Chapter 10

Hypovolemic and Hemorrhagic Shock

Ruth L. Lamm, MD, and Craig M. Coopersmith, MD

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Shock is traditionally described as tissue hypoxia due to inadequate perfusion. However, it is much more complex than this simple definition. Given the complex pathophysiological processes, myriad of presenting signs and symptoms, and dynamic and evolving principles of management, the disease state of shock eludes concise definition.

Shock, the final common pathway for multiple disease states, is classified into 4 common types: hypovolemic/hemorrhagic, cardiogenic, obstructive, and distributive. These divisions are not exclusive of one another. Cardiogenic, obstructive, and distributive shock are discussed in detail in other chapters and will not be covered here. The goal of this chapter is to provide a framework for understanding the complex entities of hypovolemic and hemorrhagic shock. The evaluation and management of hemorrhagic shock are more complicated than required for simple hypovolemia and merit special emphasis. Three specific points are addressed here:

- Pathophysiology of hypovolemic and hemorrhagic shock
- Diagnosis and assessment of hypovolemic and hemorrhagic shock
Management of hypovolemic and hemorrhagic shock including overall goals, specific resuscitation strategies, and controversies in management.

PATHOPHYSIOLOGY

Although shock is often defined as tissue hypoxia, the term *dysoxia* might be more appropriate than *hypoxia*. Hypoxia generally refers to low oxygenation. Dysoxia is the condition in which cellular metabolism is limited by poor oxygen delivery or abnormal oxygen utilization. Dysoxia stresses the imbalance between supply and demand. Hypoxia more simply refers to a low number and does not address issues of adequacy.

Shock is also more than just dysoxia. It is a disease state that encompasses the initial hypoperfusion as well the organ dysfunction and systemic disease that follow. On a cellular level, hypoxic conditions lead to mitochondrial dysfunction, alterations in the cell membrane, release of oxygen free radicals, cytokine production, and subsequent activation of multiple inflammatory cascades.

Hypovolemic shock can be defined as decreased circulating blood volume in relationship to the total vascular capacity. Hemorrhagic shock is the most common form of hypovolemic shock. The American College of Surgeons has developed a classification system for hemorrhagic shock that provides correlation between presentation and volume of blood loss (Table 1 on page 184). Although this classification system is widely accepted, patient presentations vary and may not match these classifications precisely.

Hypovolemic shock that is not caused by hemorrhage can be seen with poor intake, increased fluid losses (e.g., severe vomiting or diarrhea, burns, gastrointestinal fistulas), or redistribution of fluid (e.g., pancreatitis,"third spacing" after surgery). Hypovolemic shock can be differentiated from other forms of shock by low filling pressures and high systemic vascular resistance.

Low intravascular volume causes low stroke volume, which, if severe enough, can lead to a decrease in cardiac output and blood pressure. However, the body fights to maintain cardiac output and therefore maintain tissue perfusion with several compensatory mechanisms:

- Activation of the sympathetic nervous system leads to the release of catecholamines and subsequent tachycardia, tachypnea, increased glycogenolysis, and vasoconstriction.
- Activation of the renin–angiotensin–aldosterone system causes vasopressin-induced vasoconstriction and sodium retention. Sodium retention results in fluid shifts from the extravascular to the intravascular compartment.
- Tissue oxygen extraction increases to help meet metabolic demand. Normally, tissue oxygen extraction is around 25% and can increase to a maximum of approximately 50%.

<table>
<thead>
<tr>
<th>Class</th>
<th>Blood loss, mL</th>
<th>Blood loss, %</th>
<th>Systolic blood pressure</th>
<th>Heart rate, beats/min</th>
<th>Respiratory rate, breaths/min</th>
<th>Mental status</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt;750</td>
<td>&lt;15</td>
<td>Normal</td>
<td>&lt;100</td>
<td>14-20</td>
<td>Anxious</td>
</tr>
<tr>
<td>II</td>
<td>750-1,500</td>
<td>15-30</td>
<td>Normal</td>
<td>&gt;100</td>
<td>20-30</td>
<td>Agitated</td>
</tr>
<tr>
<td>III</td>
<td>1,500-2,000</td>
<td>30-40</td>
<td>Decreased</td>
<td>&gt;120</td>
<td>30-40</td>
<td>Confused</td>
</tr>
<tr>
<td>IV</td>
<td>&gt;2,000</td>
<td>&gt;40</td>
<td>Decreased</td>
<td>&gt;140</td>
<td>&gt;35</td>
<td>Lethargic</td>
</tr>
</tbody>
</table>
Compensated shock occurs when activation of the sympathetic nervous system and renin–angiotensin–aldosterone system and increased oxygen extraction are enough to meet tissue oxygen demands; however, these mechanisms can only compensate for a certain degree of intravascular volume loss. Decompensated shock occurs when these mechanisms are unable to keep up with oxygen demands and anaerobic metabolism begins.

