THORACOTOMY</th>
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<td><strong>INDICATIONS</strong></td>
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<tr>
<td>Salvageable postinjury cardiac arrest</td>
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<tr>
<td><em>Patients sustaining witnessed penetrating trauma with &lt;15 min of prehospital cardiopulmonary resuscitation (CPR)</em></td>
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<td><em>Patients sustaining witnessed blunt trauma with &lt;5 min of prehospital CPR</em></td>
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<td>Persistent severe postinjury hypotension (systolic blood pressure ≤60 mm Hg) due to:</td>
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<tr>
<td><em>Cardiac tamponade</em></td>
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<td><em>Hemorrhage—intrathoracic, intra-abdominal, extremity, cervical</em></td>
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<td><em>Air embolism</em></td>
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<td><strong>CONTRAINDICATIONS</strong></td>
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<tr>
<td><em>Penetrating trauma: CPR &gt;35 min, and No signs of life</em></td>
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<td><em>Blunt trauma: CPR &gt;3 min, and No signs of life</em></td>
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*No signs of life = no pupillary response, respiratory effort, or motor activity.

The use of pneumatic antishock garments (PASGs, previously military antishock trousers [MAST]) currently has a limited role in the management of hypotensive trauma patients. Although their use was almost universal for hemorrhage control in the late 1970s and 1980s, recent studies have demonstrated that they have no effect on patients with thoracic injury. In fact, some evidence suggests that mortality is higher when PASGs are applied (236,237). No survival advantage has been demonstrated in the pediatric population, although there may be a small survival benefit in children with a systolic blood pressure of less than 50 mm Hg (238). The main utility of PASGs currently is as a temporizing agent to stabilize pelvic fractures.

**Fluid Resuscitation**

Careful attention to fluid resuscitation is necessary during management of hemorrhagic shock to optimize outcome. It is still unclear which type of fluid should be employed in the initial treatment of the bleeding patient.

**Colloids versus Crystalloids**

Several meta-analyses have shown an increased risk of death in patients resuscitated with colloids as compared with crystalloids (239–243) during hemorrhagic shock. While three of these studies suggested that the effect was particularly significant in the trauma population (239,242,243), the results of a recent meta-analysis showed no significant difference (244). A recent trial evaluating 4% albumin versus 0.9% normal saline in nearly 7,000 ICU patients showed that albumin administration was not associated with worse outcome. There was a trend, however, toward higher mortality in the trauma subgroup that received albumin (p = 0.08) (245). The difficulty with interpreting these meta-analyses and the individual studies is that they are very heterogeneous. Each evaluates different patient populations and resuscitation strategies, and mortality may not always be a primary end point. However, given these results, crystalloid resuscitation is currently the accepted standard as initial therapy for hemorrhagic shock.

Many synthetic colloid solutions such as hetastarch and dextran have also been associated with coagulopathy. Recent research suggests that hetastarch solutions with a high mean molecular weight and a high C2/C6 ratio suppress coagulation more than solutions with rapidly degradable low-molecular-weight colloids (246–248). This coagulopathy may be produced by one of several potential mechanisms including a reduction in von Willebrand factor, platelet dysfunction, reduced factor VII levels, and an interaction with fibrinogen (249,250).

Crystalloid solutions are not without side effects. Resuscitation with fluids that contain supraphysiologic concentrations of chloride can lead to hyperchloremic acidosis. This can be significant in patients where lactic acidosis may already be present. Lactated Ringer solution contains a more physiologic concentration of chloride (109 mEq/L) than normal saline (NS 154 mEq/L), and therefore may be the preferred choice. Animal studies have also shown that resuscitation with normal saline can lead to more coagulopathy and increased blood loss than resuscitation with lactated Ringer solution (251).

Massive resuscitation with crystalloid fluids alone can lead to several significant complications including cardiac and pulmonary complications, gastrointestinal dysmotility, coagulation abnormalities, and immunologic dysfunction (252).

ports of lactated Ringer solution and normal saline increasing reperfusion injury and leukocyte adhesion suggest that crystalloid resuscitation may increase acute coagulopathy in severely injured patients and possibly increases the risk of ARDS, systemic inflammatory response syndrome (SIRS), and multiorgan failure (MOF) (252–256). Abdominal compartment syndrome has been clearly associated with excessive use of crystalloid resuscitation (50,257–261). Recently, there has been increased focus on early use of blood products in order to minimize crystalloid use in the resuscitation of hemorrhagic shock (262). Finally, resuscitation strategies that focus on early aggressive fluid resuscitation to normalize blood pressure before bleeding is controlled may result in increased hemorrhage and increased mortality. This has led some authors to suggest that “hypotensive resuscitation” should be the goal until the source of hemorrhage is controlled (263–265). However, the exact goals for mean arterial pressure and trigger points for bleeding have not been established. The potential adverse sequelae when used in patients with associated injuries or comorbidities (i.e., severe closed head injury) have not been clearly established (266).

In light of these potential sequelae of resuscitation, future research should focus on improvement in fluid composition and adjuncts to the administration of large volumes of fluid (266).

**Preventing Hypothermia**

All fluids during resuscitation from hemorrhagic shock should be warmed to prevent hypothermia. Equipment is now available that allows that the rapid infusion of blood and/or crystalloids at warmed temperatures (i.e., up to 750 mL fluid per minute warmed to over 37°C). This newer equipment is more effective and efficient and results in fewer complications associated with earlier models (such as air embolism and bacterial contamination) (267). Other techniques during resuscitation that can be used to prevent hypothermia in the acutely hemorrhaging patient include warming the circuit on the ventilator in ventilated patients, ensuring the patient is covered with warm blankets at all times following exposure and thorough examination, warming the resuscitation and operating rooms, using external warming blankets such as the Baer hugger during resuscitation and in the operating room, and using warm water blankets on the operating room table during exploratory operations. Hypothermia is clearly associated with increased mortality following resuscitation from hemorrhagic shock (268), and every attempt to prevent or minimize its occurrence and severity should be employed.

**Diagnostic Approach**

If no obvious source of external bleeding is identified, a rapid evaluation should be performed to identify likely occult sources of bleeding. In the trauma patient, significant internal hemorrhage can occur in four defined regions: the thoracic cavity, the peritoneal cavity, the retroperitoneum, and extremity fractures. These areas can be rapidly assessed via chest radiograph, a pelvic radiograph, FAST, and physical examination of extremities along with appropriate radiographs. In-depth coverage of the diagnosis of abdominal trauma is provided in a later chapter.

