CHAPTER 6

Shock

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PRINCIPLES

Background and Importance

In philosophic terms, shock can be viewed as a transition between life and death. Whether shock results from hemorrhage, sepsis, or cardiac failure, mortality rates exceed 20%.[1,2] In scientific lexicon, shock results from the widespread failure of the circulatory system to oxygenate and nourish the body adequately. At the cellular level, shock alters mitochondrial energy transfer and evokes the production and accumulation of toxic chemicals. The emergency clinician identifies shock by linking the qualitative clinical impression, synthesized from the patient's history of present illness, age, health status, and general appearance, to quantitative data, including vital signs, laboratory tests, urine output, and measurements of systemic oxygenation. When the clinical impression and quantitative data suggest widespread organ hypoperfusion, emergent resuscitation is used to restore tissue oxygenation and substrate delivery to prevent deterioration into a vicious cycle of systemic inflammation, organ dysfunction, and death. Anaphylaxis and its treatment are discussed in Chapter 109.

For years, shock has been classified into four broad categories based on Blalock's 1934 description—hematologic, vasogenic, cardiogenic, and neurologic. This basic organization scheme remains useful today for discussions of pathophysiology. For discussions of management, a system based on the requisite treatment response is more clinically useful. Box 6.1 outlines five categories of shock that generally have specific mechanisms and treatments. The epidemiology of shock in the emergency department (ED) context is diverse and evolving. Traumatic, cardiogenic, or septic shock are diagnosed in fewer than 3% of ED patients. Our understanding of the metabolic, systemic, and inflammatory responses that occur in all types of circulatory shock and the specific pathophysiology of the major causes of shock has led to dramatic increases in the early identification and treatment of these states, with resultant improvement in outcomes.

Anatomy, Physiology, and Pathophysiology

At the subcellular level, shock first affects the mitochondria. Mitochondria function at the lowest oxygen tension in the body, but they consume almost all the oxygen used by the body. More than 95% of aerobic chemical energy comes from mitochondrial combustion of fuel substrates (fats, carbohydrates, ketones) plus oxygen into carbon dioxide (CO_2) and water. Mitochondria have therefore been referred to as the canaries in the coal mine because they are affected first in conditions of inadequate tissue perfusion. When mitochondria have inadequate oxygen, the cell catabolizes fuels to lactate, which accumulates and diffuses into the blood. In the setting of hypoxia, mitochondria are unable to provide sufficient energy to maintain cellular processes and, at a certain point, an irreversible series of intracellular cascades leads to cellular dysfunction, organ failure, and ultimately death.

Specific Causes

Hemorrhagic Shock

Hemorrhagic shock results from a rapid reduction in intravascular blood volume from any cause. Rapid hemorrhage generally causes an increase in the strength of cardiac contraction and heart rate (HR), followed by baroreceptor activation and peripheral vasoconstriction. Typically, an initial slight increase in the diastolic blood pressure (BP) with a narrowing of the pulse pressure progresses to a decrease in ventricular filling and cardiac output, causing a reduction in systolic BP. This response varies considerably with cardiopulmonary status, age, and presence of vasoactive medications. The responses of HR and BP are therefore notoriously variable in hemorrhage, so no firm conclusion can be made at the bedside about the presence, absence, or degree of hemorrhagic shock by simple evaluation of the HR and BP.

Even before the cardiac output begins to decline, blood flow is directed away from noncritical organs and tissues, and their cells produce and release lactic acid. Consequently, acidemia often precedes any significant decrease in cardiac output. However, the blood contains bicarbonate ions that buffer the blood pH, keeping it near neutral, even as lactic acid accumulates. The base deficit—amount of strong base that would have to be added to 1 L of blood to normalize the pH—represents an index of how far the bloodstream has dipped into this reserve. A normal base deficit is more positive than −2 mEq/L. The arterial and venous blood base deficit can become more negative early in hemorrhage, even while blood pH and BP remain normal. The base deficit, therefore, crudely represents the physiologic endpoint that distinguishes trivial blood loss from clinically significant hemorrhage. In addition to chemical buffering, the body responds to small reductions in arterial pH by activating brainstem chemoreceptors, which increase minute ventilation, leading to reduced partial pressure of carbon dioxide in the arterial blood ($Paco_2$), providing an additional means of compensating for evolving acidosis.

With progressive blood loss, cardiovascular reflexes can no longer sustain adequate filling of the vasculature, and frank hypotension supervenes. Arterial hypotension is generally and arbitrarily defined as an arterial BP less than 90 mm Hg. Usually coincident with the development of hypotension, the compensatory chemical and respiratory buffering mechanisms become overwhelmed, resulting in acidosis. The hypothalamic-pituitary-adrenomedullary axis is activated, releasing stress hormones and inducing glycogenolysis, lipolysis, and mild hypokalemia. Significant traumatic hemorrhage in otherwise normal ED patients, therefore, will generally cause an arterial lactate concentration greater than 4.0 mmol/L, $Paco_2$ less than 35 mm Hg, mild hyperglycemia (150–170 mg/dL) and mild hypokalemia (3.5–3.7 mEq/L). Although hemorrhagic hypotension reduces lung perfusion, arterial hypoxemia should not be attributed simply to blood loss, but instead should prompt investigation for aspiration, airway obstruction, alveolar consolidation, or lung injury.

BOX 6.1

Five Categories of Shock According to Primary Treatment of Causes and Problems

PRIMARILY INFUSION OF VOLUME

Hemorrhagic shock
- Traumatic
- Gastrointestinal
- Body cavity

Hypovolemia
- Gastrointestinal losses
- Dehydration from insensible losses
- Third-space sequestration from inflammation

VOLUME INFUSION AND VASOPRESSOR SUPPORT

Septic shock
Anaphylactic shock
Central neurogenic shock
Drug overdose

IMPROVEMENT IN PUMP FUNCTION BY INFUSION OF INOTROPIC SUPPORT OR REVERSAL OF THE CAUSE OF PUMP DYSFUNCTION

Myocardial ischemia
- Coronary artery thrombosis
- Arterial hypotension with hypoxemia

Cardiomyopathy
- Acute myocarditis
- Chronic diseases of heart muscle (ischemic, diabetic, infiltrative, endocrinologic, congenital)

Cardiac rhythm disturbances
- Atrial fibrillation with rapid ventricular response
- Ventricular tachycardia
- Supraventricular tachycardia