**DIAGNOSIS AND ASSESSMENT**

The identification and diagnosis of shock can be difficult. Many of the parameters that are usually assessed to help make a diagnosis can be misleading or difficult to interpret. This is true for elements of the physical examination and laboratory evaluation alike. As a result, it is crucial not to interpret any one data point in isolation.

**History**

A thorough history is key for diagnosing and assessing the severity of hypovolemic and hemorrhagic shock. Specific points to address include the following:

**Hemorrhage**

- Inherited coagulopathy
- Liver disease
- Malnutrition
- Use of anticoagulants
- Traumatic bleeding: mechanism of injury, concomitant injuries, magnitude of force, trajectory (in penetrating trauma)
- Postsurgical bleeding: nature of surgery, potential sites for bleeding
- Nontraumatic, nonsurgical bleeding: comorbidities that could be associated with bleeding, such as peptic ulcer disease, atherosclerosis with abdominal aortic aneurysm

**Nonhemorrhagic volume loss**

- Environmental conditions such as extreme heat
- History of gastrointestinal losses: vomiting, diarrhea, fistula, short-gut syndrome
- Burn injury: surface area and depth
- Baseline hydration status

**Physical Examination**

As brain perfusion decreases, a patient may be anxious or have an altered mental status. Severe hypovolemic shock is associated with an altered level of consciousness. A patient usually will be tachypneic, tachycardic, and hypotensive. The skin will be pale, cool, and clammy. Urine output will progressively decline as shock worsens. In the case of trauma, a full examination is needed to look for both obvious and occult injuries.

Unfortunately, although clinicians rely heavily on vital signs, they may not reflect the presence or severity of shock. Many bedside practitioners believe that hypotension is synonymous with shock, but there is no blood pressure cutoff that reliably indicates poor tissue perfusion. For example, a systolic blood pressure of 90 mm Hg may be relatively normal for either young, healthy patients or those with chronic liver insufficiency, but in a patient with chronic hypertension this could represent a very severe decline in cardiac output and perfusion. Similarly, compensatory vasoconstriction might result in an apparently adequate blood pressure even in the setting of significant volume loss and end organ damage. A 2005 study by Brown et al. illustrated this point eloquently. The investigators evaluated patients with penetrating abdominal trauma and normal vital signs. All patients were taken to the operating room to evaluate for the presence and amount of bleeding and were followed for complications. The investigators found that whereas the majority of patients had minor (<750 mL) blood loss, more than 25% of the patients had class II, III, or IV hemorrhage despite normal vital signs. This was associated with a significantly higher number of ICU admissions as
well as the need for mechanical ventilation, vasopressors, and blood transfusions. In addition, both ICU and hospital length of stay were significantly longer in these patients.

Young patients have the ability to maintain vital signs even in the presence of significant blood loss. On the other hand, elderly patients have significantly less reserve and may be hypotensive even with minimal blood loss. Many common medications can cloud the interpretation of vital signs. The classic example is a patient on β-blockers who may not be able to mount the expected tachycardia in response to volume loss. Finally, other conditions often occur simultaneously with shock that can cause abnormal vital signs such as pain or anxiety.

**Laboratory Evaluation**

**Markers of Perfusion**

**Mixed venous oxygen saturation/central venous oxygen saturation**

Since dysxia is the crux of shock, being able to measure or trend tissue oxygen utilization may theoretically be helpful in identifying and assessing the severity of shock. The arterial oxygen saturation (Sao2) measured on an arterial blood gas is not a reliable marker as it gives no information about tissue utilization. Changes in Sao2 more likely reflect changes in gas exchange. Along with hemoglobin, Sao2 is very important in determining oxygen delivery to tissue but, again, gives no information on the balance between delivery and demand.

Venous oxygen saturation can provide information about this relationship. Venous oxygen saturation is dependent on Sao2, hemoglobin, the rate of oxygen delivery, and tissue oxygen extraction. Tissue oxygen extraction represents the change in oxygen saturation as it passes through the capillaries—the amount of oxygen the tissue is able to take from the blood to meet metabolic needs. Venous oxygen saturation is therefore the Sao2 minus the tissue oxygen extraction. **Figure 1 on page 187** shows a simplified version of these interactions. As oxygen delivery decreases, oxygen extraction will increase to help meet metabolic demands. The point of maximal extraction occurs when oxygen extraction can no longer increase and there is inadequate oxygen supply to maintain aerobic metabolism; in other words, this is the state of dysxia. Assuming no change in Sao2 or hemoglobin concentration (and therefore no change in arterial oxygen content), venous oxygen saturation will drop as tissue oxygen delivery decreases.

For example, under normal conditions the oxygen extraction is approximately 25%. For an Sao2 of 100%, this will yield of venous oxygen saturation of 75%. As oxygen delivery decreases, tissue oxygen extraction increases, up to a maximum level of 50%. At this point, again assuming no change in Sao2, the resulting venous oxygen saturation would be approximately 50%.