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**Chapter 5B: Hemorrhagic Shock**

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chapter of this book. In nontrauma patients without clear evidence of bleeding, the gastrointestinal tract should be rapidly evaluated via nasogastric tube, rectal examination, and endoscopy where appropriate. Additional diagnostic tests can be obtained based on clinical history, patient background, and condition. Abdominal aortic aneurysms can be identified on physical examination, by ultrasound, or by calcifications on abdominal radiograph. In selected instances, angiography may be used to identify and treat sources of hemorrhage not otherwise apparent (pelvic fractures, pancreatitis, lower gastrointestinal bleeding) (225–228,269–277). This should only be instituted when a specific source of hemorrhage is highly likely and therapeutic intervention is sought. Computed tomography should never be sought in hemodynamically unstable patients with hemorrhage.

Laboratory Testing and Monitoring of Resuscitation

Measurement of Bleeding
Hematocrit/Hemoglobin. Hemoglobin and hematocrit measurements have long been part of the basic diagnostic workup of patients with hemorrhage and/or trauma. However, in patients with rapid bleeding, a single hematocrit measurement on presentation to the emergency department may not reflect the degree of hemorrhage. In a short transport or presentation time, prior to initiation of resuscitation, the body’s compensatory mechanisms for fluid retention and resorption into the vasculature once hemorrhage has taken place, analysis of hematocrit levels may remain stable despite significant blood loss. A retrospective study of 524 trauma patients (278) determined that the initial hematocrit with a sensitivity of only 0.50 for detecting patients with an extent of traumatic hemorrhage requiring surgery. The diagnostic value is further confounded by the administration of intravenous fluids and red cell concentrates during resuscitation (279–281).

Two prospective observational studies determined the sensitivity of serial hematocrit measurements for detecting patients with severe injury (282,283). In the first study (282), the authors compared values of hematocrit at admission and 15 minutes and 30 minutes following arrival to the emergency department. A normal hematocrit on admission did not predict survival (289). However, its overall utility has been questioned by some because it is felt to be a late marker of tissue hypoperfusion, which can be influenced by hepatic function, and can be influenced by glycolysis and alkalosis (290–293). Despite these concerns, data do exist showing that the amount of lactate produced by anaerobic glycolysis is an accurate indirect marker of oxygen debt, tissue hypoperfusion, and the severity of hemorrhage shock (294–305). In many forms of shock, arterial lactate levels above 2 mEq/L have been associated with increased mortality (286,287,300,305). However, during hemorrhage, not only is the initial lactate level important, but also the rate of clearance (298,299). Two prospective studies confirm this. In one prospective observational study (298), 76 patients with multiple trauma were analyzed with respect to clearance of lactate between survivors and nonsurvivors over 48 hours. If lactate normalized within 24 hours, survival was 100%. Survival decreased to 77.8% if normalization occurred within 48 hours, and to 13.6% in those in whom lactate levels remained elevated above 2 mEq/L for more than 48 hours. This was confirmed in another prospective study of 129 trauma patients (299) in which initial lactate levels were higher in nonsurvivors. A prolonged time to normalization (>24 hours) was associated with the development of posttraumatic organ failure. Finally, venous lactate has been shown to be an excellent approximation for arterial lactate in acute trauma patients and is a useful marker for significant injury (306).

Taken together, these studies suggest that both the initial lactate level and the rate of clearance are reliable indicators of morbidity and mortality following trauma. However, whether lactate should be used as an end point of resuscitation or is merely a marker of tissue ischemia has not been clearly established.

Base Deficit. Base deficit values derived from arterial blood gas analysis have also been shown to provide an indirect estimation of tissue acidosis due to impaired perfusion (294,296,297, 300–303). However, base deficit can be affected by resuscitation fluids (hyperchloremic metabolic acidosis) and exogenous administration of sodium bicarbonate. Despite these potential drawbacks, initial base deficit has been shown in several retrospective studies to correlate with transfusion requirements, organ dysfunction, morbidity, and mortality following trauma (307–313). The magnitude and severity of the base deficit also correlates to outcome, and is useful in both pediatric and elderly patients (307,310–312). Base deficit has been shown to be confounded by aggressive fluid resuscitation early during resuscitation (278–281). An initial hematocrit level will help to identify patients who present with existing anemia who may have a lower threshold for hemorrhage. The hematocrit level should be used in conjunction with other measures of perfusion in order to determine the presence of occult hemorrhage.

Measurements of Perfusion
Lactate. Lactate was initially suggested as a diagnostic parameter and prognostic indicator of hemorrhagic shock in the 1960s (284). Substantial data exist that lactate levels as a marker of tissue oxygen debt can predict outcome in various forms of shock (60,285–288). In 1983, Vincent et al. performed a prospective study on 27 patients with circulatory shock and concluded that changes in lactate concentrations provided an early and objective evaluation of a patient’s response to therapy (289). However, its overall utility has been questioned by some because it is felt to be a late marker of tissue hypoperfusion, which can be affected by hepatic function, and can be influenced by glycolysis and alkalosis (290–293).
be a better predictor of outcome than pH alone following traumatic injury (309). Recently, serum bicarbonate levels have been shown to be an appropriate surrogate for arterial base deficit in the ICU (314–315).

Lactate versus Base Deficit. Although many studies have shown that both base deficit and serum lactate levels correlate with outcome following trauma and hemorrhage, these two parameters do not always correlate with each other (304,316). In fact, lactate has been found to be a superior predictor of mortality as compared to base deficit in a recent study of patients in the intensive care unit following trauma (304). Both base deficit and lactate have been shown to correlate to outcome in nontraumatic etiologies of hemorrhagic shock (268,317). Given that there are confounding variables following trauma that can affect measured levels of both lactate and base deficit, independent assessment of both parameters along with the patient’s clinical condition is recommended for the evaluation of shock in trauma patients.

Measurement of Coagulopathy

Standard Coagulation Studies. Coagulopathy associated with hemorrhagic shock may be due to one of several etiologies: (a) iatrogenic, in which a dilutional coagulopathy develops due to inadequate resuscitation with clotting factors and blood products; (b) premorbid, in which some patients may have a pre-existing coagulopathy due to underlying disease (such as cirrhosis, hemophilia, von Willebrand, renal failure, etc.); and (c) acute traumatic coagulopathy in which coagulopathy after trauma is common. Traditional teachings have been that this coagulopathy is not inherent, but rather iatrogenic, due to dilution from intravenous fluid therapy, massive blood transfusions, progressive hypothermia, and acidosis. Recent literature has now determined that an inherent acute traumatic coagulopathy is present in up to 30% of patients who present to the emergency department immediately following trauma and is an independent predictor of morbidity and mortality (318–321). Therefore, acute measurement of coagulation parameters during resuscitation from hemorrhagic shock is indicated.

