Evaluation and Management of Shock States: Hypovolemic, Distributive, and Cardiogenic Shock

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What is This?
Evaluation and Management of Shock States: Hypovolemic, Distributive, and Cardiogenic Shock

Michael P. Moranville, PharmD, BCPS¹, Katherine D. Mieure, PharmD, BCPS¹, and Elena M. Santayana, PharmD, BCPS¹

Abstract

Shock states have multiple etiologies, but all result in hypoperfusion to vital organs, which can lead to organ failure and death if not quickly and appropriately managed. Pharmacists should be familiar with cardiogenic, distributive, and hypovolemic shock and should be involved in providing safe and effective medical therapies. An accurate diagnosis is necessary to initiate appropriate lifesaving interventions and target therapeutic goals specific to the type of shock. Clinical signs and symptoms, as well as hemodynamic data, help with initial assessment and continued monitoring to provide adequate support for the patient. It is necessary to understand these hemodynamic parameters, medication mechanisms of action, and available mechanical support when developing a patient-specific treatment plan. Rapid therapeutic intervention has been proven to decrease morbidity and mortality and is crucial to providing the best patient outcomes. Pharmacists can provide their expertise in medication selection, titration, monitoring, and dose adjustment in these critically ill patients. This review will focus on parameters used to assess hemodynamic status, the major causes of shock, pathophysiologic factors that cause shock, and therapeutic interventions that should be employed to improve patient outcomes.

Keywords
cardiogenic, distributive, hypovolemic, vasopressors, shock

Introduction

Shock can be defined globally as any state in which oxygen delivery to end organs is insufficient to sustain normal metabolic processes. Although inadequate blood supply and organ failure are the end results of shock, there are a number of pathophysiologic states that trigger such a condition. For example, the origin of shock may be hypovolemic, anaphylactic, septic, neurogenic, or cardiogenic in nature.¹ No matter the etiology, early resuscitation efforts to resolve hemodynamic instability are the key for improving outcomes. The purpose of this review is to outline the etiology of shock states, provide assessment and monitoring techniques of hemodynamic status, and describe evidence-based management strategies.

Hemodynamic status can be assessed via direct measurement, with laboratory values and with physical assessment (Table 1). Laboratory data specific to end organs may also be used to assess adequate perfusion. Global hypoperfusion can result in accumulation of lactic acid due to tissue hypoxia. Liver dysfunction is apparent by reduced synthetic function (increased activated partial thromboplastin time [aPTT] and/or prothrombin time [PT]) or elevated hepatic transaminases, lactate dehydrogenase, or bilirubin. Renal function may be impaired and result in decreased urine output or elevated serum creatinine (SCr) and blood urea nitrogen (BUN). Decreased blood flow to the brain may result in encephalopathy or altered mental status. Diminished bowel sounds and ileus may be caused by insufficient gastrointestinal perfusion. Myocardial infarction or ischemia is evident by elevation in cardiac biomarkers (troponin, creatinine kinase, myoglobin) and electrocardiogram abnormalities.¹,²

Prior to discussing each shock state, clinicians must be familiar with normal hemodynamic parameters to understand how they are altered based on the specific type of shock (Tables 1 and 2). It is important to recognize these values are not to be used in isolation, rather they are assessed collectively to develop the most accurate assessment of clinical status. Patient-specific disease states must also be considered since the

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Table 1. Normal hemodynamic parameters

<table>
<thead>
<tr>
<th>Hemodynamic Parameter</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (SBP)</td>
<td>100-140 mm Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure (DBP)</td>
<td>70-90 mm Hg</td>
</tr>
<tr>
<td>Mean arterial pressure (MAP)</td>
<td>80-100 mm Hg</td>
</tr>
<tr>
<td>Heart rate (HR)</td>
<td>60-80 beats/min</td>
</tr>
<tr>
<td>Cardiac output (CO)</td>
<td>4-7 L/min</td>
</tr>
<tr>
<td>Cardiac index (CI)</td>
<td>2.8-3.6 L/min/m²</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>50%-70%</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (PCWP)*</td>
<td>8-12 mm Hg</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (PVR)</td>
<td>80-180 dynes/s/cm⁻⁵ or 1-2 Wood units</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (PAM)</td>
<td>15-20 mm Hg</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure (PAS)</td>
<td>25-30 mm Hg</td>
</tr>
<tr>
<td>Pulmonary artery diastolic pressure (PAD)</td>
<td>6-12 mm Hg</td>
</tr>
<tr>
<td>Systemic vascular resistance (SVR)</td>
<td>800-1200 dynes/s/cm⁻⁵</td>
</tr>
<tr>
<td>Central venous pressure (CVP)</td>
<td>2-6 mm Hg</td>
</tr>
<tr>
<td>Arterial oxygen saturation (SaO₂)</td>
<td>95%-100%</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation (SvO₂)</td>
<td>70%-75%</td>
</tr>
</tbody>
</table>

* PCWP may also be referred to as pulmonary artery occlusion pressure (PAOP).

Table 2. Calculations for hemodynamic parameters

<table>
<thead>
<tr>
<th>Hemodynamic Parameter</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (BP)</td>
<td>CO × SVR</td>
</tr>
<tr>
<td>Cardiac output (CO)</td>
<td>HR × SV</td>
</tr>
<tr>
<td>Cardiac output (CO) by Fick</td>
<td>[(135 mL/min O₂/m²) × BSA]/[13.4 × Hgb (SaO₂ – SvO₂)]</td>
</tr>
<tr>
<td>Cardiac index (CI)</td>
<td>CO/BSA</td>
</tr>
<tr>
<td>Stroke volume (SV)</td>
<td>CO/HR</td>
</tr>
<tr>
<td>Systemic vascular resistance (SVR)</td>
<td>[(MAP–CVP)/CO] × 80</td>
</tr>
<tr>
<td>Mean arterial pressure (MAP)</td>
<td>(SBP + 2 × DBP)/3</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (PVR)</td>
<td>([PAM – PCWP)/CO] × 80 (units = mm Hg) = [(PAM – PCWP)/CO] (units = Wood units)</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (PAM)</td>
<td>(PAS + 2 × PAD)/3</td>
</tr>
</tbody>
</table>

Abbreviations: BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; O₂, oxygen; Hgb, hemoglobin; SaO₂, arterial saturation of oxygen; SvO₂, venous oxygen saturation; PCWP, pulmonary capillary wedge pressure; HR, heart rate; CVP, central venous pressure; SVR, systemic vascular resistance; PAS, pulmonary artery systolic; PAD, pulmonary artery diastolic.

optimal goals of resuscitation for shock may not necessarily require normalization of hemodynamic markers.