For a specific tissue, the venous oxygen saturation represents the change as blood passes through the local capillary bed. The mixed venous oxygen saturation (Svo2) is measured in the pulmonary artery. As a result, it represents a more global picture as it contains the venous return from all tissues, not just one local tissue bed. Since obtaining a true mixed venous oxygen saturation requires a pulmonary artery catheter (PAC), this is not a realistic monitoring tool for most patients, as the use of PACs has decreased in recent years and evidence supporting this invasive technology is controversial. The central venous oxygen saturation (Scvo2) is drawn from a central venous catheter (CVC) from the superior vena cava. Many critically ill patients will already have a CVC in place, and the risk of CVC placement is lower than for PAC placement. In a healthy individual, the Scvo2 is usually lower than the Svo2 because of relatively low oxygen extraction by the kidneys. In the critically ill, this relationship is usually reversed. This is thought to be due to a combination of increased oxygen extraction in the renal vascular beds, shunting of blood from lower to higher extracting organs, and increased coronary oxygen extraction.

There are several limitations to using either Svo2 or Scvo2 as a marker of shock. The absolute numbers are affected by hemoglobin, gas exchange, and degree of vasoconstriction. In the critically ill patient, these are often dynamic and can affect the venous oxygen saturation regardless of oxygen delivery or oxygen extraction. Over a short period of time, these parameters are not likely to change significantly.
As oxygen delivery decreases, oxygen extraction increases but can only increase to a maximum of approximately 50% of total arterial oxygen. At all levels of oxygen delivery lower than the point of maximal extraction (*), tissue dysoxia occurs as oxygen extraction can no longer increase to meet metabolic demands. Assuming stable arterial oxygen saturation, venous oxygen saturation will decrease as oxygen delivery decreases.

and as a result the trends can be very helpful. In addition, there is significant controversy regarding how to use the $\text{ScrVO}_2$ versus the $\text{SvO}_2$. Although the absolute numbers do not seem to correlate at all, it appears that the trends do correlate. Finally, oxygen extraction can be affected by other disease processes such as severe sepsis or certain poisonings that can lead to falsely normal $\text{ScrVO}_2$ levels in the setting of hypoxia.

**Base deficit**

The base deficit is the amount of base (in millimoles) needed to titrate 1 L of whole blood to a pH of 7.40 and as a result reflects the extent of anaerobic metabolism and resulting acidosis. The value can be affected by resuscitation fluid or the administration of bicarbonate. Base deficit has been studied extensively in trauma given the ability to get a rapid result from an arterial blood gas. The initial level has been found to correlate with transfusion requirements, organ dysfunction, morbidity, and mortality following trauma. The base deficit is also a better predictor of outcome than is pH alone. In the ICU, full blood chemistry, as opposed to arterial blood gas, is used frequently. In this setting, serum bicarbonate can be a surrogate for base deficit.

**Lactic acid**

Lactic acid is a byproduct of anaerobic metabolism. As a result, it is a very good marker of tissue dysoxia. However, several other conditions can elevate blood lactic acid levels independent of dysoxia:

- Hepatic insufficiency: impairs lactic acid clearance
- Thiamine deficiency: inhibits pyruvate dehydrogenase, necessary for aerobic metabolism
- Intracellular alkalosis: stimulates glycolysis

Sepsis can cause an elevated lactic acid level independent of tissue dysoxia. It is thought that endotoxin can also inhibit pyruvate dehydrogenase in a manner similar to thiamine deficiency. As a result, an elevated lactic acid level can be seen even in the presence of stable oxygen utilization.
Despite these possible confounders, studies have shown that both the initial level of lactic acid and the rate of clearance may more accurately reflect poor prognosis than can either venous oxygenation or base deficit.

**Markers of Bleeding: Hemoglobin and Hematocrit**

Hemoglobin and hematocrit levels are not reliable in early shock. Blood loss is the loss of whole blood, and consequently all components decrease by a similar ratio; the value of the hemoglobin or hematocrit at this point will not differ significantly from value prior to blood loss. A normal hemoglobin level therefore does not rule out active bleeding. An early decrease in hemoglobin is often due to fluid resuscitation alone. As discussed previously, activation of the renin–angiotensin–aldosterone system draws fluid into the intravascular space. It is only after this has occurred that a decrease in hemoglobin will be seen. Hemoglobin values drawn early after blood loss may help to identify patients with preexisting anemia who may be more sensitive to blood loss. The rate of change in hemoglobin over time may be more predictive of the severity of bleeding.

**Markers of Coagulopathy**

Coagulopathy is quite common in shock, especially in hemorrhagic shock. It can be iatrogenic (dilutional), preexisting, or due to acute inherent coagulopathy (both iatrogenic and inherent). This is discussed in more detail later in this chapter.