TABLE 58.6

<table>
<thead>
<tr>
<th>GOALS</th>
<th>RECOMMENDED THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin/hematocrit</td>
<td></td>
</tr>
<tr>
<td>Hgb ≥ 7.0 g/dL</td>
<td>Packed red blood cells</td>
</tr>
<tr>
<td>Hemodynamic stability</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time ≤ 1.5 times normal</td>
<td>Fresh frozen plasma</td>
</tr>
<tr>
<td>Activated partial thromboplastin time ≤ 1.5 times normal</td>
<td>Prothrombin complex concentrate</td>
</tr>
<tr>
<td>Fibrinogen &gt; 100 g/dL</td>
<td>Fresh frozen plasma</td>
</tr>
<tr>
<td>Platelets &gt; 50 \times 10^9 per liter (stable, nonbleeding patient)</td>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td>Platelets &gt; 100 \times 10^9 per liter (acute, bleeding patient)</td>
<td>Platelet transfusion</td>
</tr>
</tbody>
</table>

Traditional studies of coagulation include prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level, and platelet count. Although no tightly controlled trials have been performed, current recommendations for therapeutic end points in hemorrhagic shock include maintaining a platelet count of >100 in patients with active bleeding or traumatic brain injury, and maintaining a fibrinogen level of >1 g/L (229,322,323) (Table 58.6).

While these laboratory studies are standard, they do present several drawbacks. To begin, in vitro coagulation depends on the interaction between platelets and coagulation factor enzymes. Laboratory values of PT and aPTT are performed on platelet-poor plasma and fail to evaluate the cellular interactions of clotting. PT and aPTT measurements also do not take into account hyperthermia-induced coagulopathy because samples are warmed prior to measurement. Platelet and fibrinogen assays give numerical values, but fail to assess function. Finally, each of these tests takes time, up to 30 to 45 minutes. This lag time makes these studies clinically inefficient because when the results become available, they may not truly reflect the patient’s clinical condition. During resuscitation, actively bleeding patients are in a constant state of flux. Alternative point-of-care testing such as the iSTAT handheld analyzer can provide rapid bedside results, but is currently limited to activated clotting time (ACT) and PT/international normalized ratio (INR) (230). The clinical implications of acute trauma coagulopathy and clinical testing are discussed further later in this chapter.

Thromboelastograph Analyzer. The thromboelastograph (TEG) analyzer is a bedside machine that provides a functional evaluation of overall coagulation on whole blood at the same temperature as the patient. The TEG has been shown to be a more sensitive measure of coagulation disorders than standard coagulation measures (324). The thromboelastograph assay provides a tracing that measures clotting (R value), clot formation (α angle), clot strength (maximum amplitude [MA]), and clot lysis (LY 30) (Fig. 58.5). Elongation of the R value represents a deficiency in coagulation factors. The α angle...
Thromboelastogram. The thromboelastograph (TEG) analyzer is a bedside machine that provides a functional evaluation of overall coagulation on whole blood at the same temperature as the patient. The thromboelastograph assay provides a tracing that measures time to clot formation (R value), speed to a certain clot strength (K value), rate of clot formation (a angle), overall clot strength (maximum amplitude [MA]) and clot lysis (LY 30).

$K$, $R$, $a$, MA

FIGURE 58.5. Thromboelastogram. The thromboelastograph (TEG) analyzer is a bedside machine that provides a functional evaluation of overall coagulation on whole blood at the same temperature as the patient. The thromboelastograph assay provides a tracing that measures time to clot formation (R value), speed to a certain clot strength (K value), rate of clot formation (a angle), overall clot strength (maximum amplitude [MA]) and clot lysis (LY 30).

represents the rate of fibrin accumulation and cross-linking, which can be affected by fibrinogen function and, to a lesser degree, platelet function. The MA is a measure of clot strength and is affected primarily by platelets and, to a lesser degree, fibrinogen. A study investigating the utility of the TEG in trauma patients found that 65% of patients were hypercoagulable and 10% were hypocoagulable. Of the seven hypocoagulable patients, only one had an elevated PT and PTT, but six of seven required blood transfusion (325). Only the Injury Severity Score (ISS) and TEG were predictive of early transfusion.

A large volume of literature exists describing the use of the TEG in various settings including trauma, transplant, and cardiac surgery (250,325–330). However, despite its many advantages, the TEG has not become the standard of care for measurement of coagulopathy. Using the TEG, whole blood samples must be run within 3 to 4 minutes of collection, necessitating the presence of multiple machines in critical areas of the hospital. Quality control of each of these machines is work intensive. Differences due to age, gender, blood collection sites, and sample stability have been raised (331–336). Finally, accurate readings require appropriate processing, and intensive ongoing education of hospital staff would be necessary to ensure accurate results. Although the real-time functional results of routine TEG analysis would be clinically useful, the current processing and maintenance requirements make it impractical for routine use.

RAPID DEFINITIVE CONTROL OF BLEEDING

Multiple studies have confirmed that patients in need of emergency surgery for ongoing hemorrhage have a better survival if the elapsed time to definitive care is minimized (337–347). Those patients with unnecessary delays in diagnosis and definitive treatment will have increased morbidity and mortality (344). Although there are no prospective randomized trials confirming this, multiple retrospective studies provide ample data to confirm the validity of this strategy. In trauma, early surgical control of hemorrhage has been associated with improved survival in penetrating vascular injuries (337), diuretic injuries (338), and polytrauma patients in extremis (339). A multicenter retrospective review of over 500 deaths in the operating room concluded that delayed transfer to the operating room was a cause of death that could be avoided by shortening the time to diagnosis and resuscitation (348). Similar results have been documented in the treatment of patients with ruptured abdominal aortic aneurysms who are hemodynamically unstable (345–347). The benefit for rapid transport time to the operating room is not as dramatic for patients who are hemodynamically stable following ruptured abdominal aortic aneurysm (AAA), implying that ongoing hemorrhage has been arrested in this group of patients.