Hemodynamic Monitoring

Intra-arterial catheter

In the intensive care unit (ICU), continuous blood pressure monitoring with an intra-arterial catheter is recommended due to patient instability. An intra-arterial catheter can directly measure mean arterial pressure (MAP), which is determined by cardiac output (CO) and systemic vascular resistance (SVR), and is useful to estimate end organ perfusion. The MAP will vary depending on the type of shock and will be discussed in more detail for each condition. Arterial lines are also advantageous for arterial blood gas measurements to assess pulmonary gas exchange.¹,²

Central Venous Catheter

A central venous catheter is utilized to measure central venous pressure (CVP), a marker of volume status and systemic blood return to the heart. The CVP is useful to assess changes in fluid status as low values suggest hypovolemia and high values suggest hypervolemia (Table 1). Venous compliance, right ventricular (RV) function, intrathoracic pressure, and intra-abdominal pressure can affect CVP and must be considered. Poor venous compliance reduces capacitance of these vessels and may drive up CVP. If RV dysfunction is present, systemic volume overload is likely to occur, which results in elevated CVP. Increases in intrathoracic pressure (eg, with mechanical ventilation) or intra-abdominal pressure (eg, extreme ascites or abdominal free air) will also cause increased CVP due to added external pressure on the walls of the vena cava, impairing venous compliance. Venous blood gas can be obtained from a central venous catheter, and medications or fluids can quickly be administered via this route.¹,²

Pulmonary Artery Catheter

A pulmonary artery catheter (PAC) provides a number of useful parameters including pulmonary artery systolic (PAS), diastolic (PAD), and mean (PAM) pressures, pulmonary capillary wedge pressure (PCWP), CO, SVR, and mixed venous oxygen saturation (SvO₂). The CO can be measured by thermomixation or using the Fick equation. A thermistor at the distal end of the PAC is able to monitor changes in temperature over time and calculate CO using area under the curve. Clinicians must account for tricuspid regurgitation (TR), intracardiac shunting, high positive end expiratory pressure in ventilated patients, and severely decreased ventricular function which may affect the accuracy of CO measured by thermomixation. Under these circumstances, the Fick equation (Table 2) may be utilized for greater accuracy. Bradycardia, or factors that decrease stroke volume (SV) from the left ventricle (ie, heart failure [HF] with systolic or diastolic dysfunction, mitral regurgitation, aortic stenosis, or aortic insufficiency) contribute to low CO. The SVR is a calculated value based on CO measurement. A low SVR suggests lack of vascular tone and vasodilation. If CO or SVR deviate from normal, physiologic compensation of the opposite parameter should occur to maintain blood pressure (Table 2). A SvO₂ measured from the RA, can be correlated to CO by assuming that a value below the normal range is associated with a low CO. A low value suggests poor forward blood flow, allowing more time for peripheral tissue oxygen extraction.
The PCWP is a marker of left atrial pressure (LAP) and left ventricular end diastolic pressure (LVEDP), or preload, exerted on the left side of the heart. The PAD is an approximation of PCWP and may be considered if wedge pressures are not available. Low and high preload may result in poor CO caused by inadequate filling or excessive stretch of the LV, respectively, resulting in deranged Frank-Starling forces. It should be noted that although a PAC can provide additional hemodynamic information, it has not been shown to significantly improve morbidity, mortality, or length of stay in critically ill cardiovascular, surgical, or medical patients. Patients managed with a PAC are also at higher risk of adverse effects than those managed without one. It is appropriate to utilize this device at experienced institutions for difficult to manage patients when physical assessment and other diagnostic tests are not adequate.

Hypovolemic Shock

Hypovolemic shock is a patient care emergency associated with significant loss of intravascular volume resulting in decreased preload, SV, and CO. This culminates in compensatory increases in SVR in order to maintain perfusion of end organs and if left untreated, leads to tissue hypoperfusion, organ failure, and death. Numerous etiologies may precipitate hypovolemic shock including plasma loss due to catastrophic hemorrhage or sustained fluid loss without repletion. Other causes include shifting of fluid from the vascular compartment to a nonvascular body compartment. This review provides an evaluation of current management recommendations for hypovolemic shock but does not address surgical methods for cessation of bleeding or specifics regarding fluid infusion rates, timing, or duration.

Pathophysiology

Body fluids account for approximately 60% of lean body mass in males and 50% of lean body mass in females. Of this body fluid, blood volume is approximately 11% to 12%, estimated at 5 to 6 L, of the total volume. Unlike most internal organs which can lose up to 50% of functional mass before organ failure is apparent, loss of as little as 30% to 40% of total blood volume can result in life-threatening circulatory failure.

General fluid loss and volume depletion can occur secondary to hemorrhage, diarrhea, vomiting, heat stroke, or inadequate repletion of insensible losses. Intravascular volume may also be depleted via interstitial and intravascular fluid leaking into a nonvascular space. Sequestering of fluid in a nonvascular compartment via third spacing may commonly occur in patients postoperatively, or with intestinal obstruction, cirrhosis, or thermal injury. These patients may experience volume shifts as intravascular components leak into the extracellular space thereby pulling fluid away from the vasculature. The complexity of this condition is accentuated as a number of etiologies may occur simultaneously such as in surgical or trauma patients who may have operative or injury-related blood loss and significant third spacing.

Thermal injury patients pose an interesting clinical challenge as several resuscitation formulas are used throughout the world for calculating the fluid requirement and no well-controlled trials are available to demonstrate one is better than another. Estimating the fluid requirements is generally based on the size of the patient and size of the thermal injury. The most widely used is the Parkland equation. Intravenous (IV) fluid resuscitation is recommended in adults with greater than 15% total body surface area burn.

Various forms of acute hemorrhage may result in hemorrhagic shock and not surprisingly this condition is the second leading cause of early death among trauma patients behind central nervous system (CNS) injury. Acute blood loss has been organized into 4 classifications by the American College of Surgeons (ACS; Table 3). This classification system has been designed to guide resuscitation efforts and ranges from a class I nonshock state, such as donating blood, to a class IV patient care emergency requiring immediate volume replacement. The ACS defines massive hemorrhage as loss of total blood volume within a 24-hour period or loss of half of the blood volume in a 3-hour period. Mainstays for treatment of hemorrhagic shock are to control the source of bleeding and replace circulating blood volume. Uncontrolled bleeding may lead to the devastating combination of acidosis, hypothermia, and coagulopathy. These abnormalities are referred to as the “lethal” triad because each element exacerbates the other and in combination can rapidly lead to death if hemorrhage is not controlled.

Treatment

**Fluid Replacement and Blood Product Administration.** The magnitude and duration of decreased organ perfusion in hypovolemic shock is directly related to mortality. Intravascular volume can be replenished with a variety of resuscitative agents (Table 4). The ideal resuscitation fluid for hypovolemic shock would be small in volume, highly portable, easy to prepare and administer, effective for prolonged expansion of the intravascular space, and inexpensive. Traditionally, crystalloids...
have been recommended by the ACS for fluid replacement; however other treatment approaches include colloid containing fluids and pharmacologic adjunctive agents.11 The use of blood and blood products is not recommended for volume expansion but rather replacement of oxygen carrying capacity which is lost due to class III or IV hemorrhage.11-13

While crystalloids and colloids are recommended to maintain or increase intravascular volume, clinical trials have not demonstrated benefit of colloids over crystalloids, thus less certainty exists as to which solution improves morbidity or mortality.20-22 Data from a large controlled trial comparing 0.9% sodium chloride to 4% albumin for fluid resuscitation in ICU patients demonstrated similar 28-day mortality rates.23 Several meta-analyses performed using the Cochrane Central Registrar of Controlled Trials found no significant difference in mortality between crystalloid and colloid solutions.24-26 However, another meta-analysis demonstrated a 4% increase in the absolute risk of death when colloids were compared to crystalloid solutions for resuscitation.27 Collectively these data challenge the role of colloid products for resuscitation and suggest the substantial cost of these products, specifically albumin, precludes use until supported by randomized trials.