Septic shock with myocardial failure (hypodynamic shock)
Overdose of negative inotropic drug
- Beta blocker
- Calcium channel antagonist

Structural cardiac damage
- Traumatic (eg, flail mitral valve)
- Ventriculoseptal rupture
- Papillary muscle rupture

IMMEDIATE RELIEF FROM OBSTRUCTION TO CARDIAC OUTPUT

Pulmonary embolism
Cardiac tamponade
Tension pneumothorax
Valvular dysfunction
- Acute thrombosis of prosthetic valve
- Critical aortic stenosis

Congenital heart defects in newborn (eg, closure of patent ductus arteriosus, with critical aortic coarctation)
Critical idiopathic subaortic stenosis (hypertrophic obstructive cardiomyopathy)

SPECIFIC ANTIDOTES DUE TO CELLULAR OR MITOCHONDRIAL POISONS

Carbon monoxide
Methemoglobinemia
Hydrogen sulfide
Cyanide

The second phase of organ injury from hemorrhagic shock occurs during resuscitation. The acute phase of hemorrhage initiates the inflammatory cascade, and resuscitation unleashes these volatile inflammatory mediators on the body, inducing organ injury. During resuscitation, neutrophils become more aggressive, binding to the lung endothelium and causing capillary leakage that characterizes acute respiratory distress syndrome (ARDS). Inflammatory cytokines are liberated, causing additional cellular damage and compounded by persistent microischemia in numerous organs due to an imbalance between vasodilation by nitric oxide (NO) and vasoconstriction by endothelins. The liver demonstrates centrilobular injury, demonstrated clinically by elevated transaminase levels, whereas the kidney may manifest acute spasm of the preglomerular arterioles, with resultant acute tubular necrosis. A growing body of evidence has suggested that resuscitation from hemorrhage exerts greater injury on the heart than the actual hypotensive insult.

Septic Shock

Although historically presented as the archetype of vasogenic or distributive shock, in reality the clinical course of septic shock is much more complex and varies over the course of the disease, with variables degrees of intravascular volume depletion, peripheral vasodialation, and impaired cardiac function. Septic shock can be produced by infection with any microbe, although in half or more of cases of septic shock, no organism is identified. One well-known mediator of sepsis is lipopolysaccharide (LPS), contained in the outer cell membrane of gram-negative bacteria; however, gram-positive organisms are now the primary cause of sepsis in hospitalized patients, indicating that the pathophysiology of sepsis cannot be explained simply by the response to LPS.

Septic shock often causes three major effects that must be addressed during resuscitation—hypovolemia, cardiovascular depression, and induction of systemic inflammation. Septic shock produces relative and absolute hypovolemia, reducing right ventricular filling. Absolute hypovolemia results from gastrointestinal volume loss, tachypnea, sweating, and decreased fluid intake during development of the illness. Further relative hypovolemia results from increasing venous capacitance in conjunction with increased capillary leak and resultant loss of intravascular volume into third spaces. Septic shock causes direct myocardial depression. Measurements of cardiac contractility have shown that mechanical function becomes impaired early in the course of septic shock, even in the hyperdynamic stages. Circulating mediators, myocardial cellular injury from inflammation, and deranged metabolism interact synergistically to injure the heart during septic shock, and specific cytokines (most notably tumor necrosis factor alpha [TNF-α] and interleukin-1 beta [IL-1β]), overproduction of NO by inducible nitric oxide synthase (iNOS), and possibly impairment in mitochondrial oxidative phosphorylation, may all play a role. Similar to hemorrhagic shock, systemic inflammation causes capillary leak in the lung, resulting in ARDS. Widespread systemic inflammation likely plays a role in the development and persistence of multisystem organ failure in sepsis through microvascular and mitochondrial dysfunction. Clinical trials to date have yet to demonstrate the effectiveness of specific or general antiinflammatory therapies in mitigating this response, and the treatment of septic shock relies primarily on the reversal of shock, supportive care, and source control.

Cardiogenic Shock

Cardiogenic shock results when more than 40% of the myocardium becomes dysfunctional from ischemia, inflammation, toxins, or immune injury. Otherwise, cardiogenic shock essentially produces the same circulatory and metabolic alterations as those that are observed with hemorrhagic shock. Undoubtedly, impaired baseline cardiac function can contribute to the development of circulatory shock secondary to infection, hemorrhage, or vasodilatory drug overdose. However, when shock results from a pure cardiac cause, severe left ventricular dysfunction will be evident on echocardiography early in the course. Patients with severe underlying dysfunction are far more likely to have a cardiogenic cause of shock than patients with normal or moderate left ventricular dysfunction.

Neurogenic Shock

Neurogenic shock results from interrupted sympathetic and parasympathetic input from the spinal cord to the heart and peripheral vasculature, typically resulting from acute traumatic injury. Traditionally, it has been described as peripheral vasodilation in conjunction with bradycardia. However, ED patients with shock from acute spinal injury actually manifest a range of heart rates and peripheral vascular resistance, most likely due to variable location of injury and the balance between disrupted efferent sympathetic and parasympathetic tone.[3] As a result, no single presentation adequately summarizes patients with neurogenic shock. It is likely that the downstream pathophysiologic consequences of persistently impaired perfusion mimic those of cardiogenic and hemorrhagic shock.

MANAGEMENT

Decision Making

Patients presenting to the the ED in shock frequently have no obvious cause. Rapid recognition of shock requires the integration of information from the immediate history and physical examination and is strongly supported by the presence of a worsening base deficit or lactic acidosis. In general, patients with shock exhibit a stress response; they are ill appearing, asthenic, pale, often sweating, usually tachypneic, and often have a weak and rapid pulse (Box 6.2). In all patients with shock, HR, BP, and oxyhemoglobin saturation are continuously monitored. HR can be normal or low in shock, especially in cases complicated by prescribed drugs that depress HR. BP initially can be normal because of adrenergic reflexes. Noninvasive measurement of BP may be inaccurate in severe hypotensive states, and insertion of an arterial pressure monitoring line improves the ability to monitor the dynamic response to therapy, which is particularly important if vasoactive medications are administered. BP and HR correlate poorly with the cardiac index (CI) in shock and often underestimate the severity of systemic hypoperfusion. Moreover, children with hypovolemic shock frequently demonstrate a normal BP until they rapidly deteriorate.