FIGURE 58.6. Lethal triad of hemorrhagic shock. The development of acidosis, hypothermia, and coagulopathy during resuscitation from hemorrhage, shock is described as the “lethal triad,” “bloody vicious cycle,” or “spiral of death”—terms used to describe the combination of profound acidosis, hypothermia, and coagulopathy (Fig. 58.6). Each of these factors has been independently associated with increased risk of death

LETHAL TRIAD OF RESUSCITATION: HYPOTERMIA, ACIDOSIS, AND COAGULOPATHY

Patients with severe hemorrhagic shock requiring massive resuscitation are at risk for exhaustion of their physiologic reserves, leading to irreversible shock and the inability to recover despite ongoing resuscitation. The common denominator in these patients is the development of the “lethal triad,” “bloody vicious cycle,” or “spiral of death”—terms used to describe the combination of profound acidosis, hypothermia, and coagulopathy (Fig. 58.6). Each of these factors has been independently associated with increased risk of death
(268,303,319,349–354). There also seems to be a cumulative synergistic effect for each of these risk factors in patients with hemorrhagic shock. In one retrospective study of 39 patients with abdominal packing for surgically uncontrollable bleeding (331), five risk factors for death were identified: pH < 7.18, temperature < 33°C, PT ≥ 16, PTT ≥ 50, and transfusion greater than 10 units of blood. Patients with zero to one risk factor had an 18% mortality, two to three risk factors 83% mortality, and four to five risk factors 100% mortality. Similar findings were reported by Cosgriff et al., who identified risk factors for the development of life-threatening coagulopathy (352). Patients with an ISS of > 25, pH < 7.1, temperature less than 34°C, and systolic blood pressure ≤ 70 mm Hg had a 98% chance of developing life-threatening coagulopathy, whereas patients with none of these risk factors had a 1% chance of developing coagulopathy.

The development of profound acidosis, hyperthermia, and coagulopathy is a lethal combination in patients during the resuscitation from hemorrhagic shock. Resuscitation strategies should be designed at limiting the development of these complications.

### Damage Control Laparotomy

Damage control laparotomy (355) is a concept that was initially introduced by Pringle in 1908 when he described the use of hepatic sutures over packs to control bleeding. In 1913, Halsted detailed the procedure and modified its techniques. During World War II, damage control laparotomy fell out of favor and was not reintroduced until 1955 when Madding et al. reported the use of packs to temporize intraoperative bleeding, but felt that they needed to be removed prior to abdominal closure. In the 1970s, Ledgerwood had successful case reports using abdominal packing to control bleeding following trauma. However, the modern era of damage control laparotomy is attributed to Stone et al. who, in 1983, described the techniques of abbreviated laparotomy, packing to control hemorrhage, and deferred definitive surgical repair of injuries until coagulation had been established (356). Since then, a number of authors have described the beneficial effects of damage control laparotomy (357–366). Although retrospective, studies have documented a nearly 50% decrease in operative times for the most severely injured patients treated by this approach and salvage rates of 20% to 60% in patients who would have formerly died in the operating room (351,353,358,367).

The principle of damage control surgery is to obtain rapid control of hemorrhage and contamination, with early completion of the operation, with a goal to restore normal physiology as opposed to normal anatomy (Table 58.7). The ultimate goal is to prevent patients from exhausting their physiologic reserves by developing the “lethal triad of death,” or profound hyperthermia, acidosis, and coagulopathy. Damage control surgery has three basic components. First, an abbreviated laparotomy for control of bleeding, control of contamination, and restoration of blood flow are necessary. The goal is to achieve these end points as quickly as possible without spending unnecessary time on traditional organ repairs that can be performed at a later time. The abdomen is packed and a temporary abdominal closure is performed (Fig. 58.7). The second component involves treatment in the intensive care unit that is focused on core re-warming, correction of acidosis, and reversal of coagulopathy, as well as optimizing ventilation and resuscitation from hemorrhagic shock. Resuscitation strategies should be designed at limiting the development of these complications.

### Table 58.7

**DAMAGE CONTROL LAPAROTOMY AND DAMAGE CONTROL RESUSCITATION**

<table>
<thead>
<tr>
<th>DAMAGE CONTROL LAPAROTOMY</th>
<th>Damage Control Resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Abbreviated laparotomy (initial procedure)</td>
<td>1. Hypotensive resuscitation*</td>
</tr>
<tr>
<td>Control of bleeding</td>
<td><strong>Hemorrhagic Shock</strong></td>
</tr>
<tr>
<td>Control of contamination</td>
<td><strong>Hemostatic resuscitation</strong></td>
</tr>
<tr>
<td>2. Resuscitation in the intensive care unit (24–48 h)</td>
<td>FIGURE 58.7: Open abdomen with temporary abdominal closure. A key component to damage control laparotomy is to perform an abbreviated laparotomy for control of bleeding, control of contamination, and restoration of blood flow. The goal is to achieve these end points as quickly as possible to avoid the development of irreversible shock and the lethal triad of acidosis, hyperthermia, and coagulopathy. Frequently, the abdomen is temporarily closed and the fascia left open to prevent the development of abdominal compartment syndrome during resuscitation. Re-exploration usually takes place 24 to 48 hours later, and every few days thereafter until the fascia is closed. Occasionally, the fascia cannot be reapprimated due to loss of domain. In this circumstance, a ventral hernia remains, which can be repaired at a later date (usually 6–12 months postinjury).</td>
</tr>
<tr>
<td>Core re-warming</td>
<td><strong>Hypotensive resuscitation</strong></td>
</tr>
<tr>
<td>Correction of acidosis</td>
<td><strong>Hypotensive resuscitation</strong></td>
</tr>
<tr>
<td>Reversal of coagulopathy</td>
<td><strong>Hypotensive resuscitation</strong></td>
</tr>
<tr>
<td>Optimization of ventilation and hemodynamics</td>
<td><strong>Hypotensive resuscitation</strong></td>
</tr>
<tr>
<td>3. Definitive surgical repair (days to weeks)</td>
<td><strong>Hypotensive resuscitation</strong></td>
</tr>
<tr>
<td>Restoration of continuity</td>
<td><strong>Hypotensive resuscitation</strong></td>
</tr>
<tr>
<td>Completion of resection</td>
<td><strong>Hypotensive resuscitation</strong></td>
</tr>
<tr>
<td>Removal of packs</td>
<td><strong>Hypotensive resuscitation</strong></td>
</tr>
<tr>
<td>Closure of abdomen</td>
<td><strong>Hypotensive resuscitation</strong></td>
</tr>
</tbody>
</table>

**Abbreviated laparotomy (initial procedure)** and **Damage control resuscitation** are still considered experimental and require experienced physician oversight and careful patient selection.
Massive Transfusion

Definition

In the 1970s, massive transfusion was defined as greater than 10 units of blood transfused in a 24-hour period of time, and survival rates were dismal (6.6%) (390). Over the last two decades, however, survival rates have improved, and the criteria to define massive transfusion have evolved (367, 383, 384, 391–396). Recent reports use variable end points, increasing the number of transfusions to greater than 20 units in 24 hours (383) or defining transfusions during the entire hospital stay.
Recent data have suggested that a more aggressive approach is warranted for massive transfusion (367). During ongoing hemorrhage, empiric transfusion should occur in the ratio of 1:1 for FFP per unit of blood transfused if there is no pre-existing coagulopathy, and a ratio of 1.5 units of FFP per unit of PRBCs if coagulopathy exists on presentation (399). Moreover, both of these mathematical models underestimate the potential need for clotting factor replacement because only dilutional coagulopathy is taken into account; there is no assessment for the relative contributions of consumption, acidosis, and hypothermia, which are frequently seen in the acute trauma patient.