**Crystalloid fluids.** Crystalloid solutions, such as lactated Ringer’s (LR) solution, 0.9% sodium chloride, and 5% dextrose are the most widely available agents for resuscitation and are classified by tonicity. Hypotonic fluids such as 5% dextrose solutions provide a lower solute concentration surrounding the cells (<270 mmol/L), which results in an intracellular shift of water, thereby leaving less volume remaining in the vasculature (Table 4). Consequently, this is not effective for resuscitation but may be considered for hemodynamically stable cases of dehydration.

Isotonic fluids such as 0.9% sodium chloride and LR are so named because they have similar tonicity to plasma (270-300 mmol/L). These solutions are preferred for resuscitation because they are useful in expanding intravascular volume without altering cellular fluid shifts. Isotonic solutions are inexpensive electrolyte solutions containing small molecules that diffuse rapidly and distribute evenly throughout the extracellular compartment. Two thirds of the extracellular fluid comprises interstitial fluid; therefore, the predominant effect of isotonic crystalloids on volume resuscitation is replenishment of interstitial volume rather than intravascular volume deficits. Secondary to this rapid equilibration into the extracellular fluid, larger volumes of crystalloids may be needed to adequately replace intravascular volume.28,29 However, aggressive crystalloid resuscitation is not without side effects as it can induce platelet dysfunction and dilution of clotting factors, which may extenuate hemorrhagic situations. In addition, excessive administration of crystalloid solutions may lead to hyperchloremic metabolic acidosis and has been shown to induce pulmonary edema, cardiovascular dysfunction, abdominal compartment syndrome, and ileus.30,31

Hypertonic saline products (3%-7.5% sodium chloride solutions) have significantly higher tonicity versus plasma and consequently impact volume resuscitation and intravascular expansion through mobilization of endogenous fluids. Secondary to the high osmolality of these products, administration of small volumes may have expansive impact on the vascular space. While limited studies demonstrate thermal injury and traumatic brain injury patients benefit from hypertonic saline resuscitation,32-34 a large multicenter clinical trial of hypertonic saline in trauma patients with hypovolemic shock and traumatic brain injury was stopped because hypertonic saline did not demonstrate a significant benefit.35 Despite the theoretical advantages, hypertonic saline does not have a clear indication for resuscitation and additional data appear to be needed.36-38

**Colloid fluids.** Colloid fluids, such as albumin, hydroxyethyl starch, and dextrans, are more effective at adding to plasma volume than crystalloid solutions.11,39,40 The large molecules contained in these products poorly diffuse outside of the vascular space and thereby maintain an osmotic pressure which promotes water to remain in the vascular space (Table 4). As much as 75% to 80% of the infused volume of colloid will remain in the vascular space and increase CO for up to 2 hours. Consequently less volume is required when these agents are administered. As with hypertonic crystalloids, it is important to note this approach does not completely replace lost volume but rather, shift fluid from one compartment to another. Therefore, these agents should not be used for resuscitation of acute or

### Table 4. Fluids used for shock resuscitation

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Na</th>
<th>Cl</th>
<th>K</th>
<th>Ca</th>
<th>Mg</th>
<th>Buffers</th>
<th>pH</th>
<th>Osmolarity (mOsm/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>140</td>
<td>103</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>Bicarb (25)</td>
<td>7.4</td>
<td>290</td>
</tr>
<tr>
<td>0.9% NaCl</td>
<td>154</td>
<td>154</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5.7</td>
<td>308</td>
</tr>
<tr>
<td>7.5% NaCl</td>
<td>1,283</td>
<td>1,283</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5.7</td>
<td>2,567</td>
</tr>
<tr>
<td>Lactated Ringer’s</td>
<td>130</td>
<td>109</td>
<td>4</td>
<td>3</td>
<td>–</td>
<td>Lactate (28)</td>
<td>6.4</td>
<td>273</td>
</tr>
<tr>
<td>5% dextrose</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>4.0</td>
<td>252</td>
</tr>
<tr>
<td>5% albumin</td>
<td>130-160</td>
<td>130-160</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Sodium bicarbonate, hydroxide, or acetic acid</td>
<td>6.4-7.4</td>
<td>309</td>
</tr>
<tr>
<td>25% albumin</td>
<td>130-160</td>
<td>130-160</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Sodium bicarbonate, hydroxide, or acetic acid</td>
<td>6.4-7.4</td>
<td>312</td>
</tr>
</tbody>
</table>
severe blood loss and should be reserved for hypovolemia due to interstitial fluid shifts.

It is generally agreed during the early phase of resuscitation following thermal injury, colloid solutions should be avoided for first 12 to 24 hours due to capillary permeability and accumulation of plasma proteins outside the vascular compartment, which contributes to edema.9,41 Crystalloid solutions, specifically LR, are the preferred initial volume expander in burn victims.

The largest disadvantage of colloid resuscitation therapy is cost and product availability. Hydroxyethyl starch and dextrans cause an increased risk of bleeding by inhibiting factor VII and von Willebrand factor and impairing platelet adhesiveness.42,43 Dextrans also may cause severe life-threatening anaphylactic reactions.

**Blood products.** Transfusion of blood products should not be used to expand blood volume. Instead blood and blood products should be administered when blood loss exceeds 30% of total blood volume to assure adequate oxygen delivery and to restore normal coagulopathy as part of a balanced management of hemorrhagic shock.10 Packed red blood cells (PRBCs), fresh frozen plasma (FFP), and platelets (PLT) transfusions are currently the most accessible resuscitative fluid available to accomplish this. The decision to use blood products is also impacted by the presence and degree of hemodilution induced by other replacement fluids. With the exception of whole blood, all IV solutions unfortunately induce hemodilution, which falsely lowers the hemoglobin concentration. This is also true for transfusions with PRBCs which contribute to hemodilution due to the low volume of plasma contained within each unit.44 Due to the low availability of whole blood, numerous organizations have created guidelines for massive transfusion of blood products to include balanced infusion ratios of FFP and PLT to RBC.35-47 This practice is supported by evidence which demonstrates the benefit of increased survival with early administration of balanced blood products. Although the optimal blood component resuscitation ratio has not been demonstrated, most protocols target at least a 1 to 3 ratio of plasma-to-RBC transfusions and some promote a 1 to 2 ratio.45,46 In fact, a strategy of 1 to 1 involving RBC, FFP, and PLT transfusion has been recently proposed.48 These protocols allow for early replacement of non-RBC components, increased replenishment of clotting factors, and minimized crystalloid volume administered.