Urine output provides an excellent indicator of vital organ perfusion and is readily available with insertion of a Foley catheter. Measurement of urine output, however, requires 30 to 60 minutes for accurate determination of whether output is normal (>1.0 mL/kg/h), reduced (0.5–1.0 mL/kg/h), or severely reduced (<0.5 mL/kg/h), and is of limited use in patients with preexisting renal disease. Arterial or venous lactate concentration and the base deficit provide accurate assessment of global perfusion status. A lactate concentration greater than 4.0 mM or base deficit more negative than −4 mEq/L indicates circulatory insufficiency severe enough to cause subsequent multiple organ failure.[4] A downward trend of the serum lactate concentration or upward trend of the base deficit, with correspondingly improving vital signs and urine output, reliably gauge the adequacy of resuscitation and prognosis in shock from any cause. A rising lactate concentration (or refractory hypotension, with worsening base deficit), despite ongoing resuscitation, calls for more intensive measures. Once the empirical criteria for circulatory shock have been discovered, the next step is to consider the cause of the shock. Fig. 6.1 shows a potential sequence of decisions to help arrive at a diagnosis in a patient with undifferentiated shock.

The history, vital signs, and physical examination documented by prehospital providers can be useful in ED evaluation and management. Patients with prehospital hypotension, whether of medical or traumatic origin, have up to a fourfold higher in-hospital mortality rate than patients without hypotension.[5]

On physical examination, dry mucous membranes suggest dehydration, whereas jugular venous distention suggests congestive cardiac failure or right ventricular strain from pulmonary embolism (PE). Muffled heart sounds with jugular venous distention suggest cardiac tamponade, whereas a loud, machine-like, systolic murmur indicates acute rupture of a papillary muscle or interventricular septum. Diffuse rhonchi suggest bronchospasm, cardiac failure, or PE. Abdominal tenderness may indicate peritonitis, intestinal perforation, or occult trauma. The presence of melanotic stool on rectal examination indicates gastrointestinal hemorrhage. The neurologic examination documents responsiveness, cognition, and presence of any focal deficits and can be a means of clinically assessing end-organ perfusion. In children, documentation should include response to parents, appropriateness of crying, symmetry of grimace, symmetry of extremity movements, and motor tone.

Laboratory, radiographic, and other ancillary data can be useful to assess tissue and vital organ perfusion and diagnose injury from trauma, find the source of infection with sepsis, or identify the cause of cardiac failure. Chest radiography, electrocardiography, finger stick glucose measurement, complete blood count (CBC), urinalysis, serum electrolyte levels, and kidney and liver function tests are indicated for most patients with suspected shock. Arterial blood gas determination provides the base deficit and allows correlation of arterial gas tensions (Pao_2 and $Paco_2$) with those measured by pulse oximetry and capnography. Serum lactate level measurement is performed as early as possible in patients with suspected shock; venous or arterial lactate concentrations can be used. If the peripheral venous lactate level is used, the effect of time, storage temperature, and tourniquet use have no significant effect if the measurement is done within 15 minutes after the sample was obtained. Cardiac and abdominal bedside ultrasound scanning can screen for inadequate central venous volume, occult hemoperitoneum, abdominal aortic aneurysm, left ventricular failure, and cardiac tamponade. A systematic ultrasound protocol can significantly improve the

BOX 6.2

Empirical Criteria for Diagnosis of Circulatory Shock[a]

- Ill appearance or altered mental status
- Heart rate > 100 beats/min
- Respiratory rate > 20 breaths/min or $Paco_2$ < 32 mm Hg
- Arterial base deficit < –4 mEq/L or lactate level > 4 mM/L
- Urine output < 0.5 mL/kg/h
- Arterial hypotension > 30 min duration, continuous

[a]Regardless of cause. Four criteria should be met.

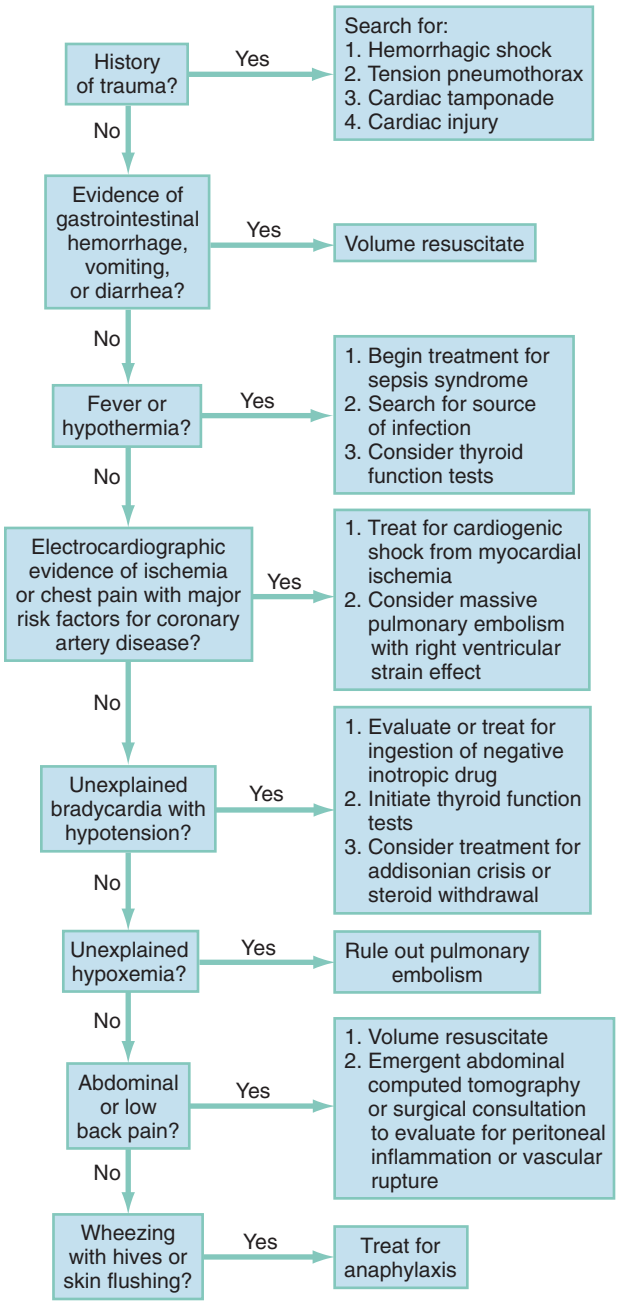

Fig. 6.1. Flow diagram to classify undifferentiated shock.

emergency clinician's ability to accurately diagnose the cause of undifferentiated shock in ED patients, and the finding of hyperdynamic left ventricular function in patients with undifferentiated shock strongly suggests sepsis.[6,7]

Consensus definitions of shock show the spectrum of hypoperfusion for the following three common causes of shock (Box 6.3):

1. *Hemorrhagic shock.* The American College of Surgeons has divided hemorrhagic shock into four stages, depending on the severity of blood loss and physiologic response to this loss, but such arbitrary divisions are of little value and are not accurate reflections of degree of hemorrhage in clinical practice.[8] A more useful approach defines hemorrhagic shock as being present when systemic hypoperfusion manifests as lactic acidosis or increasing base deficit with concomitant organ dysfunction.