Standard markers of coagulopathy include prothrombin time/international normalized ratio, partial thromboplastin time, fibrinogen, and platelet count. There are several drawbacks to using these parameters to evaluate coagulopathy in acute shock states. Most important, laboratory tests of the prothrombin time/international normalized ratio and partial thromboplastin time do not reflect in vivo conditions. Specifically, clotting in the laboratory does not depend on the complex cellular interactions necessary for activation of clotting cascade in vivo. Furthermore, blood samples are warmed to normal body temperature. Many patients with shock have significant hypothermia and as a result have a significant coagulopathy that will not be reflected in standard laboratory tests. In addition, testing of platelet and fibrinogen levels is quantitative, and as such, there is no assessment of function. Finally, these tests are time consuming. Decisions regarding the critically ill often must be made quickly even if this means not having all the information desired. Even if there is time to wait for laboratory results, in an actively bleeding patient the laboratory results will not reflect the current condition and will not be helpful guiding resuscitation. Thromboelastograph (TEG) analysis may be a more useful way to assess coagulopathy. It can be done at the bedside and provides a functional evaluation of blood clotting. Figure 2 on page 188 is an example of a TEG result. The tracing quantifies the kinetics of clot formation and lysis. The components of the TEG include the following:

- **R** (reaction) time: The time to initial fibrin formation. This will be prolonged by factor deficiency and reduced in hypercoagulable conditions.
- **K** (clot formation) time: The time from the R time until the clot has reached a particular level of firmness; a measure of clot kinetics.
- **α angle**: Angle formed by a line from the TEG tracing to the end of the R time. If the clot never reaches the

**Figure 2.**

Thromboelastogram.

\[
\begin{align*}
\text{START} & \quad \alpha \\
R & \quad K \\
\text{MA} & \quad A_{30} \\
\end{align*}
\]

R, reaction time; K, clot formation time; α, alpha angle; MA, maximal amplitude; A_{30}, amplitude at 30 minutes.
specific firmness, K is undefined. The $\alpha$ angle is another measurement of clot kinetics and can be used if K is undefined. Both the K time and $\alpha$ angle are affected by factor levels, platelet number and function, and fibrin levels.

- MA (maximum amplitude): Greatest amplitude reached; represents maximum clot strength. This is affected most by platelet number and function.
- LY30/A30: Measures percentage of lysis 30 minutes after MA. This component reflects fibrinolysis.

Using the results of the TEG, the clinician can determine the exact nature of coagulopathy and thus resuscitate the patient more appropriately.

Several significant drawbacks of the TEG limit its widespread use. The physical machines require a financial investment, and staff must be specially trained to perform the tests. Quality control is also problematic. The analysis is made by the interactions of a small oscillating cup and a thin plastic pin suspended in the sample. Even a small perturbation will alter results significantly. Situations in which the TEG could be useful, such as busy trauma resuscitation bays, are likely not the optimal environment for the TEG. Finally, definitive proof of the superiority of TEG over conventional evaluation of coagulopathy at the bedside is lacking.

**Other Modes of Evaluation**

Since there is no perfect way to identify and assess the severity of shock, there is a constant search for better methods of monitoring shock. Some of these include the following:

- Gastric tonometry: This is the measurement of gastric carbon dioxide as a surrogate of perfusion. It is measured via a nasogastric tube, which many critically ill patients already have.
- Sublingual capnometry: This is based on a similar principle as gastric tonometry but using a more accessible vascular bed.

- Tissue oximetry: This method uses monitors that detect tissue oxygenation in either the deltoid muscle or thenar eminence.
- Acoustic arterial flow analysis: This analysis is used to determine the degree of local vasoconstriction.

Although each of these has theoretical advantages ranging from ease of use to pathophysiological benefits, evidence supporting the use of each of these technologies is lacking, and none is widely used.

**MANAGEMENT**

The overall goal in the management of shock is to correct dysxia and maintain oxygen delivery to tissues to support aerobic metabolism. Functionally, the management of hypovolemic or hemorrhagic shock starts with the recognition that a patient is in shock. Next, it is important to recognize the distinction between simple hypovolemic shock, controlled or minor hemorrhagic shock, and uncontrolled or severe hemorrhagic shock. With the former 2 conditions, management is straightforward. Shock will improve with volume replacement and simple blood product transfusion. However, patients with severe hemorrhagic shock will be critically ill, and the clinician must understand different resuscitation principles. Additionally, it is critical to understand that resuscitation is not a substitute for hemorrhage control. Resuscitation should support the patient until direct control of bleeding is possible.

Treatment of dysxia involves improving oxygenation and perfusion. Optimizing perfusion involves optimizing all contributing factors, including volume status/stroke volume, heart rate, cardiac contractility, vascular tone, and intrathoracic pressures. One important caveat to this is in the case of ongoing bleeding, when increasing the cardiac output can cause increased blood loss (discussed in more detail subsequently).
Airway and Breathing

There should be a low threshold to establish a secure airway and initiate mechanical ventilation in a patient in hemorrhagic shock. These procedures improve oxygen delivery and have several other advantages as well. Respiratory muscles require a disproportionate percentage of the cardiac output, especially in the case of increased work of breathing that would be required to help support declining oxygen delivery to tissues. Intubating a patient redistributes this blood flow. In addition, when the work of breathing is decreased, more oxygen is available for perfusion of other organs.