The Advanced Trauma Life Support (ATLS) resuscitation guidelines recommend early transfusion of RBC in trauma patients with evidence of hemorrhagic shock unresponsive to 2 L of crystalloid fluids.11 The decision to administer RBC transfusion in hemorrhagic shock should not be based on the hemoglobin concentration but rather the physiologic state of the patient, amount of blood loss, and potential for "ongoing hemorrhage."10 During the post-resuscitative period for critically ill patients, guidelines suggest transfusing to a hemoglobin level between 6 and 8 g/dL.49-51 However, maintaining hemoglobin values between 7 and 9 g/dL versus 10 to 12 g/dL have demonstrated no difference in mortality, suggesting there is no incentive to transfuse due to low hemoglobin without concomitant signs and symptoms of poor oxygen delivery.52 Thus, clinicians must adhere to ATLS recommendations and base their decision for transfusion on clinical status and not a laboratory value.

Transfusions are not risk free and massive transfusion, defined as more than 10 units of RBCs in 24 hours, in the setting of acute hemorrhage is a predictor of mortality.44,53 Studies also link RBC transfusion to pulmonary edema, fever, transfusion-related reactions, increased multiple organ failure, decreased immunity, increased rate of infection, citrate toxicity, electrolyte abnormalities, and transfusion-associated lung injury.10,54 Adverse effects of FFP have been described as allergic reactions, fever, infection, transfusion-associated over-load, and acute lung injury.55-57 PLTs have been associated with each of these in addition to thrombosis.57,58

**Pharmacologic agents.** Due to poor outcomes associated with overly aggressive crystalloid administration, vasopressor therapy has been evaluated for hemodynamic support during fluid resuscitation for hemorrhagic shock. In a multicenter prospective cohort, the use of vasoconstrictors early in the resuscitative period for hemorrhagic shock patients demonstrated an increase in mortality when compared to aggressive fluid resuscitation.59 Poor mortality outcomes were observed with norepinephrine, phenylephrine, dopamine, and vasopressin (Table 5). Despite this, animal data demonstrate circulating endogenous vasopressin levels are depleted with prolonged hypotension in hemorrhagic shock, leading to vasodilatation and hypoperfusion of end organs.60 Animal models have demonstrated use of vasopressin in hemorrhagic shock to provide a favorable response to hypotension refractory to volume expansion.61-65 Human data, however, are limited to case reports and large prospective data are still needed.66-67

Recombinant factor VIIa (rFVIIa) initiates hemostasis through the formation of a complex between tissue factor and FVIIa and was developed for treatment of bleeding in hemophilia patients with inhibitors to exogenous factors VIII and IX.68 Off-label use of rFVIIa has been published in numerous case reports describing the management of bleeding in trauma patients and patients undergoing extensive surgery.69-79 A prospective, randomized, double-blinded, placebo-controlled trial in severe penetrating and blunt trauma patients showed a decrease in the number of transfusions required in 48 hours post-injury.77,78 Although several case reports detail successful hemostasis with various forms of uncontrolled hemorrhage, the dosing strategy utilized in these reports is frequently the same strategy utilized for management of hemophilic patients (90 mcg/kg), despite the lack of clear evidence to support this large dose.58 Recent observations with higher cumulative rFVIIa off-label doses suggest prothrombotic complications including deep vein thrombosis, pulmonary embolism (PE), myocardial infarction (MI), and stroke may limit its usefulness.80-82

In fact, the manufacturer has terminated a phase III trial citing futility based on a lower mortality in the placebo group than expected.77 Until the risk—benefit ratio is fully understood, it
is reasonable to limit rFVIIa use to treatment of diffuse hemorrhage following appropriate replacement of coagulation factors with FFP, PLTs, and cryoprecipitate and correction of hypothermia and acidosis.

**Distributive Shock**

Distributive shock is characterized by a decrease in SVR, with or without an associated decrease in CO. It is associated with an abnormal distribution of microvascular blood flow in the presence of normal or increased CO.\(^5\) There are several causes of distributive shock but the most common include anaphylaxis, neurogenic shock after acute CNS or spinal cord injury, and septic shock.

**Septic Shock**

Severe sepsis and septic shock impact millions of patients per year and despite decades of experience with this disease, the associated morbidity and mortality remain fairly stable.\(^6\) One in four patients die as a result of their illness and outcomes are dependent on the appropriateness and efficiency of the care provided in the first hours after development of severe sepsis.\(^8\)

Sepsis is a systemic response of the body caused by invasion of pathogenic microorganisms. This response results in significant reduction of effective tissue perfusion, which can lead to irreversible cellular damage if not controlled quickly. Clinically, this cellular damage presents as a continuum from sepsis, to severe sepsis, and culminating in septic shock with an associated increase in mortality at each stage.\(^\) Septic shock is defined as sepsis-induced hypotension (SBP < 90 mm Hg or MAP < 70 mm Hg or a decrease in SBP of > 40 mm Hg), despite adequate fluid resuscitation along with evidence of hypoperfusion. Perfusion abnormalities may include lactacidosis (lactate acid > 4 mmol/L), oliguria, or altered mental status. Septic shock results in a characteristic hyperdynamic state with high CO and an abnormally low SVR.\(^8\)

**Pathophysiology.** Severe sepsis and septic shock are the manifestations of interactions between infecting organisms and an

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**Table 5. Pharmacology, dose, and therapeutic effect of vasopressors and inotropes**

<table>
<thead>
<tr>
<th>Drug/Mechanism</th>
<th>Dose/Onset and Duration</th>
<th>Use/Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine</td>
<td>Dose: Begin at 100-180 mcg/min; once BP stabilized, decrease rate to 40-60 mcg/min and titrate to MAP</td>
<td>Vasodilatory shock, shock due to aortic stenosis and hypotension, left ventricular outflow tract obstruction in hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Dose: Begin at 2-12 mcg/min and titrate to MAP</td>
<td>Vasodilatory shock (usually drug of choice for sepsis), cardiogenic shock (refractory hypotension with SBP &lt; 70 mmHg)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Dose: Begin at 2-10 mcg/min and titrate to MAP</td>
<td>Vasodilatory shock, cardiac arrest, cardiogenic shock, anaphylaxis</td>
</tr>
<tr>
<td>Vasopressin(^a)</td>
<td>Dose: Fixed dose 0.04 units/min; cardiac arrest: 40 units IV bolus</td>
<td>Vasodilatory shock, cardiogenic shock, cardiac arrest</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Dose: Start at 2.5-5 mcg/kg/min and increase by 2.5-5 mcg/kg/min q 10-15 min. Normal dosing range 2.5-20 mcg/kg/min</td>
<td>Vasodilatory shock, cardiogenic shock, bradycardia</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Dose: 2.5-20 mcg/min; MAX: 50 mcg/min</td>
<td>ADHF, low CO state, cardiogenic shock, septic shock as outlined in early goal directed therapy, bradycardia</td>
</tr>
<tr>
<td>Milrinone</td>
<td>Dose: 50 mcg/kg IV bolus over 10 minutes (rarely used for ADHF) followed by 0.375-0.75 mcg/kg/min(^b)</td>
<td>ADHF, low CO state</td>
</tr>
</tbody>
</table>

Abbreviations: ADHF, acute decompensated heart failure; CI, cardiac index; HR, heart rate; BP, blood pressure; SVR, SV, systemic vascular resistance; PVR, CO, cardiac output; \(\uparrow\), increase; \(\downarrow\), decrease. 