BOX 6.3

Definitions and Criteria for Septic, Hemorrhagic, and Cardiogenic Shock

SEPTIC SHOCK

Systemic Inflammatory Response Syndrome (SIRS)

Two or more of the following:

1. Temperature > 38°C or < 36°C
2. Heart rate > 90 beats/min
3. Respiratory rate > 20 breaths/min or $Paco_2$ < 32 mm Hg
4. White blood cell count > 12,000/mm^3, < 4,000/mm^3, or > 10% band neutrophilia

Severe Sepsis

SIRS with suspected or confirmed infection and associated with organ dysfunction or hypotension; organ dysfunction may include presence of lactic acidosis, oliguria, and/or altered mental status.

Septic Shock

SIRS with suspected or confirmed infection with hypotension despite adequate fluid resuscitation requiring vasopressor support; septic shock should still be diagnosed if vasopressor therapy has normalized blood pressure.

HEMORRHAGIC SHOCK

Simple Hemorrhage

Suspected bleeding with pulse rate < 100 beats/min, normal respiratory rate, normal blood pressure, and normal base deficit

Hemorrhage with Hypoperfusion

Suspected bleeding with base deficit < –4 mEq/L *or* persistent pulse rate > 100 beats/min

Hemorrhagic Shock

Suspected bleeding, with at least four criteria listed in Box 6.2

CARDIOGENIC SHOCK

Cardiac Failure

Clinical evidence of impaired forward flow of the heart, including presence of dyspnea, tachycardia, pulmonary edema, peripheral edema, and/or cyanosis

Cardiogenic Shock

Cardiac failure plus four criteria listed in Box 6.2

2. *Septic shock.* International consensus definitions distinguish septic shock from its precursor conditions—systemic inflammatory response syndrome (SIRS), sepsis, and severe sepsis.[9] SIRS is often a precursor of shock, but the nonspecific criteria for SIRS are found in a large variety of conditions, many of which are benign, so the clinical context is vital to understanding the significance of these physiologic variations. Although a consensus definition of septic shock requires persistent hypotension after fluid resuscitation, initiation of treatment for empirically diagnosed severe sepsis or septic shock should not await the onset of hypotension. The incorporation of an indicator of tissue hypoperfusion (Box 6.4) into the clinical assessment may improve identification of hypoperfusion, particularly in subtle cases.[10]
3. *Cardiogenic shock.* Cardiogenic shock should be thought to be present whenever cardiac failure (ischemic, toxic, or obstructive) causes systemic hypoperfusion that manifests as lactic acidosis with organ dysfunction.

Box 6.5 presents the general treatment approach for these three common causes of shock.

BOX 6.4

Variables Indicating Tissue Hypoperfusion

Hypotension
Tachycardia
Low cardiac output
Dusky or mottled skin
Delayed capillary refill
Altered mental state
Low urine output
Low central venous oxygen saturation
Elevated lactate level

BOX 6.5

Clinical Management Guidelines for Three Common Causes of Shock

HEMORRHAGIC SHOCK

- Ensure adequate ventilation and oxygenation.
- Provide immediate control of hemorrhage, when possible (eg, traction for long bone fractures, direct pressure), and obtain urgent consultation as indicated for uncontrollable hemorrhage.
- Initiate judicious infusion of isotonic crystalloid solution (10–20 mL/kg).
- With evidence of poor organ perfusion and 30-min anticipated delay to hemorrhage control, begin packed red blood cell (PRBC) infusion (5–10 mL/kg).
- With suspected massive hemorrhage, immediate PRBC transfusion may be preferable as the initial resuscitation fluid.
- Treat coincident dysrhythmias (eg, atrial fibrillation with synchronized cardioversion).

CARDIOGENIC SHOCK

- Ameliorate increased work of breathing; provide oxygen and positive end-expiratory pressure (PEEP) for pulmonary edema.
- Begin vasopressor or inotropic support; norepinephrine (0.5 μg/min) and dobutamine (5 μg/kg/min) are common empirical agents.
- Seek to reverse the insult (eg, thrombolysis, percutaneous transluminal angioplasty).
- Consider intraaortic balloon pump counterpulsation for refractory shock.

SEPTIC SHOCK

- Ensure adequate oxygenation; remove work of breathing.
- Administer 20 mL of crystalloid/kg or 5 mL of colloid (albumin)/kg, and titrate infusion based on dynamic indices, volume responsiveness, and/or urine output.
- Begin antimicrobial therapy; attempt surgical drainage or débridement.
- Begin PRBC infusion for hemoglobin level <7 g/dL.

If volume restoration fails to improve organ perfusion, begin vasopressor support with norepinephrine, infused at 0.5 μg/min.

Monitoring Perfusion Status

Patients with cardiac failure or renal failure may benefit from closer measurement of dynamic variables of fluid responsiveness that can be measured from an arterial line (eg, stroke volume variation or stroke volume index) or a central venous line (central venous pressure [CVP]).[11] A triple-lumen catheter allows for accurate measurement of the CVP, although the clinical utility of these measurements has been debated. However, a triple-lumen catheter also allows for safe infusion of vasopressors in hypotensive patients unresponsive to an initial fluid bolus, as well as more rapid simultaneous infusion of intravenous (IV) fluids and antibiotics in patients with limited IV access. In children, a 3- or 5-Fr bilumen catheter can be placed in the femoral vein with few complications. If unable to attain adequate peripheral or central venous access rapidly in patients with shock, intraosseous (IO) access should be established, because it is easy and can provide a temporary method of administering fluid resuscitation and medications to adults and children. However, IO access should be considered a bridge to definitive IV access due to the risk of complications with prolonged usage in the inpatient setting. If vasoactive medications are administered, additional peripheral IV catheters will be required for infusion of crystalloid and other treatments. Many patients with renal disease or cancer have indwelling catheters in place. In patients with empirical criteria for shock, this catheter should be used for IV access, unless satisfactory access has already been established at other anatomic sites. In EDs where the standard practice is not to use these ports at the request of other emergency clinicians, a specific hospital policy and training session should be developed to make an exception in the case of circulatory shock. In general, failure to administer fluids rapidly and in sufficient quantity outweighs considerations about preservation of the line for future therapy.