Vascular Access

Securing vascular access is one of the early priorities in the management of any patient with hypovolemic or hemorrhagic shock. Although many practitioners place a CVC in patients with hypovolemic or hemorrhagic shock, a standard triple-lumen CVC is generally not appropriate for these patients. Flow rate is determined by the Poiseuille equation and is directly proportional to radius of the catheter and inversely proportional to catheter length. Thus, long catheters will have significantly slower flow rates than short catheters. In isolation, the only indication for placing a CVC in early resuscitation for hypovolemic or hemorrhagic shock is the inability to cannulate peripheral vessels with a large-bore IV tube. In this case it is essential to place a large introducer catheter, as the multilumen catheters will have much smaller radii.

Control Bleeding

Localize the Source

Resuscitation will not be successful in hemorrhagic shock without control of bleeding. In many cases the source of bleeding will be obvious. Significant bleeding can occur in the chest, abdomen, retroperitoneum/pelvis, and long bones without obvious external bleeding. The most common injuries to cause hemorrhagic shock include pelvic or femur fracture, liver/spleen/kidney rupture, and injury to large thoracic or abdominal vessels. Because of the Mono-Kellie doctrine, it is not possible to have a hemodynamically significant intracranial bleed. The elevation in intracranial pressure would result in brain herniation before a significant volume of blood could be lost. Even in the case of significant trauma, the cause of internal bleeding may not be obvious. In these cases, a systematic workup is essential and includes the following:

- Chest radiograph: This is used to evaluate for hemothorax.
- Pelvis radiograph: The diagnosis of pelvic fracture would raise suspicion for pelvic or retroperitoneal bleeding.
- FAST examination: FAST stands for “focused assessment with sonography in trauma” and can diagnose intra-abdominal bleeding and pericardial effusion/tamponade (Figure 3 on page 191). It cannot quantify the amount of blood nor can it differentiate between blood and other fluid (e.g., ascites). It also cannot diagnose retroperitoneal bleeding.
- Extremity radiographs as indicated.

If the patient is still unstable, more definitive action is needed, possibly including a diagnostic peritoneal lavage, exploratory surgery, angiography, or emergent thoracotomy. If the source of bleeding is still not identified and the patient is stable, a computed tomography scan is indicated. Not only can a computed tomography scan show evidence of intrathoracic or intra-abdominal bleeding, it can also show retroperitoneal bleeding.

The evaluation of nontraumatic bleeding follows a similar workup, because significant bleeding can occur in the same locations as seen with traumatic bleeding. Chest radiographs can show evidence of aortic dissection or aneurysm. Although the FAST examination might not be as helpful, abdominal ultrasound may be helpful in certain diagnoses such as ruptured aortic aneurysm or ruptured ectopic pregnancy. Computed tomography scans will be useful for evaluation of retroperitoneal bleeding. Historical factors that may indicate retroperitoneal bleeding include anticoagulation or coagulopathy, femoral artery cannulation, or recent major surgery. Another potential source of nontraumatic hemorrhage is gastrointestinal
bleeding. Rectal examination, nasogastric tube placement, or endoscopy will aid in the diagnosis.

**Control the Source**

There are a limited number of ways to control bleeding. For external bleeding, compression and pressure are the easiest and most efficient methods. For extremity bleeding, a tourniquet can be applied proximal to the injury if compression is not possible or effective. A tourniquet should never be the initial treatment as it can cause significant ischemia distal to the injury from both lack of arterial inflow and venous outflow obstruction. A traction splint can be applied to long bone fractures, typically femur fractures. It controls bleeding by realigning fracture
fragments to reduce potential injury to adjacent vessels. In addition, it is thought that by realigning the bone back to anatomical position, the normal circumference and length of the thigh are restored, reducing the potential space into which bleeding could occur.

Compression can be applied to pelvic injuries by reducing the area of the pelvis. This is known as fixation or stabilization. Although commercial pelvic fixation devices are available, a sheet carefully tied around the patient’s pelvis is also effective.

Stabilization works best in anterior–posterior compression fractures with symphysis diastasis (“open book” fractures). Stabilization will not affect arterial bleeding and can cause more hemorrhage if the act of stabilizing dislodges a clot or causes additional injury by movement of fracture fragments. Stabilization is not definitive control. Pelvic bleeding must be controlled by surgical pelvic packing or, more commonly, angiography and embolization.

For intra-abdominal bleeding and for uncontrolled bleeding of other causes, surgical control is often necessary. If there is not a discrete, repairable injury, packing acts as direct compression of the injured area.

**Volume**

Intravenous fluids (IVFs) are the mainstay of resuscitation. Intravenous fluids are given to restore blood volume and increase blood pressure in order to restore perfusion. In the case of intravascular fluid loss (not bleeding) or limited and controlled bleeding, restoring blood volume and increasing blood pressure will help to perfuse areas of dysoxia. In these settings, IVFs should be the first-line treatment and in many cases will be all that is needed to improve oxygen balance.