Based on these data, old transfusion strategies appear to be fundamentally flawed in the acutely hemorrhaging patient. Current recommendations suggest that, in patients with ongoing hemorrhage, empiric transfusion should occur in the ratio of 1:1:1 (1 unit of fresh frozen plasma to 1 unit of packed red blood cells to 1 unit of platelets). Two studies utilizing computer modeling have suggested that more aggressive resuscitation is necessary to correct coagulopathy. In the first study, the optimal replacement ratios were 1:2:3 of FFP to PRBCs and 8:10 of platelets to PRBCs (398). Interestingly, a second computer model found similar results, suggesting a transfusion rate of 1:1 for FFP per unit of blood transfused if there is no pre-existing coagulopathy, and a ratio of 1.5 units of FFP per unit of PRBCs if coagulopathy exists on presentation (399). Moreover, both of these mathematical models underestimate the potential need for clotting factor replacement because only dilutional coagulopathy is taken into account; there is no assessment for the relative contributions of consumption, acidosis, and hypothermia, which are frequently seen in the acute trauma patient.

Survival
As technology and blood banking procedures have improved, patient outcomes following massive transfusion have also improved (397). Although early survival rates were dismal, recent reviews report survival rates as high as 60% in patients requiring over 30 units of blood in the early resuscitation period (Table 58.8). Moreover, many of these patients can ultimately return to work (75% of survivors), and survival in elderly patients has also been reported in several studies (367,392,394,395). This dramatic improvement in survival over the past several decades can be attributed to many factors including an improved understanding of the consequences of massive resuscitation (268,389,392), improved technology for massive resuscitation (i.e., rapid transfusion with warmed fluids), increased use of damage control techniques (353,367), improved trauma systems (343), improved transfusion practices during resuscitation (367), and improved blood banking techniques (367). Based on these results, massive transfusion in trauma patients receiving over 50 units of blood in the acute period following injury is justified, with acceptable survival and functional capacity following discharge (367,383,384,391–397).

### Transfusion Protocols
Historically, massive transfusion protocols have been developed to assist clinicians in the resuscitation of hemorrhaging patients. However, a recent review of massive transfusion protocols globally revealed wide variation in practice (389). Most protocols recommend empiric strategies of 1 unit of fresh frozen plasma (FFP) for every 4 to 10 units of packed red blood cells (PRBCs) and 1 plateletpheresis for every 10 to 20 units of PRBCs (380). Organizational guidelines recommended transfusing to laboratory end points (322). However, recent literature suggests that a more aggressive approach is warranted (368,380,387,388). During ongoing hemorrhage, the clinical situation of the patient changes too rapidly to depend on laboratory values sent 20 to 45 minutes prior. Thus, empiric strategies to correct or avoid coagulopathy need to be employed. These strategies need to be modified for two clinical conditions: (a) ongoing hemorrhage and (b) coagulopathy following hemorrhage control.

<table>
<thead>
<tr>
<th>Study/year</th>
<th>No. of patients</th>
<th>Transfusion volume (avg. units)</th>
<th>Overall survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson et al., 1971 (390)</td>
<td>45</td>
<td>&gt;25</td>
<td>7</td>
</tr>
<tr>
<td>Phillips et al., 1987 (383)</td>
<td>56</td>
<td>33</td>
<td>39</td>
</tr>
<tr>
<td>Kivioja et al., 1991 (391)</td>
<td>29</td>
<td>36</td>
<td>38</td>
</tr>
<tr>
<td>Wadel et al., 1991 (392)</td>
<td>92</td>
<td>33</td>
<td>52</td>
</tr>
<tr>
<td>Harvey et al., 1995 (384)</td>
<td>45</td>
<td>19</td>
<td>60</td>
</tr>
<tr>
<td>Velmahos et al., 1998 (393)</td>
<td>141</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Cinat et al., 1999 (367)</td>
<td>46</td>
<td>63</td>
<td>45</td>
</tr>
<tr>
<td>Hakala et al., 1999 (394)</td>
<td>23</td>
<td>79</td>
<td>69</td>
</tr>
<tr>
<td>Vadel et al., 2002 (395)</td>
<td>44</td>
<td>75</td>
<td>43</td>
</tr>
<tr>
<td>Huber-Wagner et al., 2007 (396)</td>
<td>148</td>
<td>41</td>
<td>40</td>
</tr>
</tbody>
</table>

TABLE 58.8

Survival following massive transfusion.
surgery, the situation is more controlled and resuscitation can be initiated immediately. A premorbid coagulopathy may or may not exist. Goals in resuscitation in this circumstance are similar: maintain adequate tissue perfusion to avoid acidosis, correct coagulopathy, and prevent hypothermia.

**Resuscitation Once Hemorrhage Is Controlled.** Once hemorrhage is controlled, goal-directed transfusion can be pursued based on laboratory data and clinical variables. Many clinicians will work to achieve normal coagulation parameters for 24-hour post-injury and control of hemorrhage (PT INR < 1.5, platelet count > 100 × 10⁹ per liter) (387). In a patient who no longer shows evidence of medical or surgical bleeding, traditional guidelines for transfusion therapy can be employed (322). These include using red blood cell transfusion for symptomatic anemia or a hemoglobin concentration of less than 80 to 100 mg/dL; and cryoprecipitate for a fibrinogen level <80 to 100 mg/dL and platelet transfusion for a platelet count <50 × 10⁹ per liter (Table 58.6).

### Complications of Massive Transfusion

Despite acceptable survival rates, there are several known complications to massive transfusion (Tables 58.10 and 58.11) (397,404–409). Physicians caring for patients who require massive transfusion must anticipate, identify, and rapidly treat these potential complications in order to optimize outcomes.

**Disordered hemostasis following massive transfusion** is a known complication of massive blood transfusion (397,404,401). Stored blood is lacking in factors V and VIII. These factors degrade over time in stored blood, and thus become deficient in the massively transfused patient. This can contribute to the coagulopathy seen following massive transfusion. Dilutional thrombocytopenia also occurs during massive transfusion, and is more common after 1.5 times the normal blood volume is transfused. However, thrombocytopenia can occur earlier, especially if there is disseminated intravascular coagulation, pre-existing thrombocytopenia, or a consumptive coagulopathy. As discussed previously, resuscitation of hemorrhagic shock must include clotting factors and platelets to avoid ongoing coagulopathy.