\(^a\) Ensure adequate volume resuscitation before adding vasopressor or inotropic agents. 

\(^b\) May adjust for impaired renal function to prevent accumulation.
inappropriate host response. In septic shock, there is dysfunction of virtually all aspects of the immune response. Immune dysfunction begins almost immediately with overexpression of inflammatory mediators such as tumor necrosis factor-α (TNF-α) and interleukin 1β (IL-1β). This activation of cytokines can cause host tissue injury and play a role in the development of shock. Another important aspect of sepsis pathophysiology is the development of a procoagulant state. Inflammatory cytokines activate the coagulation cascade and inhibit fibrinolysis. This state is manifested by disseminated intravascular coagulation (DIC), a life-threatening complication of septic shock. In addition, an inadequate response later in the infectious process allows for further proliferation of the pathogen. Although the abnormal host responses seen in septic shock receive much attention, the role of the pathogen (bacteria, virus, or fungi) is significant and is becoming better understood. Bacterial and nonbacterial pathogens possess virulence mechanisms that allow them to evade host defenses and continue to proliferate. These virulence factors vary across species but allow the pathogenic organisms to adhere to host epithelia surfaces (eg, adhesins), invade host tissues or cells more readily (eg, bacterial protein secretion systems I, II, III, and IV), or evade specific host defense mechanisms (eg, biofilms, antiphagocytosis mechanisms).

**Treatment.** Early goal-directed resuscitation initiated in the first 6 hours after recognition of septic shock has been shown to improve 28-day survival of emergency department patients in a single-center, randomized, controlled study. The Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock recommend initiating early goal-directed therapy to include all of the following as part of a sepsis response protocol: CVP 8 to 12 mm Hg (12-15 mm Hg in mechanically ventilated patients), MAP > 65 mm Hg, urine output > 0.5 mL/kg/hr, and SevO₂ or SvO₂ > 70% or > 65%, respectively. Some argue the specialized equipment, cost, and time required for monitoring ScvO₂ is a barrier in the implementation of protocol-based resuscitation programs. An alternative method of determining oxygen delivery is to assess lactate clearance which only requires two blood samples. A recent study found that in patients with septic shock who were resuscitated to normalize CVP and MAP, additional resuscitation to obtain lactate clearance of at least 10% was noninferior to targeting ScvO₂. Fluid resuscitation with crystalloids or colloids (Table 4) should be initiated immediately and titrated to achieve predefined goals. There remains controversy regarding crystalloids versus colloids and there is no evidence to support one type of fluid over another. Resuscitation with crystalloids requires more fluid to achieve the same clinical end points, but they remain inexpensive and readily available and should be considered first line for the initial resuscitation in severe sepsis or septic shock. If venous oxygen saturation is not achieved, one can consider further fluid resuscitation or transfusion of PRBCs to target a hematocrit >30% and/or initiation of a dobutamine infusion. Appropriately IV broad-spectrum antimicrobial therapy should be initiated within the first hour of severe sepsis onset. The timely administration of this therapy is associated with improved outcomes. In the setting of septic shock, every hour of delay in administration of antimicrobials is associated with a measurable increase in mortality. Cultures should be obtained prior to initiating antimicrobial therapy as long as this does not result in a significant delay in treatment. The initial empiric antibiotics should be selected based on patient-specific factors such as medical history, allergies, clinical signs and symptoms, and community and institutional patterns of susceptibility. Recently used antibiotics should be avoided. Antimicrobials should be reevaluated daily to optimize efficacy, prevent resistance, and avoid toxicity.

Vasopressor therapy may be required to maintain adequate MAP and tissue perfusion when hypotension is not responsive to fluid resuscitation. This is especially important for perfusion of the organs since severely low MAP leads to loss of autoregulation in vascular beds, which makes perfusion of the organs solely dependent on pressure. A vasopressor infusion titrated to maintain a MAP of at least 65 mm Hg is recommended. Patients with severe or poorly controlled hypertension at baseline may require a higher MAP to maintain perfusion to vital organs. Assessing surrogate markers such as urine output and serum lactate concentration is helpful for ensuring perfusion is appropriate for the individual patient. The Surviving Sepsis Campaign guidelines recommend norepinephrine or dopamine (Table 5) as first-line vasopressors in septic shock. Alternative or additional vasopressors that may be of use in septic shock include phenylephrine, epinephrine, and vasopressin (Table 5). Despite recommendations in the guidelines for vasopressors of choice, there is no high-quality evidence to support one vasopressor over another. Vasopressin may have additional benefits in sepsis beyond blood pressure augmentation. Early in septic shock, vasopressin concentrations are elevated but the concentrations decrease to the normal range as shock continues. These normal levels are actually indicative of a relative vasopressin deficiency since in a state of stress, vasopressin levels should be elevated.

For patients with measured or suspected low CO and elevated cardiac filling pressures, inotropic support with dobutamine is recommended. In the early goal-directed therapy protocol published by Rivers, patients received sequential administration of fluid resuscitation, PRBCs and then dobutamine in order to achieve an ScvO₂ > 70%. In clinical practice, the use of dobutamine versus blood products may be dependent on patient-specific factors and clinician preference. The efficacy of dobutamine later in the care of a septic patient to improve oxygen delivery to target organs is more questionable. Two large prospective clinical trials included patients with severe sepsis in the ICU failed to show a benefit of dobutamine therapy.

There are several adjunctive therapies used for the treatment of severe sepsis and septic shock. These include corticosteroids and recombinant human-activated protein C (rhAPC).
drotrecogin alpha). The use of corticosteroids in sepsis remains controversial despite decades of experience. Short bursts of high-dose corticosteroids were considered standard for some time until additional studies found no mortality benefits and an additional risk for superinfection-related mortality. Therefore, more recent studies have used lower doses of hydrocortisone (200-300 mg/d) and reported earlier reversal of shock as well as mortality benefits. It seemed, however, these results were limited to patients who had no response to a corticotropin test. In 2008, the CORTICUS trial found no mortality benefit from hydrocortisone therapy (50 mg IV every 6 hours) compared to placebo in patients with or without response to a corticotropin test. Those treated with hydrocortisone did have a more rapid reversal of shock. Based on the available literature to date, corticosteroids cannot be recommended as adjunctive therapy for all patients with septic shock, but they may improve or hasten reversal of shock in patients who receive early resuscitation and remain hypotensive despite aggressive vasopressor support. It is also important to consider patient-specific factors such as chronic steroid use or other risk factors for relative adrenal insufficiency which may impact the need for stress-dose steroids.