The patient should be assessed for the response to initial fluid resuscitation. Rapid responders will completely stabilize with an initial 2-L fluid bolus. Transient responders will respond initially but will deteriorate if fluid is slowed or stopped. This usually indicates ongoing bleeding or volume loss. Nonresponders fail to respond to initial therapy. These are the patients who have active hemorrhage and need more aggressive resuscitation and possible intervention.¹⁴

For the critically ill patient with uncontrolled bleeding, the basis for the use of IVFs as the mainstay of resuscitation has been challenged. In fact, a clear benefit to fluid resuscitation has never been demonstrated in trauma patients. Multiple animal studies show decreased cumulative hemorrhage, decreased duration of bleeding, and increased hemoglobin in animals not resuscitated with any fluid when compared with animals resuscitated by Advanced Trauma Life Support protocols. Although there are no controlled trials, military data from battlefield injuries tend to support these findings.

In the 1990s, 2 landmark studies were done that questioned the role of IVF resuscitation in trauma patients.¹⁵ The first, by Bickell et al¹⁶, randomized patients with penetrating torso trauma to either immediate or delayed fluid resuscitation. The delayed group received significantly less fluid and had significantly improved mortality and a shorter hospital length of stay. The second, by Dutton et al,¹⁷ randomized patients to receive IVFs to a systolic blood pressure goal of greater than 100 (liberal IVF) or greater than 70 (controlled IVF). The investigators found that there was no change in mortality between the groups. Time to control of bleeding was also significantly longer in the liberal IVF group. These results mirrored outcomes that had been seen with military/medical antishock trousers (MAST). It was thought that use of MAST would improve outcome by decreasing blood flow to the lower extremities and increasing systemic vascular resistance, therefore increasing blood pressure and blood flow to more vital organs. However, multiple studies have shown that the use of MAST does not improve survival and in fact may be associated with increased risk of death.

There are several reasons why resuscitation with IVF may not improve outcomes in patients with hemorrhagic shock. Intravenous fluids worsen coagulopathy through dilution of clotting factors and platelets. Coagulopathy is usually present even on arrival in many of these patients and is thought to be one of the main causes for secondary injury.
Coagulopathy is also associated with higher mortality. Fluid resuscitation can worsen acidosis and hypothermia. Increasing hydrostatic pressure, especially in the setting of worsening coagulopathy, can dislodge early, soft clots and increase bleeding. This is also known as the “pop the clot” theory. This increase in hydrostatic pressure combined with an increase in cardiac output due to increased stroke volume will further increase blood loss. The transient increase in blood flow from fluid resuscitation can cause reperfusion injury because increased blood flow brings increased levels of circulating toxins produced by initial ischemic injury and subsequent inflammation. Basic science research has shown that resuscitation fluid alone can activate inflammatory and immune cascades, compounding cytotoxicity caused by the initial insult and dysxia. Large-volume resuscitation leads to pulmonary volume overload and abdominal compartment syndrome. Finally, it is important to remember that resuscitation fluid has no oxygen-carrying capacity.

When managing shock, it is therefore important to differentiate hypovolemia and controlled bleeding versus uncontrolled bleeding. In the former, IVFs are the first-line therapy as the restoration of blood volume is vitally important to maintain perfusion. However, IVFs should be thought of as drugs with indications, therapeutic dosing ranges, side effects and complications.

**Crystalloid Versus Colloid**

Crystalloid fluid contains only electrolytes and small molecules. It is inexpensive, easily stored, and readily available. Crystalloid can be infused quickly given its low viscosity; however, there are significant disadvantages. Because crystalloid contains only small molecules, it can freely cross cell membranes. The majority of fluid administered (up to 80%) will shift from the intravascular space to the interstitial space within minutes. As a result, large volumes of up to 3 or 4 times the initial deficit are necessary to restore lost circulating volume. If volume deficits are primarily interstitial fluid losses, this may actually be desired. This is not the case with primarily intravascular volume loss. Normal saline especially can produce a metabolic acidosis with large-volume infusions.

Additionally, crystalloids can produce harmful cellular effects by affecting neutrophil activity, upregulating inflammatory cascades, and even altering gene expression.\(^8\)

Both beneficial preclinical trials and pathophysiological rationales during the last decade brought significant interest in the use of hypertonic solutions for early resuscitation.\(^9\) Hypertonic solutions cause redistribution of water from the extravascular to the intravascular space, which could in theory restore intravascular volume and avoid the negative consequences of large-volume resuscitation. In addition, hypertonic solutions may exert anti-inflammatory and immunomodulatory effects that could be beneficial in critically ill patients. Unfortunately, large-scale studies failed to demonstrate a benefit of hypertonic solutions. In 2009, the US National Institutes of Health stopped enrolling patients in 2 of the largest studies on hypertonic saline after interim analyses showed no benefit of treatment.