Quantitative Resuscitation

Quantitative resuscitation, also called goal-directed therapy, goal-oriented resuscitation, or hemodynamic optimization, was first described in 1988 and refers to the practice of resuscitating patients to predefined physiologic endpoints indicating that systemic perfusion and vital organ function have been restored. Since that time, many studies have evaluated the efficacy of such a therapeutic approach to shock and have confirmed its benefit for reducing mortality. For many years, in the intensive care unit (ICU), clinicians have relied on the use of the pulmonary artery catheter to help optimize left ventricular filling indices, but data supporting the efficacy of this practice on patient-centered outcomes such as mortality are lacking. There is insufficient evidence to support the use of pulmonary artery catheters for ED patients, and their significant complication rate, in the context of uncertain or no benefit, leads us to recommend against their routine use.

Lactate clearance refers to serial measurements of the venous or arterial lactate level and is calculated according to the following formula:

$$([\text{Lactate}_{\text{initial}} - \text{lactate}_{\text{delayed}}]/\text{lactate}_{\text{initial}}) \times 100$$

Lactate clearance has been shown to be equivalent to central venous oxygen saturation as an endpoint of early septic shock resuscitation.[12] Lactate clearance measurements are easily obtained from peripheral venous blood and are a preferred endpoint of resuscitation. If the lactate concentration has not decreased by 10% to 20% 2 hours after resuscitation has begun, additional steps are undertaken to improve systemic perfusion. Resuscitation should continue until the lactate concentration drops below 2 mM/L.[13]

Mixed venous oxygen saturation ($S\bar{v}O_2$) measurements reflect the balance between oxygen delivery and oxygen consumption. The $S\bar{v}O_2$ can be used as a surrogate for CI—targeting an $S\bar{v}O_2$ of 65% is equivalent to reaching a CI of 2.5–3.5 L/min/m^2—as a therapeutic endpoint in critically ill patients. Although $S\bar{v}O_2$ requires the use of a pulmonary artery catheter, the central venous oxygen saturation ($Sc\bar{v}O_2$) drawn from the central circulation has been shown to parallel changes or trends over time and is the

preferable method for pulmonary artery catheter placement in the ED.

Quantitative resuscitation, which incorporates multiple indices of circulatory and oxygenation status, has been shown in meta-analyses to reduce mortality and morbidity in ED patients with severe sepsis or septic shock significantly when instituted as early in the disease course as is practical. In such an approach, patients are resuscitated early, within the first 6 hours, to achieve normalization of markers of volume status, perfusion, and adequate oxygen delivery (Fig. 6-2). The first description of an ED-based quantitative resuscitation strategy targeted specific volume, perfusion, and oxygen delivery endpoints and was termed *early goal-directed therapy* (EGDT).[14] Recently, three large multicenter trials did not demonstrate a mortality advantage for patients receiving the complex and invasive physiologic interventions associated with EGDT as compared to the appropriate volume resuscitation and targeted therapies that constitute the current usual care of shock.[11,15,16] Patients in these studies received 2 to 4 L early volume resuscitation and relatively prompt antibiotic administration, suggesting that early recognition and initiation of fluid and antibiotic therapy, in conjunction with close monitoring and thoughtful care, may be more important than the use of invasive measurements to attain the specific resuscitation goals suggested by earlier studies.

Pharmacology

Volume Replacement

Most patients with shock can be fully resuscitated with peripheral venous access established with at least two 18-gauge two catheters. The goal in volume replacement is slightly elevated left ventricular end-diastolic volume, which is difficult to measure in the ED. Historically, CVP has been used to estimate right ventricular filling pressure and is used in some quantitative resuscitation algorithms. However, CVP measurement does not accurately reflect left ventricular end-diastolic volume, and CVP poorly predicts the hemodynamic response to a fluid challenge. Thus, assessment of fluid responsiveness and fluid resuscitation should not be based solely on CVP. A better approach would include the use of the clinical response to fluid resuscitation, such as increases in urine output, BP, and decreasing lactate concentrations, alone or in combination with CVP measurements. In patients for whom fluid resuscitation may be associated with higher risk of harm (eg, severe systolic heart failure), the use of dynamic variables of fluid responsiveness that can be measured from an arterial line (eg, stroke volume variation, stroke volume index, passive straight leg raise) may be beneficial over empirical fluid boluses, but their use in the ED has not been studied.

Crystalloids. Standard treatment for hemorrhagic shock historically consisted of rapidly infusing several liters of isotonic crystalloid in adults or three successive 20-mL/kg boluses in children. Recent studies have endorsed the concept of delayed resuscitation or hypotensive resuscitation for hemorrhagic shock (see Chapter 33). No study to date has demonstrated the survival benefit of one type of crystalloid versus another; therefore, the choice of fluids may be less important than scrupulous monitoring for adequate tissue perfusion. Although a single Australian study has suggested an association between use of chloride-rich solutions and subsequent renal dysfunction in ICU patients, the study solutions included colloids as well as crystalloids and were not randomized, so any causative inference is not justified.[17] Normal saline or lactated Ringer's solution may be used for volume replacement during resuscitation, with no evidence clearly supporting one over the other. Accordingly, the selection of isotonic crystalloid solution may be based on institutional, departmental, or individual preferences. Initial volume replacement consists of the rapid infusion of 20 to 25 mL of isotonic crystalloid per kilogram.