Drotrecogin alpha (or rhAPC) has antithrombotic, profibrinolytic, and anti-inflammatory properties like endogenous activated protein C. It is theorized to work by mediating the procoagulant state and inhibiting the systemic inflammatory response seen in patients with severe sepsis or septic shock. Drotrecogin alpha was approved in 2001 for use in septic patients with increased risk of death (APACHE II > 25) based on the results of the PROWESS trial which reported a decrease in 28-day mortality (24.7% with drotrecogin alpha vs 30.8% with placebo, P = .005), when the drug was started within 24 hours of the onset of sepsis. However, a post-marketing study in less severely ill patients (single-organ failure or APACHE II < 25) was stopped early due to a lack of benefit (ADDRESS trial). The most feared adverse event associated with drotrecogin alpha is serious bleeding. The incidence of serious bleeding in the PROWESS study was higher in the drotrecogin alpha treatment group compared to placebo (3.5% vs 2%, P = .06), with 24.9% of patients receiving drotrecogin alpha experiencing at least 1 bleeding event compared to 17.7% in the placebo group (P = .001). The current Surviving Sepsis Campaign guidelines suggest considering drotrecogin alpha for “adult patients with sepsis-induced organ dysfunction associated with a clinical assessment of high risk of death, most of whom will have an APACHEII score > 25 or multiple organ failure” in the absence of contraindications (Grade 2B; Grade 2C in patients with history of surgery in the last 30 days).

Finally, investigational agents being studied for the treatment of septic shock include IV immunoglobulins (IVIGs), HMG CoA-reductase inhibitors, and beta-adrenergic antagonists to name a few. Based on currently available literature, none of these therapies can be considered more than experimental. Research continues to focus on therapies that may mediate the immunologic response to infection.

### Anaphylactic Shock

#### Pathophysiology

Anaphylaxis is an immunoglobulin (IgE)-mediated, rapid-onset systemic allergic reaction. Nonallergic anaphylaxis (anaphylactoid) reactions are not IgE-mediated. Instead, they are due to mast cell degranulation induced by the offending agent. Anaphylaxis can be mild, moderate, or severe. Severe anaphylaxis and/or anaphylactic shock is characterized by hypoxia (cyanosis or PaO2 < 92%), hypotension (SBP < 90 mm Hg), or neurologic compromise (confusion or loss of consciousness). In nonlethal cases, hypotension is often accompanied by nausea, vomiting, dyspnea, dizziness or syncope, diaphoresis and flushing, and pruritus and/or hives. Serious reactions occur within minutes of exposure to the offending agent, but some patients may have a delayed reaction hours after exposure. Biphasic reactions are also possible in which patients experience a recurrence of symptoms after 4 to 8 hours. The progression to anaphylactic shock occurs due to hypoperfusion of end organs. The patterns of end organ involvement are variable and may differ between individuals and among episodes. It is important to note the severity of a previous reaction does not predict the severity of future reactions. Diagnosis is primarily based on physical examination and history. In some cases, confirmation can be provided by an elevated serum B-trypase level. However, the absence of an elevated tryptase level does not exclude anaphylaxis and the variability in symptoms makes early recognition and diagnosis more difficult. The median time from onset to cardiac arrest can be as fast as 5 to 15 minutes with the most common causes of death being airway obstruction followed by hypotension. The American Academy of Allergy, Asthma, and Immunology has created diagnostic criteria for the diagnosis of anaphylaxis based on the aforementioned signs and symptoms to aid in the early recognition and treatment.

The most common triggers for anaphylaxis include foods, Hymenoptera (bees, wasps, fire ant) stings, medications, latex, blood products, seminal fluid, and physical factors (eg, cold temperature or exercise). Anaphylaxis can also be idiopathic. Common medications known to cause anaphylaxis include antibiotics, aspirin, and other nonsteroidal anti-inflammatory drugs. In children, foods are the most common triggers, while medications and insect stings are more likely to trigger anaphylaxis in adults.

Anaphylaxis is caused by sensitization to an antigen, which results in formation of a specific IgE to that antigen. Upon reexposure to the antigen, IgE on mast cells and basophils bind to the antigen and cross-link the IgE receptor which activates the cells. This activation causes the release of inflammatory mediators including histamine. It is the release of these mediators that causes capillary leakage, cellular edema, and smooth muscle contractions. Anaphylactic shock is typically classified as a distributive shock although it likely has characteristics consistent with multiple shock states. There is a component of hypovolemia due to capillary leak, distributive shock characterized by vasodilation and decreased SVR, and cardiogenic shock (CS) caused by reduced contractility and, in some cases,
inappropriate bradycardia. Pulmonary vasospasm has also been described, which adds an obstructive shock component. It is theorized this combination of effects does not allow for compensation resulting in the rapid onset of severe hypotension, loss of consciousness, and cardiovascular collapse observed in severe anaphylaxis.

Certain comorbidities or medications can worsen the severity of anaphylactic reactions. Patients with poorly controlled or persistent asthma, other respiratory disorders such as chronic obstructive pulmonary disease (COPD) or pneumonia are at higher risk of death from anaphylaxis. Cardiovascular disease is another risk factor for death from anaphylaxis in middle-aged or elderly patients. Other systemic forms of illness such as acute infection, or psychological stress may play a role in the severity of anaphylaxis but have not been systematically studied. Medications such as beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and alpha-blockers have been implicated in increasing the likelihood of severe or fatal anaphylaxis. Furthermore, they may interfere with the patient’s response to treatment.

Treatment. Due to the potential for anaphylaxis to progress to shock or death within minutes, rapid assessment and treatment is crucial. Immediate administration of epinephrine is the mainstay of treatment. There are several options for administering epinephrine including intramuscular (IM), IV, or sublingual administration as well as administration via an endotracheal tube. Since the leading cause of death in anaphylaxis is airway obstruction, airway management is a critical priority. Supplemental oxygen therapy should be administered and the patient should be evaluated for endotracheal intubation. In cases of severe laryngeal edema, cricothyroidotomy or tracheostomy may be performed. If significant bronchospasm persists, inhaled beta-adrenergic agonists (eg, albuterol) may be useful. Volume expansion plays an important role in the treatment of anaphylaxis, especially in severe cases of shock. Upon presentation, it is recommended to provide a fluid bolus and infusion to maintain blood pressure and adequate urine output. Glucocorticoids (methylprednisone 125 mg IV or hydrocortisone 500 mg IV) may be administered to prevent relapse of symptoms during severe reactions. However, glucocorticoids have no significant immediate effects. Antihistamines such as H2 antagonists are also commonly administered. These agents are helpful for relieving skin symptoms and may shorten the duration of the reaction but, like glucocorticoids, have no immediate effects. There are case reports showing resolution of symptoms with the administration of glucagon for inotropic support in patients who are taking beta-adrenergic antagonists. The recommended dose is a 1 mg IV bolus followed by a continuous infusion of up to 1 mg/h. There is insufficient evidence to recommend glucagon for most patients, but this strategy may be considered for patients on regular beta-blockers when standard therapies have failed.

Neurogenic Shock

Pathophysiology. Neurogenic shock refers to reduced SVR and hypotension which is most commonly caused by spinal cord injuries at or above the level of the sixth thoracic vertebrae. It is caused by sympathetic denervation and interruption of autonomic output from the spinal cord. This results in arteriolar dilation and decreased venous return to the heart resulting in systemic hypotension. Hypotension may also be accompanied by symptomatic bradycardia caused by unopposed vagal stimulation in the setting of sympathetic denervation. Bradycardia is typically exacerbated by manipulating or stimulating the patient such as during endotracheal suctioning, turning, or in the setting of hypoxia. Bradycardia can be severe and progress to complete heart block or cardiac arrest. Neurogenic shock can present any time after spinal cord injury but usually within several weeks of the initial event. Prompt recognition and treatment is crucial in order to maintain perfusion to target organs and the spinal cord as hypoperfusion of the spinal cord can cause a secondary injury.