Colloid fluid contains large molecules such as human albumin or high-molecular-weight glucose polymers. These large molecules cannot cross cell membranes as easily and do not redistribute to the extracellular space as readily as crystalloid fluid does. Usually, much smaller volumes of colloid are needed to correct the fluid deficit. In fact, colloid fluids with very high oncotic pressure, like 25% albumin, may actually draw fluid into the intravascular space with a resulting increase in intravascular volume larger than the fluid bolus. Unfortunately, like crystalloids, colloids can diffuse to the extravascular space, albeit not as quickly. In addition, in times of altered capillary permeability such as inflammation or infection, albumin is more freely moveable and oncotic force becomes less important than hydrostatic force, so the beneficial effect of colloids remaining intravascular is likely diminished or lost in critically ill patients. Like crystalloid, colloids can be infused quickly because of low viscosity. In addition, albumin may have some anti-inflammatory and antiapoptotic effects. As with crystalloids, colloids have several disadvantages. All colloids are more expensive and are more difficult to store. The synthetic colloids have many potentially dangerous side effects, one being that
they can activate inflammatory cascades. Hydroxyethyl starch inhibits platelet function and can cause a significant coagulopathy. Dextran also increases bleeding tendencies and is nephrotoxic. Albumin, the most commonly used colloid fluid, contains human albumin and will likely not be accepted by patients who will not accept blood product transfusion.

The crystalloid versus colloid controversy is long-standing. Large-scale meta-analyses have shown no difference in outcomes regardless of whether albumin or crystalloid was used. The largest trial addressing this is the SAFE (Saline versus Albumin Fluid Evaluation) study, which examined 7000 critically ill patients.39 There was no difference in all-cause 28-day mortality or any other marker of illness severity (number of organ failures, need for mechanical ventilation, need for renal replacement therapy, and ICU/hospital length of stay). Subgroup analyses showed an insignificant trend toward harm with the use of albumin in trauma patients (although this may have been due to a disproportionate number of patients with traumatic brain injury) and a similar insignificant trend toward benefit in patients with severe sepsis. There are several important limitations to this study. The study was not powered to be a superiority study or to fully evaluate subgroups. In addition, many will question the use of all-cause, 28-day mortality as a realistic endpoint, especially for such a diverse patient population as was included. There is no compelling evidence suggesting that patients in hypovolemic or hemorrhagic shock should receive resuscitation with colloids.

Resuscitation Strategies
The most critically ill patients frequently require coordinated resuscitation strategies.32 As outlined earlier, not only will standard treatments potentially not help, they may in fact cause harm.22 The initiation of aggressive IVF resuscitation, minimal transfusion, and resuscitation end points of increased blood pressure and cardiac output prior to hemorrhage control can significantly worsen the "lethal triad" that occurs with bleeding, coagulopathy,33 hypothermia, and acidosis.34 Worsening of any one of these variables leads to a worsening of all of them in a vicious cycle that leads to deterioration and ultimately death. The care of the sickest patients and the implementation of these strategies require a careful and coordinated approach between the emergency center, the operating room, and the ICU. These strategies are often used simultaneously in the same patient.

Hypotensive Resuscitation/Permissive Hypotension
Avoiding aggressive IVF resuscitation will avoid the direct coagulopathy, acidosis, hypothermia, and tissue edema caused by fluid resuscitation. Fluid is given selectively and in lower volumes. All IVFs should be warmed. The goal of treatment is directed by clinical end points (eg, appearance of a radial pulse, improvement in mental status) combined with direct blood pressure goals. Care should be taken with patients who are hypertensive at baseline or patients who have severe cerebrovascular disease, as they may not tolerate lower blood pressures.

Hemostatic Resuscitation
One of the most important goals of resuscitation is to correct coagulopathy and limit blood loss. Hemostatic resuscitation calls for early transfusion of blood components, as opposed to IVFs, to restore both perfusion and normal coagulation function.

Damage Control Resuscitation/Delayed Resuscitation
This strategy combines elements of the strategies described previously.27 It dictates that resuscitation should be held or minimized until definitive hemorrhage control is achieved.30 The focus is on restoring normal physiological and anatomical parameters to prevent worsening of the lethal triad. This strategy is based on the theory of damage control surgery developed by the military. Damage control surgery is made up of 3 components. The first involves an abbreviated laparotomy to control bleeding and contamination and restore blood flow without traditional and potentially time-consuming repairs. The abdomen is packed and left open with a temporary closure. Next, treatment in the ICU focuses on rewarming, correction of acidosis, reversal of coagulopathy, and optimization of
hemodynamics and ventilation. Finally, definitive surgical repair is performed 24 to 72 hours after physiological parameters have been met. This may require several staged procedures. These ideas are extrapolated to the entire resuscitation for damage control resuscitation. The main goal is to do what is needed to stop bleeding. A priority is placed on correcting the coagulopathy until definitive repair can be performed. 