Colloids and Hypertonic Saline. Colloids, including albumin, have been used in patients with hemorrhage, but at considerable increase in cost and without effect on morbidity or mortality. Colloids offer the theoretic advantage of a high osmotic pressure, which should help maintain normal intravascular volume. Initial resuscitation fluid treatment with hypertonic saline or hypertonic saline and dextran, compared with normal saline, has not been found to result in superior 28-day survival.[18]

In the setting of septic shock, initial fluid resuscitation should consist of serial boluses of IV isotonic crystalloid as long as the patient continues to demonstrate a positive hemodynamic response to fluid loading. Persistent hypotension, despite 30 mL/kg of IV fluid, indicates the need to add vasopressors to the resuscitation (see below). If patients require large volumes of crystalloid (>4 L), we recommend adding 5- to 10-mL/kg boluses of a natural colloid (eg, albumin), rather than additional isotonic crystalloid alone, until volume responsiveness is achieved.[19] We do not recommend use of synthetic colloids, such as hydroxyethyl hetastarch, which have recently been demonstrated to be associated with a higher risk of renal failure.[20] The infusion of hemoglobin-based blood substitutes as alternatives to packed red blood cells (PRBCs) for the resuscitation of hemorrhagic shock has been extensively studied and is associated with significant increased risk of death and myocardial infarction; we recommend against their use.

Blood Products. In the setting of hemorrhage or a critically low hemoglobin level (<7g/dL), if criteria for shock persist despite crystalloid infusion (see Box 6.2), we recommend transfusion of PRBCs (1–2 units in adults or 5–10 mL/kg in children). Fully crossmatched blood is safest and is always preferable unless the patient's need is considered sufficiently urgent to justify the use of type-specific or even uncrossmatched blood. Use of the latter is generally confined to patients with hemorrhagic shock with persistent, severe, arterial hypotension and massive or uncontrolled hemorrhage. O-negative blood is used in women of childbearing age, and O-positive blood is used in all others (see Chapter 111). If patients require more than 2 units of PRBCs for hemorrhage, we recommend a balanced resuscitation using PRBCs, fresh-frozen plasma, and platelets in a 1 : 1 : 1 ratio, which is associated with better hemostasis and lower death due to exsanguination by 24 hours.[1]

The goal hemoglobin target for patients with septic shock in the acute resuscitation window, generally defined as the first 6 hours following presentation, remains controversial. A recent large randomized controlled trial (RCT) in ICU patients with septic shock found similar rates of ischemic events, use of life support, and 90-day mortality among patients transfused at a threshold of 7 g/dL as compared to 9 g/dL.[6] Thus, we recommend transfusion of PRBCs at a threshold of 7 g/dL in patients with septic shock unless specific contraindications exist or patients refuse transfusion.

Vasopressors

The primary goal of vasopressor support is to increase cardiac output and oxygen delivery to vital organs when crystalloid resuscitation alone is inadequate. To reduce the potential for limb damage from extravasation from a peripheral IV injection, vasoactive medications are optimally administered through a central venous catheter, although this is not always feasible in the acute setting. Patients with septic shock who remain hypotensive after