### Oxygen Delivery to Tissues

Oxygen delivery to tissues is also affected by blood transfusion. Transfused blood tends to have a higher affinity for oxygen, thus leading to decreased oxygen delivery to tissues. Longer storage periods for blood lead to a reduction in red cell deformability, altered red cell adhesiveness, and other red cell storage lesions. These changes reduce red blood cell viability after transfusion, reduce tissue oxygen availability, and promote the inflammatory response, specifically neutrophil priming and pulmonary endothelial cell activation.

Systemic inflammation and potential tissue injury may also be induced by the transfusion of aged blood. Transfusion of aged blood (>14 days of storage) in the first 6 hours of resuscitation has been shown to be an independent risk factor for postinjury multiorgan failure (410) and is associated with increased mortality (411). A premorbid coagulopathy may or may not exist. Goals in resuscitation in this circumstance are similar: maintain adequate tissue perfusion to avoid acidosis, correct coagulopathy, and prevent hypothermia.
delayed apoptosis of neutrophils (411), increased infection rates (412), and a longer ICU stay (413). This may be particularly significant in large trauma centers and transplantation centers where older blood is preferentially distributed because of their high-volume use.

Allimmunization can occur when an immunocompetent host develops an immune response to donor antigens. The antigens most often involved include the human leukocyte antigen (HLA) class I and II on platelets and leukocytes, granulocyte-specific antigens, platelet-specific antigens, and red blood cell-specific antigens. Consequences of allimmunization include a refractory response to platelet transfusion, posttransfusion purpura, neonatal alloimmune thrombocytopenia, acute intravascular hemolytic transfusion reaction, hemolytic disease in newborns, and febrile nonhemolytic reactions against granulocytes. Clinical manifestations can be minor, such as fever, leading to active bleeding and hemolysis, which can be fatal. Workup and treatment vary, depending on the severity of the reaction (414,415).

Metabolic and electrolyte disturbances can also occur following massive transfusion (397). Citrate toxicity can occur in patients with abnormal liver function or in whom the administration of blood is very rapid. The healthy adult liver will metabolize 3 g of citrate every 5 minutes. Each unit of blood contains approximately 3 g of citrate. Therefore, transfusion rates higher than 1 unit every 5 minutes can exceed the liver’s capacity to handle this overload. Citrate then binds to calcium and can lead to clinical hypocalcemia. Patients may exhibit temporary tetany and hypotension. Calcium replacement should occur concurrently during massive transfusion.

Electrolyte disturbances such as hyperkalemia or hypokalemia can occur with massive transfusion. The longer the shelf life, the higher the potassium concentration; sometimes concentrations may even exceed 30 mmol/L. Unless very large amounts of blood are transfused, hyperkalemia is generally not a problem. On the other hand, as red cells begin active metabolism, intracellular uptake of potassium begins, and hypokalemia may result.

Acid-base disturbances can also occur with massive blood transfusions. Stored blood contains lactate at levels up to 30 to 40 mmol/L. In addition, citric acid is present and may be metabolized to bicarbonate, resulting in severe metabolic alkalosis. Conversely, the patient’s overall condition and tissue hypoperfusion may actually lead to metabolic acidosis.

Although rare, blood transfusion can also result in the induction of acquired inhibitors of coagulation. The most common antibodies are directed against coagulation factor VIII. This can result in massive bleeding, which is difficult and costly to treat. The main goals of treatment are to stop hemorrhage and remove the inhibitor. Factor VIII concentrate is used only if transfusion needs exist. The diagnosis of TRALI in the patients requiring massive transfusion is usually established only if a history of additional risk factor exists, then possible TRALI is diagnosed (Table 58.12) (417–420).

The pathogenesis can be either immune (antibody) mediated or nonimmune mediated (Table 58.13) (418–422). Immune-mediated TRALI is most common and is due to the presence of leukocyte antibodies in the donor transfusion (421,422). These antibodies form immune complexes that are deposited in the pulmonary vascular bed, leading to release of vasoactive substances, leakage of fluid into alveolar spaces, activation of complement, leukostasis, and activation of polymorphonuclear neutrophils. Immune-mediated TRALI occurs more commonly with fresh frozen plasma than with platelet concentrates, is associated with multiparous female donors (423), can occur in healthy recipients, and is usually severe, requiring mechanical ventilation in 70% of individuals. Non-immune-mediated TRALI is thought to be due to the presence of biochemically active lipids in the donor transfusion (418–420). It occurs with stored platelet concentrates more commonly than stored red cells, occurs predominantly in critically ill patients with a primed immune system, and is usually mild and transient, requiring only supplemental oxygen support. Treatment of TRALI is generally supportive and includes ventilatory and hemodynamic assistance. There are no data to support the use of corticosteroids, and additional blood component therapy should be given only if transfusion needs exist. The criteria for TRALI in the patients requiring massive transfusion is as follows:

**TABLE 58.12: CRITERIA FOR TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)**

<table>
<thead>
<tr>
<th>CRITERIA FOR TRALI</th>
<th>CRITERIA FOR POSSIBLE TRALI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute onset</td>
<td>No pre-existing ALI before transfusion</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>Occurs during or within 6 h of transfusion</td>
</tr>
<tr>
<td>PaO\textsubscript{2}/FiO\textsubscript{2} ratio &lt;300</td>
<td>A clear temporal relationship to an alternative risk factor for ALI</td>
</tr>
<tr>
<td>SpO\textsubscript{2} &lt;90% on room air</td>
<td></td>
</tr>
<tr>
<td>No pre-existing ALI before transfusion</td>
<td></td>
</tr>
<tr>
<td>Occurs during or within 6 h of transfusion</td>
<td></td>
</tr>
</tbody>
</table>


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Chapter 58: Hemorrhagic Shock

913

Acute lung injury (ALI) as defined by acute onset, hypoxemia (PaO\textsubscript{2}/FiO\textsubscript{2} ratio ≤ 300), bilateral infiltrates on frontal chest radiograph, and no evidence of left atrial hypertension or circulatory overload

No pre-existing ALI before transfusion

Occurs during or within 6 hours of transfusion

No temporal relationship to an alternative risk factor for ALI (i.e., burns, aspiration, multiple trauma, cardiopulmonary bypass, sepsis, etc.)

If an additional risk factor exists, then possible TRALI is diagnosed (Table 58.12) (417–420).