It is very important to remember the 2 major caveats to these resuscitation strategies: (1) they are not meant for the management of patients with concomitant severe brain injuries since any decrease in blood pressure will decrease cerebral perfusion pressure and can worsen outcome significantly; (2) they are not meant for patients in whom bleeding is controlled or is mild. In these circumstances, the patient will benefit from early volume replacement and could be harmed by further treatments.

Blood Products

All of the resuscitation strategies described previously place emphasis on blood product transfusion. Most patients with hypovolemic or hemorrhagic shock will not need blood at all. If bleeding is controlled, crystalloid alone should make up the deficit in intravascular volume needed to increase cardiac output and provide adequate perfusion and oxygenation. A commonly accepted standard calls for the infusion of blood if 2 L of crystalloid fails to reverse the signs of shock. However, if a patient only transiently responds or does not respond sufficiently to IVFs, there should be high suspicion that there is ongoing bleeding and transfusion should not be delayed. The aim of transfusing early is to help restore oxygen delivery to tissues and normalize coagulopathy. This minimizes the negative synergistic effects of acidosis, hypothermia, and coagulopathy. Of course, there are risks associated with blood product transfusion, including immunosuppression, transfusion-related acute lung injury, transfusion reaction, and potential for disease transmission; other drawbacks include cost and limited availability. 

The ability to fractionate whole blood into separate components was developed around the time of World War II. Most transfusions today are component therapy and are given in the setting of controlled bleeding or defined coagulation defect. As a result, component therapy offers several logistic advantages over transfusion of fresh whole blood (FWB). First, component therapy can be stored for much longer than FWB. Second, the ability to use only the specific component that is needed makes use of blood much more efficient.

In contrast to civilian medicine, the military has recently gained more experience with the use of FWB transfusions. Although component therapy offers logistic advantages in the civilian world, the opposite is true for the military. Forward surgical teams have limited carrying, refrigerating, and storage capacity, making the use of component therapy unrealistic for combat situations. Over time, blood products, especially red blood cells, lose potency as the cells age. Since the cells are by definition fresh in whole blood transfusions, there is less cellular dysfunction. Finally, the indications for transfusion in combat are different than those for most civilian transfusions. Combat injuries cause hemodynamically significant large-volume hemorrhage. Whole blood offers the perfect physiological mixture to maintain oxygen delivery and correct coagulopathy. Just as IVF can contribute to worsening acidosis and coagulopathy, so can inappropriate blood transfusion. Red blood cell transfusion alone is not going to treat coagulopathy. In fact, it will make it worse by diluting out platelets and coagulation factors. Similarly, platelet and fresh frozen plasma transfusion might help the coagulopathy and slow further bleeding, but it can do nothing to restore oxygen balance.

The military’s experience with FWB transfusions challenged the traditional use of mostly red blood transfusion in significant hemorrhage. Although the use of FWB is not practical in civilian situations, the physiological processes are the same and the treatments should have the same goals. Ultimately, patients who are bleeding the most will have severe and complex coagulopathy. As a result, they will have increased transfusion requirements to treat both anemia and coagulopathy. This led to the concept of massive transfusion and protocols to guide such transfusion in severe bleeding.
Massive transfusion is usually defined as more than 10 U of blood transfused in 24 hours, although this definition is evolving. It is guided by the principles that correcting coagulopathy is just as important as maintaining oxygen-carrying capacity and that patients with active bleeding have rapidly changing physiological parameters, so traditional laboratory tests to determine transfusion needs are of very limited utility. There is significant controversy regarding optimal transfusion ratios in a massive transfusion protocol. Early data by Borgman et al. from the Joint Theater Trauma Registry showed that injury severity scores and mortality improved the closer the ratio of fresh frozen plasma to red cell transfusion was to 1:1. Although several subsequent studies have found similar results, many have found inconclusive or opposing results. Further study is needed to determine the appropriate transfusion ratio. There is less evidence on how to transfuse platelets and cryoprecipitate in a massive transfusion protocol.

Novel and Potential Future Treatments

Several emerging therapies have potential utility in the management of hypovolemic and hemorrhagic shock. None of these are currently in widespread use given the lack of evidence supporting their safety and efficacy.

- Synthetic hemoglobin/hemoglobin-based oxygen carriers. Several types of synthetic hemoglobin are available. Unfortunately, early studies showed safety issues with evidence of severe hypertension and increased incidence of myocardial infarction. There have been safety improvements, but more studies are needed to show that hemoglobin-based oxygen carriers lead to decreased transfusion requirements, decreased mortality, and minimal side effects.

- Factor VIIa: No studies have shown clear benefit, and there may be increased arterial thromboembolic indications when this is used off label.

- Freeze-dried plasma: This does not require freezing and has much longer shelf life than fresh frozen plasma, leading to theoretical logistic and resource utilization benefits.

- Sex steroids: Estrogen may have beneficial effect on cytokine response and neutrophil activation after hemorrhage.

- Naloxone: Opiate receptors may have a role in response to hemorrhage.

- Histone acetylation/gene therapy: Drugs like valproic acid may block changes in gene transcription related to hemorrhage and the subsequent stress response.

REFERENCES