Treatment. Fluid resuscitation is considered first line for hypotension, but vasopressors may be used in refractory patients. While a specific blood pressure target has not been validated with large clinical trials, based on small studies and expert opinion, the acute spinal cord injury guidelines recommend maintaining an SBP of 85 to 90 mm Hg to prevent secondary spinal cord injury. Atropine can be used for acute, symptomatic bradycardia in doses ranging from 0.4 to 0.6 mg IV every 4 hours as necessary. It is recommended to have atropine readily available for patients with spinal cord injuries since bradycardia may occur suddenly especially early after injury. The vasopressor of choice is not well defined but phenylephrine is often avoided due to its ability to cause marked reflex bradycardia. For patients with hypotension and bradycardia, dopamine or epinephrine (Table 5) infusions may be helpful due to their chronotropic effects. In refractory bradycardia or for patients requiring long-term pharmacologic management, methylxanthines (aminophylline or theophylline) and propantheline have been used as a bridge to pacemaker implantation or for patients who are not candidates for a pacemaker.

Cardiogenic Shock

Incidence and Causes. Cardiogenic shock (CS) may occur for a number of reasons such as derangements in intravascular volume in HF and pulmonary hypertension (PH), massive PE with resultant right ventricular HF, severe mitral regurgitation, ventricular septal rupture, free wall rupture, chordae tendineae or papillary muscle rupture, valvular disease, cardiac tamponade, or acute MI. The most common cause of CS is acute ST-elevation (STEMI) or non-ST-elevation MI (NSTEMI) with LV failure. Approximately 5% to 15% of STEMI cases are complicated by CS, which is the leading cause of death in these patients. Risk factors for developing CS include age (>75 years), female gender, history of hypertension
(HTN), diabetes (DM), previous acute coronary syndrome, multivessel coronary artery disease, HF, low systolic blood pressure ([SBP] <80 mm Hg), and rapid heart rate (>100 beats/min). In general terms, CS can be described as a state of hypoperfusion due to cardiac failure. Using hemodynamic parameters, CS can be defined as hypotension (SBP <80-90 mm Hg or MAP 30 mm Hg lower than baseline) with severe reduction in cardiac index ([CI] < 1.8 L/min/m² without or <2.0 to 2.2 L/min/m² with supportive measures) and adequate or elevated filling pressure (eg, LVEDP >18 mm Hg or RVEDP greater than 10-15 mm Hg). A PAC is helpful during CS to measure PCWP, CI, and SVR to monitor hemodynamic changes. Echocardiography is used to evaluate cardiac filling pressures, left ventricular ejection fraction (LVEF), and valvular integrity to rule out mechanical causes of CS. 

Pathophysiology

Left ventricle. Any mechanical or ischemic insult as well as progressive cardiomyopathy may compromise CO, cause hypotension, and result in CS. Severe MI can cause hemodynamic instability, especially if there is significant anterior wall (left ventricular) involvement. This is exacerbated further by hypotension, impaired coronary perfusion, and infarct expansion. Progression of HF to stage IV as classified by the American College of Cardiology and the American Heart Association (ACC/AHA), with resultant pump failure or acute decompensated HF (ADHF) with volume overload may also cause CS. Restrictive LV compliance and impaired diastolic filling has been associated with CS as well due to reduced SV and CO. One compensatory response to low output involves catecholamine release to trigger vasoconstriction, inotropy, and chronotropy. These responses, however, are also detrimental due to increased myocardial wall tension and oxygen demand. It is important to note that CS is not solely characterized by reduced cardiac contractility. Despite receiving mechanical or pharmacologic support, the mean LVEF in the SHOCK trial coincides with numerous studies of systolic HF patients who had good functional status. This lends support to multifactorial processes beyond cardiac function which are implicated in CS. Chronic systolic HF patients express ventricular dilation to maximize SV and CO through Frank-Starling forces. This adaptive response, however, does not occur acutely in patients with MI and CS.

Right ventricle. Right ventricular (RV) failure is implicated in CS when there is not adequate preload for the LV, resulting in insufficient SV and systemic CO. In addition to inferior wall MI, RV hypertrophy and failure can result from longstanding PAH due to chronically elevated pulmonary vascular resistance (PVR). Excessive RV hypertrophy reduces coronary perfusion to this region of the heart, further exacerbating the condition. Massive PE and obstruction of pulmonary circulation can also cause acute RV failure. Under these conditions, high preload compromises ventricular interdependence which causes bowing of the ventricular septum into the LV chamber. This obstructs LV filling via the mitral valve, compromises CO, and decreases systemic perfusion.

Vasculature. Several compensatory mechanisms are activated in the setting of CS due to end organ hypoperfusion. Neurohormonal imbalance is well defined for patients with chronic HF, and these same processes are upregulated during acute MI. Release of catecholamines from the sympathetic nervous system (SNS) induces vasoconstriction, inotropy, and chronotropy to maintain MAP. The renin-angiotensin-aldosterone system (RAAS) plays a significant role in exacerbating CS via production of angiotensin II, a potent vasoconstrictor. Aldosterone release causes salt and water retention in an attempt to increase preload, LV filling, and CO. Vasopressin is released in response to hypotension to induce vasoconstriction via V1a receptors and water reabsorption by activating V2 receptors in the nephron. These responses increase myocardial workload, afterload, and preload, in addition to causing reduced coronary perfusion which culminates in myocardial stress and increased oxygen demand.

Inflammatory response. Inflammation and vasodilation are not as well defined but may be present during acute MI and CS. In the SHOCK trial, median SVR was relatively normal despite low CO when systemic inflammatory response syndrome (SIRS) or sepsis was suspected. Even in patients without suspected SIRS or sepsis, SVR was inappropriately low, suggesting the presence of other vasodilatory factors. SIRS has been identified in acute MI by high serum concentrations of inflammatory markers such as IL-6, TNF-α, and white blood cell count. Toxic level of nitric oxide due to inducible nitric oxide synthetase have also been documented to be elevated in CS.

Treatment. A PAC is useful for management of CS to help guide therapy based on hemodynamic parameters since small changes can have a significant impact on patient stability. Knowing PCWP, CI, and SVR is beneficial when titrating IV inotropic or vasopressor agents and high doses of these medications have been linked to increased mortality. Clinicians must balance adverse effects with the sequelae of hypotension. The ACC/AHA for STEMI provide guidance for selection of inotropic and vasopressor medications during CS. Fluid resuscitation is recommended for patients who do not display signs and symptoms of volume overload. In patients unresponsive to fluid resuscitation or when not indicated, dobutamine may be considered for SBP between 70 and 100 mm Hg if there are no signs and symptoms of CS. Dopamine is recommended for patients presenting with signs and symptoms of CS due to its additional vasoconstrictive properties (Table 5). Combined, moderate doses of these agents may be more beneficial than maximizing a single agent to minimize toxicity. For refractory patients or those presenting with a SBP less than 70 mm Hg, norepinephrine should be considered. A recent trial evaluated 28-day mortality for patients in shock who were...
randomized to dopamine or norepinephrine to maintain blood pressure. There was no difference in the primary end point for the 1679 patients enrolled, but a subgroup analysis of 280 patients with CS revealed a lower rate of death and fewer of tachyarrhythmias favoring norepinephrine. This was a post hoc, subgroup analysis and the study was not powered to detect such a difference.\textsuperscript{150} Clinicians should keep in mind the risk of using potent vasoconstricting agents, such as norepinephrine (Table 5), which can significantly increase SVR in patients with already poor cardiac contractility.