The pathogenesis can be either immune (antibody) mediated or nonimmune mediated (Table 58.13) (418–422). Immune-mediated TRALI is most common and is due to the presence of leukocyte antibodies in the donor transfusion (421,422). These antibodies form immune complexes that are deposited in the pulmonary vascular bed, leading to release of vasoactive substances, leakage of fluid into alveolar spaces, activation of complement, leukostasis, and activation of polymorphonuclear neutrophils. Immune-mediated TRALI occurs more commonly with fresh frozen plasma than with platelet concentrates, is associated with multiparous female donors (423), can occur in healthy recipients, and is usually severe, requiring mechanical ventilation in 70% of individuals. Non-immune-mediated TRALI is thought to be due to the presence of biochemically active lipids in the donor transfusion (418–420). It occurs with stored platelet concentrates more commonly than stored red cells, occurs predominantly in critically ill patients with a primed immune system, and is usually mild and transient, requiring only supplemental oxygen support. Treatment of TRALI is generally supportive and includes ventilatory and hemodynamic assistance. There are no data to support the use of corticosteroids, and additional blood component therapy should be given only if transfusion needs exist. The criteria for TRALI in the patients requiring massive transfusion is as follows:

**TABLE 58.13: CRITERIA FOR TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)**

<table>
<thead>
<tr>
<th>CRITERIA FOR TRALI</th>
<th>CRITERIA FOR POSSIBLE TRALI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lung injury (ALI)</td>
<td>No pre-existing ALI before transfusion</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>Occurs during or within 6 h of transfusion</td>
</tr>
<tr>
<td>PaO\textsubscript{2}/FiO\textsubscript{2} ratio ≤ 300</td>
<td>A clear temporal relationship to an alternative risk factor for ALI</td>
</tr>
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<td>SpO\textsubscript{2} &lt;90% on room air</td>
<td></td>
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<td></td>
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<tr>
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<td></td>
</tr>
</tbody>
</table>

New developments in transfusion therapy include the discovery and use of recombinant coagulation factor VIIa (rFVIIa). Recombinant factor VIIa is a synthesized analog of human factor VII that has been used effectively in the treatment of patients with hemophilia as well as other congenital and acquired coagulopathies. Recently, there have been reports of the successful use of rFVIIa in treating coagulopathic trauma patients (426). In this study, patients with active hemorrhage and clinical coagulopathy from diverse causes such as traumatic hemorrhage, traumatic brain injury, warfarin use, congenital factor VII deficiency, and other acquired hematologic defects were coagulopathic on presentation to the emergency department, with a significant decrease in transfusion of packed red blood cells, fresh frozen plasma, platelets, and need for massive transfusion (>20 units of packed red blood cells) was reduced (14% vs. 33%, \( p = 0.03 \)). In patients with penetrating trauma, the trends were similar, but not significant (reduction in red cell transfusion 1.0 unit, \( p = 0.10 \); massive transfusion 7% vs. 19%, \( p = 0.08 \)). Trends toward reduction in mortality and critical complications were also observed. A subgroup analysis from this trial found particular benefit in those patients who were coagulopathic on presentation to the emergency department, with a significant decrease in transfusion of packed red blood cells, fresh frozen plasma, platelets, and need for massive transfusion. In addition, treatment with rFVIIa was also associated with a significant reduction in multiorgan failure and/or acute respiratory distress syndrome (3% vs. 20%, \( p = 0.004 \), without an increase in thromboembolic events (428).

Recombinant factor VIIa, however, must be used responsibly. Recent studies have shown that early administration following trauma is more effective than late administration (429,430). Furthermore, the presence of profound acidosis, coagulopathy, and signs of irreversible hemorrhagic shock predict failure of rFVIIa therapy (431). Current recommendations suggest that optimal preconditions should be present prior to administration of rFVIIa, which include a fibrinogen concentration of >50 mg/dL, a platelet count of >50 \( \times 10^9 \) per liter, and a pH \( \geq 7.2 \) (432,433). Although early results in traumatic hemorrhage appear promising, rFVIIa should still be considered experimental and further investigation is warranted. Recombinant factor VIIa has shown promise for perioperative bleeding during liver transplantation (434) and in patients undergoing cardiac surgery (435,436). Investigations for its utility in perioperative bleeding for other surgical procedures have been mixed (437–442).

A prospective randomized trial investigating the use of rFVIIa in patients with cirrhosis and upper gastrointestinal bleeding who were treated with standard endoscopic therapy and pharmacologic interventions showed that the administration of rFVIIa was not more effective than placebo with respect to the primary end point of failure to control bleeding within 24 hours and failure to prevent rebleeding or death within 5 days (441). However, subgroup analysis of patients with more severe cirrhosis showed that rFVIIa showed a reduction in the composite primary end point (8% vs. 21%, \( p = 0.03 \)). None of the rFVIIa patients had rebleeding within the first 24 hours, whereas rebleeding occurred in 13% of the placebo group (\( p = 0.01 \)) (443).

As with any hemostatic agent, there are concerns over the potential thrombogenicity of rFVIIa (444). Although preliminary evidence shows a favorable safety profile (445,446), thrombogenic effects are being followed closely in ongoing clinical trials.

### RECOMBINANT FACTOR VIIA IN MASSIVE TRANSFUSION AND HEMORRHAGE

**TABLE 58.13**

| Characteristics of Immune and Nonimmune Transfusion-Related Acute Lung Injury (TRALI) |
|---------------------------------|---------------------------------|
| **Immune TRALI** | **Nonimmune TRALI** |
| Trigger | Leukocyte antibodies | Biologically active lipids |
| Blood components implicated | Fresh frozen plasma > platelet concentrates | Stored platelet concentrates > stored red blood cells |
| Host | Healthy or critically ill | Predominantly in critically ill |
| Clinical course | Severe, often life threatening | Mild, self-limiting |
| Mechanical ventilation | | Supplemental oxygen |


**RECOMBINANT FACTOR VIIA IN MASSIVE TRANSFUSION AND HEMORRHAGE**

New developments in transfusion therapy include the discovery and use of recombinant coagulation factor VIIa (rFVIIa). Recombinant factor VIIa is a synthesized analog of human factor VII that has been used effectively in the treatment of patients with hemophilia as well as other congenital and acquired coagulopathies. Recently, there have been reports of the successful use of rFVIIa in treating coagulopathic trauma patients (426). In this study, patients with active hemorrhage and clinical coagulopathy from diverse causes such as traumatic hemorrhage, traumatic brain injury, warfarin use, congenital factor VII deficiency, and other acquired hematologic defects were coagulopathic on presentation to the emergency department, with a significant decrease in transfusion of packed red blood cells, fresh frozen plasma, platelets, and need for massive transfusion (>20 units of packed red blood cells) was reduced (14% vs. 33%, \( p = 0.03 \)). In patients with penetrating trauma, the trends were similar, but not significant (reduction in red cell transfusion 1.0 unit, \( p = 0.10 \); massive transfusion 7% vs. 19%, \( p = 0.08 \)). Trends toward reduction in mortality and critical complications were also observed. A subgroup analysis from this trial found particular benefit in those patients who were coagulopathic on presentation to the emergency department, with a significant decrease in transfusion of packed red blood cells, fresh frozen plasma, platelets, and need for massive transfusion. In addition, treatment with rFVIIa was also associated with a significant reduction in multiorgan failure and/or acute respiratory distress syndrome (3% vs. 20%, \( p = 0.004 \), without an increase in thromboembolic events (428).