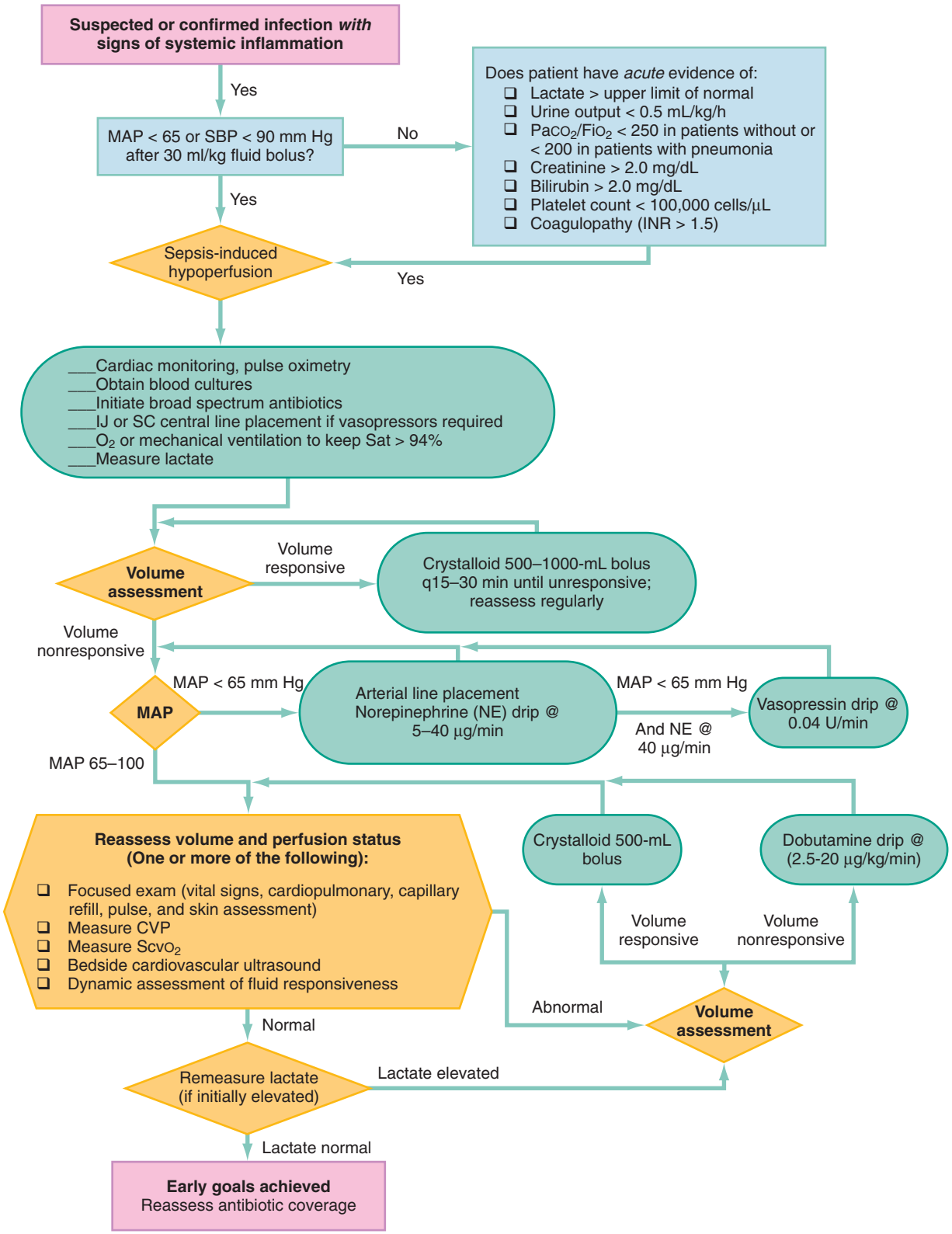

Fig. 6.2. Flow diagram outlining an example of a formalized resuscitation strategy. This figure illustrates the sequential targeting of preload, afterload, oxygen supply, and demand matching for sepsis-induced hypoperfusion. The protocol outlines specific hemodynamic and physiologic parameters that the emergency clinician should seek to attain within the first 6 hours of care. This protocol is focused on resuscitation and should be used in conjunction with standard clinical care for patients with suspected infection, such as appropriate diagnostic studies, to determine the focus of infection and appropriate antimicrobial agents to treat the infection. *HCT,* Hematocrit; *ICU,* intensive care unit; *IJ,* internal jugular; *INR,* international normalized ratio; *MAP,* mean arterial pressure; *NS,* normal saline; $Paco_2$, partial pressure of carbon dioxide, arterial; *Sat,* peripheral oxygen saturation; *SBP,* systolic blood pressure; *SC,* subclavian; $Scv\bar{o}_2$, central venous oxygen saturation; *SIRS,* systemic inflammatory response syndrome; *WBC,* white blood cell count.

a 30-mL/kg fluid bolus generally require vasopressor support. Several randomized trials and a meta-analysis have suggested that norepinephrine (5–30 μg/min) is associated with improved efficacy and lower rates of adverse effects, making norepinephrine the vasopressor of choice for correction of hypotension in septic shock.[7] In patients who remain in shock after initial crystalloid boluses, norepinephrine should be initiated at a rate of 0.05 μg/kg/min and titrated at 3- to 5-minute intervals until the mean arterial pressure is greater than 65 mm Hg or the systolic BP is greater than 90 mm Hg. There are no clear data regarding an absolute maximum dose, but generally there is little or no additional pressor effect once a dose of 30 μg/min has been reached. Vasopressin can be added as a second vasopressor agent when norepinephrine reaches the maximum dose of 30 μg/min. Vasopressin should be administered at a fixed rate of 0.03 to 0.04 units/min and should not be titrated. A trial of vasopressin cessation can be attempted once the patient demonstrates improving hemodynamics over at least a 6-hour period. Except in cases of a prolonged stay in the ED, vasopressors will not be stopped until the patient is in the ICU. Following vasopressor initiation, particularly in patients who require high or rapid upward titration of the vasopressor dose, patients should be reassessed for their responsiveness to additional fluid boluses through the use of dynamic variables or empirical 500-mL boluses, with careful attention to the clinical response. Vasopressor support, along with crystalloid therapy, is continued until the patient can maintain the blood pressures listed without vasopressor support, which can be tested at the bedside by weaning the vasopressor agent at a rate of 2 to 3 μg/min every 5 to 10 minutes.

Inotropes

Dobutamine may also be used with norepinephrine to increase cardiac output and maintain adequate oxygen delivery in cardiogenic and septic shock. In the setting of cardiogenic shock, dobutamine may be indicated by some combination of hypotension, cool extremities, poor urine output, and elevated lactate level. In the setting of septic shock, if the lactate level does not decrease at least 10% and/or the measured $Sc\bar{v}O_2$ does not reach 70%, despite fluid resuscitation and vasopressor administration (see earlier), dobutamine can be added at a dose of 2 μg/kg/min and titrated every 5 to 10 minutes, to a maximum of 20 μg/kg/min. Due to stimulation of vasodilating peripheral beta receptors, dobutamine does have the potential to decrease the BP, so careful attention to a patient's individual response is necessary. If simultaneous BP and inotropic support is necessary for septic shock, epinephrine alone, 0.2 μg/kg/min starting dose, provides similar outcomes and adverse event rates as a combination of norepinephrine plus dobutamine. When norepinephrine is the first pressor initiated and an inotrope is indicated, we recommend the addition of dobutamine, with the ability to titrate each agent individually. However, it is acceptable as an alternative to discontinue the norepinephrine and initiate epinephrine infusion to provide vasopressor and inotropic support via a single agent.

Antimicrobial Therapy

Treatment of the infection with antimicrobial therapy and, where necessary, surgical drainage (see later, "Source Control"), should be instituted as soon as practical in cases of septic shock.[10] Current evidence does not support an absolute time requirement for administration but, when septic shock is the working diagnosis in the ED, we recommend initiation of appropriate antibiotics as soon as practical after the diagnosis is made, ideally within 4 hours of ED presentation. When there is no focus of infection identified in a patient with presumed septic shock, a semisynthetic penicillin with a β-lactamase inhibitor, in combination with a fluoroquinolone and vancomycin, is a rational empirical choice. One such regimen would include piperacillin-tazobactam, 4.5 g IV every 6 hours, plus levofloxacin, 750 mg IV every 12 hours, and vancomycin, 30 mg/kg (maximum dose, 2 g) given every 12 hours, adjusted as appropriate for trough levels and renal failure.

Patients with neutropenia and sepsis syndrome are at particular risk for progressive sepsis, organ failure, and death. Neutropenia can be suspected in patients who have recently undergone chemotherapy, and these patients often know that they are neutropenic. Antimicrobial administration is particularly urgent for these patients and should occur rapidly after blood cultures are obtained, in parallel with crystalloid administration. Antibiotic considerations for the neutropenic patient are discussed in Chapter 115. Chemotherapy patients with sepsis represent a special challenge because the pathophysiology may be complicated by anemia, thrombocytopenia, dehydration from vomiting, and the effects of adjunctive steroid therapy. Chemotherapy patients often have indwelling catheters, which predispose them to more unusual causes of sepsis, including gram-positive bacteria and fungi (see Chapters 115 and 187).

Corticosteroids

There is no evidence for high-dose, short-course corticosteroid therapy in unselected patients with septic shock. Most current guidelines recommend that low-dose hydrocortisone be administered only to patients receiving chronic steroid replacement and in patients with refractory shock, despite adequate fluid and vasopressor support. Even this is only marginally supported, if at all, by scientific evidence. Corticotropin stimulation testing is no longer considered of value.

Special Cases

Systemic thrombolytic therapy is indicated in patients with shock from pulmonary embolism (see Chapter 78) without contraindications.[21] Specific treatments for shock as a result of poisoning with vasoactive medications and other toxins are discussed in the relevant chapters in this text.