Many studies have helped shape practice by providing data that support early reperfusion. A predefined sub-study of the GUSTO-I trial evaluated treatment of CS caused by acute MI using various thrombolytic regimens (streptokinase and/or recombinant tissue plasminogen activator (rt-PA)) in addition to standard medical therapy with aspirin, heparin, and atenolol. The primary end point, 30-day all-cause mortality, was significantly higher in patients who developed CS compared to those who did not (57\% vs 3\%, \(P < .01\)). Patients who did not present with CS, but who developed it during the hospitalization experienced a longer time to administration of thrombolytic therapy (3.20 ± 1.75 hours vs 3.09 ± 1.62 hours, \(P = .01\)). Beyond medication therapy, a post hoc analysis of GUSTO-I showed percutaneous transluminal coronary angioplasty (PTCA) significantly reduced 30-day mortality (32\% vs 61\%, \(P < .001\)) in patients who developed CS.\textsuperscript{119} The SHOCK trial is the largest prospective study evaluating treatment of CS due to acute MI. Patients were randomized to emergency revascularization (PTCA or coronary artery bypass grafting [CABG]) within 18 hours or intensive medical therapy (including thrombolytic agents). The basis for this trial came from previous nonrandomized reports of improved outcomes when revascularization was utilized for patients with acute MI and CS. The primary end point, 30-day mortality, occurred in 46.7\% and 56\% of patients randomized to revascularization versus medical therapy, respectively (\(P = .11\)), which translates to a 17\% relative risk reduction. There was a 12.8\% absolute risk reduction in 6-month mortality (\(P = .027\)) and 13.1\% absolute risk reduction at 1 year, both favoring revascularization (\(P = .03\)).\textsuperscript{117,151} A multivariate analysis of the SHOCK trial revealed that older age, shock on admission, creatinine >1.9 mg/dL, history of hypertension, and noninferior MI were independent risk factors for mortality.\textsuperscript{117}

While reperfusion has been proven effective for treatment of acute MI complicated by CS, not all hospitals have a cardiac catheterization laboratory and may not be able to facilitate quick access to a PCI-capable center (90-minute door-to-balloon time from initial presentation). When high-risk patients present with ACS and delays in transfer are anticipated, the ACC/AHA STEMI guidelines provide strong recommendations to administer thrombolytics plus antithrombotic therapy before and during transfer with the intention of proceeding to angiography at the receiving center.\textsuperscript{152-154} The primary literature supporting this recommendation used aspirin and heparin or enoxaparin in addition to thrombolytic therapy. CARESS-AMTI utilized half-dose reteplase, upstream abciximab, and clopidogrel at the discretion of the physician prior to patient transfer. The TRANSFER-AMI protocol included full-dose tenecteplase, recommended clopidogrel, and glycoprotein IIb/IIIa inhibitors were given at the time of PCI according to standard practice of the receiving center.

In addition to thrombolysis and PCI, adjunctive, antithrombotic therapy should be implemented. An in-depth discussion of these therapies is beyond the scope of this review but deserves mention as these agents are critical to maximize the effectiveness of thrombolysis and PCI. Antiplatelet agents including aspirin and clopidogrel should be administered for PCI, thrombolysis, or medical management unless contraindicated. Aspirin and clopidogrel have data from multiple trials supporting their use for these indications.\textsuperscript{155-158} A new thienopyridine, prasugrel, is a viable option in lieu of clopidogrel for PCI with stent placement.\textsuperscript{159} There is no data available to support the use of prasugrel as medical management or in conjunction with thrombolytic agents. Additional antiplatelet therapy with a glycoprotein IIb/IIIa inhibitor is commonly used during PCI. There are also multiple anticoagulant options for management of ACS including heparin, low-molecular-weight heparin, bivalirudin, and fondaparinux which are described in greater detail in the ACS guidelines.\textsuperscript{155}

Mechanical support can be employed for the management of CS to help relieve myocardial work and ischemia as well as maintain sufficient tissue perfusion. Placement of an intra-aortic balloon counterpulsation pump (IABP) is a standard of care that is recommended by the ACC/AHA for STEMI complicated by CS when pharmacological therapy is ineffective and until revascularization can be performed.\textsuperscript{149} This device provides a reduction in afterload to minimize myocardial work-load and augments diastolic filling of coronary arteries. The SHOCK trial registry, including patients who were ineligible for the trial, showed a statistically significant reduction of inhospital mortality favoring use of an IABP compared to those who did not receive one.\textsuperscript{160} More complete cardiac support can be supplied by placement of a left ventricular assist device (LVAD) in cases of severe LV failure. There are multiple types of devices which can be placed peripherally or surgically to provide extracorporeal or intracorporeal circulation. An LVAD may be placed temporarily if LV failure is thought to be reversible or may be utilized as a bridge to more definitive therapy such as implantation of a permanent, surgically placed LVAD or heart transplant. When compared to an IABP for circulatory support in the setting of CS, a peripherally placed LVAD has not shown significant reductions in mortality, but hemodynamic parameters such as CO and PCWP are improved.\textsuperscript{161-164} Patients with chronic HF and LV systolic dysfunction may present with hypotension and CS due to ADHF or progression to pump failure. Diuretics or ultrafiltration is necessary to restore euvolemia, but vasoactive agents may also be necessary. Although inotropic therapy has been proven to increase mortality in a number of previous trials, these agents may be necessary during CS to maintain adequate blood pressure for perfusion to end organs.\textsuperscript{128,129,165} However, when blood pressure tolerates, vasodilators (nitroglycerin, nitroprusside,
nesiritide) are preferred. These patients may have increased preload and afterload due to excessive edema and overexpression of neurohumoral systems, respectively. Using vasodilators to reduce LV wall tension and myocardial stretch (preload) as well as SVR (afterload) may help increase CO and SBP. However, inotropes may be considered if a patient has SBP < 90 mm Hg, is symptomatically hypotensive despite adequate filling pressure (preload), or is unresponsive to or intolerant of vasodilators. In addition to SBP < 90 mm Hg, worsening renal function, cool extremities, narrow pulse pressure, and altered mental status are indicators of a low output state. Inotropes are useful as a bridge to long-term therapy such as revascularization, placement of an LVAD, or heart transplantation.

Conclusion
No matter the etiology, any shock state can be rapidly fatal if not treated. The primary goal of therapy, guided by patient-specific signs and symptoms as well as hemodynamic parameters, should be aimed at restoring perfusion to vital organs. It is critical to differentiate between shock states in order to accurately diagnose patients and reverse underlying causes. Early resuscitation is a mainstay of therapy in all shock states followed by treatment of underlying causes or triggers and appropriate supportive care.

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