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**PREVENTION OF HEMORRHAGIC SHOCK**

**Antifibrinolytic Therapy**

Antifibrinolytic therapy has been shown to significantly reduce the risk of bleeding following cardiac surgery in several
randomized controlled trials. Aprotinin has been studied most extensively (447–451), followed by tranexamic acid, then amniocapric acid. However, recent information raises concern for the risk of renal failure following use of aprotinin with cardiac surgery (448,449) and a potential for increased mortality at 5 years following use of aprotinin (450). Although clearly the risk of postoperative bleeding following cardiac surgery is reduced, further investigation into these potential side effects is warranted.

A recent systematic review of randomized controlled trials of antifibrinolytic agents (mainly aprotinin or tranexamic acid) in elective surgical procedures identified 89 trials including 8,580 randomized patients (74 cardiac, eight orthopedic, four liver, three vascular). Results demonstrated that these treatments reduced the number of patients needing transfusion by one third, reduced the volume needed per patient by 1 unit, and halved the need for further surgery to control bleeding. These differences were all statistically significant. There was also a trend toward a reduction in the risk of death (risk ratio = 0.85; 95% confidence interval, 0.63–1.14), although this was not statistically significant (452).

To date, there are limited data on the use of antifibrinolytic agents in other clinical scenarios (453). However, at this time, the CRASH-2 trial (Clinical Randomization of an Anti-fibrinolytic in Significant Hemorrhage) is ongoing in Europe and is designed to evaluate the utility of antifibrinolytic agents in the management of acute traumatic injury (454).

Experimental Therapy

Red Cell Substitutes

Although the blood supply in the United States is safe and currently has sufficient capacity to meet most patient needs, there is room for considerable improvement. The current system is dependent on blood donors on a regular basis, and the blood supply is subject to seasonal shortages due to holidays and convenience. The gap between the donor pool and the increasing demand must be direct, efficient, and multifactorial in order to avoid must be direct, efficient, and multifactorial in order to avoid.

Red blood cell substitutes are hemoglobin-based oxygen carriers, able to access all areas of the human body (including the brain, liver, lungs). Results demonstrated that these treatments reduced the number of patients needing transfusion by one third, reduced the volume needed per patient by 1 unit, and halved the need for further surgery to control bleeding. These differences were all statistically significant. There was also a trend toward a reduction in the risk of death (risk ratio = 0.85; 95% confidence interval, 0.63–1.14), although this was not statistically significant (452).

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Chapter 58: Hemorrhagic Shock

Hypertonic saline (7.5% saline ± 6% dextran-70) has been investigated as an alternative resuscitation strategy in critically injured patients (458–464). Hypertonic resuscitation evokes an increase in serum osmolality, which results in the redistribution of fluid from the interstitial and intracellular space to the intravascular space. This leads to a rapid restoration of circulating intravascular volume with a small amount resuscitation fluid. Hypertonic saline has also been shown to decrease intracranial pressure via its osmotic effects (125,126). This is particularly beneficial in patients with hypovolemic shock and closed head injury due to the ability of hypertonic saline resuscitation to concurrently restore circulating blood volume, improve tissue (including cerebral) perfusion, and lower intracranial pressure (126,465–466).

Hypertonic saline resuscitation has also been shown to have significant immunomodulatory effects that could mitigate the dysfunctional inflammatory response seen after traumatic injury (108,109,111,150,233,467–472). The hypotonicity associated with hypertonic saline resuscitation is associated with significant effects on the innate and adaptive immune systems. There is suppression of the neutrophil oxidative burst, potentially leading to an attenuation of inflammatory organ injury (150,473).

Several clinical trials and meta-analyses have suggested improved outcome in patients resuscitated with hypertonic saline (474–477). Despite these results, hypertonic saline resuscitation has not gained widespread acceptance in North America. However, in 1999, the U.S. Navy, through the Office of Naval Research, requested that the Institute of Medicine (IOM) recommend that hypertonic saline be used as the initial resuscitation fluid for combat casualty (256,478). The rapid restoration of intravascular volume and possible immunomodulatory effects associated with hypertonic saline resuscitation make it an attractive alternative for the resuscitation of severe hemorrhagic shock. However, it is still considered experimental and prospective randomized trials are needed to confirm its utility.

SUMMARY

Hemorrhagic shock is a common, yet complicated, clinical condition that physicians are frequently called upon to evaluate and treat. Diagnosis must be accurate and expedient. Therapy must be direct, efficient, and multifactorial in order to avoid adverse effects associated with HBOCs include (a) severe vasoconstriction due to binding of nitric oxide and dysregulation of endothelial; (b) nephrotoxicity; (c) interference of macrophage function; (d) antigenicity; (e) oxidation on storage; (f) activation of complement, kinin, and coagulation; (g) iron deposition with concerns of hemochromatosis and iron overload; (h) gastrointestinal distress; (i) neurotoxicity; (j) free radical generation; and (k) interference with diagnosis of transfusion reactions. Adverse effects of PFCs include (a) limited shelf life, (b) flu-like symptoms during infusion, (d) complement and phagocytic activation, and (d) short circulation time (456).

Despite much research, no product to date has been able to meet all of the previously mentioned criteria or meet the U.S. Food and Drug Administration’s requirements of purity, potency, and safety. At the time of this publication, three HBOC products continue in advanced clinical trials (455).
the potential multitasking sequela. Metabolism and function of all organs are altered during hemorrhagic shock. A better understanding of the pathophysiology of hemorrhagic shock has led to improved resuscitation techniques and improved survival over recent years. Damage control laparotomy and damage control resuscitation have changed the approach to management in patients with multisystem trauma and hemorrhagic shock. Staged resuscitation and operative intervention to avoid irreversible shock are now the mainstays of care. Recognition of acute traumatic coagulopathy has improved the composition of massive transfusion protocols to include increased use of clotting factors early during resuscitation. New experimental therapies for resuscitation are being evaluated and appear promising. Overall, survival following hemorrhagic shock has improved. Early diagnosis, definition of resuscitation bleeding, and comprehensive hemostatic resuscitation are the key elements to successful outcome.

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base deficit in the surgical intensive care unit which one do you trust? 


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Section VI: Shock States