Devices and Procedures

Ventilation

Rapid sequence intubation is the preferred method of airway control in most patients with refractory shock (see Chapter 1). Tissue hypoperfusion leads to increasing fatigue of the muscles of respiration, and respiratory failure commonly supervenes in patients with persistent shock. Intubation prevents aspiration, increases oxygenation, treats acute respiratory failure, provides initial treatment for metabolic or hypercarbic acidemia, and protects the patient who will be sent to an uncontrolled environment (eg, for testing). Intubation also reduces the work of breathing, which, in the patient with hypoperfusion, further exacerbates lactic acidemia. Strenuous use of accessory respiratory muscles can increase oxygen consumption by 50% to 100% and decrease cerebral blood flow by 50%. More importantly, if the patient has increased airway resistance (eg, bronchospasm with anaphylaxis) or a decrease in lung compliance (eg, pulmonary edema, ARDS), a more negative intrathoracic pressure must be generated to fill the lungs with each inspiration. The greater suction effect is also exerted on the left ventricle, impeding its ability to eject and increasing functional afterload. Positive-pressure ventilation removes this impedance and can improve ventricular function and cardiac output up to 30%. The use of etomidate for patients with septic shock is discussed in Chapter 1.

Source Control

Controlling hemorrhage remains the cornerstone of treating hemorrhagic shock, and evidence continues to support immediate surgery when direct vascular control cannot otherwise be obtained (see Chapters 33 and 41). Gastrointestinal bleeding may require urgent endoscopy, often in the ED or ICU, and aortic rupture requires emergency consultation by a vascular surgeon. In septic shock related to an abscess, aggressive infection (eg, necrotizing fasciitis; see Chapter 129) or wound (eg, toxic shock syndrome; see Chapter 130), removal of the infectious stimulus through surgical intervention should proceed as soon as practical.

Intraaortic Balloon Pumps and Percutaneous Coronary Intervention

The use of intraaortic balloon counterpulsation and percutaneous coronary intervention in selected patients with cardiogenic shock or acute cardiovascular emergencies is discussed in Chapter 68.

Pericardiocentesis and Thrombectomy

Shock caused by mechanical obstruction can be managed by direct intervention. Large, acute pericardial effusions should be managed with pericardiocentesis. Surgical thrombectomy for massive pulmonary embolism is performed rarely. Direct thrombolysis via interventional radiology, however, has been gaining acceptance as a therapeutic option in patients with shock, particularly if systemic thrombolytics are contraindicated.

OUTCOMES

Outcomes for patients with shock vary with the underlying cause of the shock state and the premorbid or comorbid status of the patient. Outcomes have progressively improved, with emphasis on early diagnosis and treatment. In general, persistent hypotension (refractory shock) is associated with worse outcomes. Patients meeting consensus definitions for hemorrhagic shock have a mortality rate of about 20%,[1] whereas this exceeds 40% in septic and cardiogenic shock.[2]

KEY POINTS

- Circulatory shock can occur with normal arterial blood pressure, and not all patients with arterial hypotension have circulatory shock.
- A base deficit more negative than –4 mEq/L or a serum lactate level greater than 4.0 mmol/L warrants a presumptive diagnosis of shock.
- Urine output is a reliable index of vital organ perfusion in patients with suspected shock. Normal urine output is 1.0 mL/kg/h. Output less than 0.5 mL/kg/h indicates severe renal hypoperfusion.
- A combination of a worsening base deficit, increasing lactate level, and low urine output represents persistent or worsening circulatory shock.
- Early initiation of fluid resuscitation, with pressor support as needed, and appropriate antimicrobial therapy improve the outcomes in patients with septic shock.
- The use of defined physiologic endpoints to measure systemic perfusion during resuscitation (quantitative resuscitation) improves outcomes for ED patients with shock.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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CHAPTER 6: QUESTIONS & ANSWERS

6.1. Which of the following is considered one of the empirical criterion for the diagnosis of circulatory shock?
- **A.** Partial pressure of carbon dioxide ($Paco_2$) < 40 mm Hg
- **B.** Partial pressure of oxygen (Pao_2) < 55 mm Hg
- **C.** Serum lactate level < 4 mM/L
- **D.** Systolic blood pressure (SBP) < 100 mm Hg
- **E.** Urine output < 0.5 mL/kg/h

Answer: E. Four of the following criteria should be met for the diagnosis of circulatory shock:
1. Ill appearing or altered mental status
2. Heart rate > 100 beats/min
3. Respiratory rate > 20 breaths/min or $Paco_2$ < 32 mm Hg
4. Arterial base deficit < −4 mEq/L or lactate level > 4 mM/L
5. Urine output < 0.5 mL/kg/h
6. Arterial hypotension > 20 min duration

6.2. Which of the following, when present and in the setting of suspected or confirmed infection, helps distinguish severe sepsis from systemic inflammatory response syndrome?
- **A.** Heart rate > 90 beats/min
- **B.** Hypotension
- **C.** $Paco_2$ < 32 mm Hg
- **D.** Temperature < 36°C
- **E.** >10% band neutrophilia

Answer: B. The diagnosis of severe sepsis is made in patients who meet the criteria for systemic inflammatory response syndrome (SIRS) with suspected or confirmed infection and associated with organ dysfunction or hypotension. The organ dysfunction mentioned may include the presence of lactic acidosis, oliguria, and/or altered mental status. The diagnosis of SIRS is made when two or more of the following are present:
1. Temperature > 38°C or < 36°C
2. Heart rate > 90 beats/min
3. Respiratory rate > 20 breaths/min or $Paco_2$ < 32 mm Hg
4. White blood cell count > 12,000/mL, < 4,000/mL, or > 10% band neutrophilia

6.3. An 18-year-old unrestrained driver is transported to the emergency department (ED) after being thrown from his vehicle during a motor vehicle collision. He was intubated in the field and received an intravascular bolus of 3 L of normal saline before arrival to the ED. His initial Glasgow Coma Score (GCS) is 7, and his blood pressure on arrival is 80/50 mm Hg. Which of the following would be the most appropriate to initiate immediately on arrival to the ED?
- **A.** Dobutamine
- **B.** Dopamine
- **C.** Hetastarch
- **D.** Norepinephrine
- **E.** Packed red blood cell (PRBC) transfusion

Answer: E. In patients with signs of hemorrhagic shock and suspected central nervous system trauma or GCS < 9, immediate PRBC transfusion should be initiated. This assists with volume expansion and oxygen delivery to the brain. Pressors and positive inotropes will be of little benefit before volume replacement, and hetastarch has no proven benefit for initial resuscitation in head injury patients.