Shock

Phoebe Yager and Natan Noviski

Pediatrics in Review 2010;31;311

DOI: 10.1542/pir.31-8-311

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

http://pedsinreview.aappublications.org/content/31/8/311

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Shock

Phoebe Yager, MD,*

Natan Noviski, MD†

Objectives   After completing this article, readers should be able to:

1. Describe the basic pathophysiology of shock.
2. Characterize the various causes of shock and recognize their clinical presentations.
3. Discuss the importance of early, goal-directed treatment of shock.
4. Know the guidelines for the type and volume of fluid to be infused initially in hypovolemic or septic shock.
5. Choose the correct drug for the initial management of septic versus cardiogenic shock.
6. Be familiar with some of the recent therapies under investigation for the treatment of shock.

Introduction

A 9-month-old girl presents to the emergency department (ED) with a 4-day history of profuse diarrhea and poor oral intake. On physical examination, she appears irritable. Her respiratory rate (RR) is 70 breaths/min, heart rate (HR) is 180 beats/min, and blood pressure (BP) is 80/50 mm Hg. She has cool, mottled extremities, with sluggish capillary refill and weak peripheral pulses. Is this just a case of dehydration or could this be shock?

A 17-year-old boy presents to the ED with a 1-day history of headache, general malaise, and fevers. On physical examination, he appears confused. He has a temperature of 39.9°C, HR of 120 beats/min, and BP of 85/28 mm Hg. His skin appears plethoric. His extremities are hot, with flash capillary refill and bounding pulses. Is this the same entity that is affecting the previous patient?

A 2-week-old boy presents to the ED with a 1-day history of poor feeding. On physical examination, he is difficult to arouse. His RR is 80 breaths/min, HR is 220 beats/min, and BP is undetectable. He appears cyanotic and has cold extremities and a 5-second capillary refill time. Is this the same entity as seen with the other two patients? How should you proceed?

All three scenarios describe patients in various stages of shock, the first due to hypovolemic shock, the second due to septic shock, and the third due to cardiogenic shock.

The presentation of shock may vary, depending on the cause and stage of illness, although the pathophysiology and general management are similar. Prompt recognition of shock followed by early, goal-directed therapy and frequent reassessment are paramount to a successful outcome.

Definition and Pathophysiology

Shock is a life-threatening state that occurs when oxygen and nutrient delivery are insufficient to meet tissue metabolic demands. The crisis may occur when a disease compromises any of the factors that contribute to oxygen and nutrient delivery. Familiarity with a few simple equations is key not only to understanding the myriad factors that may contribute to shock but to understanding how the body

Abbreviations

ACCM:	American College of Critical Care Medicine
ALCAPA:	anomalous left coronary artery from the pulmonary artery
ALI:	acute lung injury
ARDS:	acute respiratory distress syndrome
BP:	blood pressure
CO:	cardiac output
CVP:	central venous pressure
ECMO:	extracorporeal membrane oxygenation
ED:	emergency department
Hgb:	hemoglobin
HR:	heart rate
PALS:	Pediatric Advanced Life Support
PVR:	pulmonary vascular resistance
rhAPC:	recombinant human activated protein C
RR:	respiratory rate
SIRS:	systemic inflammatory response syndrome
SV:	stroke volume
SVR:	systemic vascular resistance

*Instructor in Pediatrics, Harvard Medical School; Pediatric Intensivist, MassGeneral Hospital for Children, Boston, Mass.
†Associate Professor of Pediatrics, Harvard Medical School; Chief, Pediatric Critical Care Medicine, MassGeneral Hospital for Children, Boston, Mass.

attempts to compensate for the condition and how the clinician may intervene to reverse shock.

Oxygen delivery (DO_2) is determined by cardiac output (CO) and the arterial content of oxygen (CaO_2):

$$DO_2 \text{ (mL/min)} = CO \text{ (L/min)} \times CaO_2 \text{ (mL/L)}$$

Cardiac output is the product of stroke volume (SV) and HR:

$$CO \text{ (L/min)} = SV \text{ (L)} \times HR/min$$

Stroke volume is determined by:

- Preload: the amount of filling of the ventricle at end-diastole
- Afterload: the force against which the ventricle must work to eject blood during systole
- Contractility: the force generated by the ventricle during systole
- Lusitropy: the degree of myocardial relaxation during diastole

Heart rate variability relies on an intact autonomic nervous system and a healthy cardiac conduction system.

Arterial oxygen content also dictates oxygen delivery and is determined by hemoglobin (Hgb), oxygen saturation (SaO_2), and the partial pressure of oxygen (PaO_2), as follows:

$$CaO_2 \text{ (ml/L)} = \{[\text{Hgb (g/dL)} \times 1.34 \text{ (mL O}_2/\text{g Hgb)} \\ \times (SaO_2/100)] + (PaO_2 \times 0.003 \text{ mL O}_2/\text{mm Hg/dL})\} \\ \times 10 \text{ dL/L}$$

For example, for a patient who has an Hgb value of 15 g/dL, PaO_2 of 100 torr, CO of 5 L/min, and SaO_2 of 98%, the DO_2 can be calculated as follows:

$$CaO_2 = \{[15 \text{ g/dL} \times 1.34 \text{ mL O}_2/\text{g Hgb} \times (98/100)] \\ + (100 \times 0.003 \text{ mL O}_2/\text{mm Hg/dL})\} \times 10 \text{ dL/L}$$

$$CaO_2 = 200 \text{ mL/L}$$

$$DO_2 = 5 \text{ L/min} \times 200 \text{ mL/L} = 1,000 \text{ mL/min}$$

It is important to recognize that oxygen is not distributed uniformly to the body. Modulation of systemic vascular resistance (SVR) in different vascular beds is one of the body's primary compensatory mechanisms to shunt blood preferentially to vital organs such as the heart and brain. In this way, an increase in SVR may maintain a normal blood pressure even in the face of inadequate oxygen delivery. In other words, hypotension need not be present for a child to be in shock.

Shock refers to a dynamic state ranging from early, compensated shock to irreversible, terminal shock. During the earliest stage of shock, vital organ function is maintained by a number of compensatory mechanisms, and rapid intervention can reverse the process. If unrecognized or undertreated, compensated shock progresses to decompensated shock. This stage is characterized by ongoing tissue ischemia and damage at the cellular and subcellular levels. Inadequate treatment leads to terminal shock, defined as irreversible organ damage despite additional resuscitation.

Classification and Clinical Presentation
Hypovolemic Shock

Hypovolemic shock is the most common form of shock occurring in children around the world. Diarrheal illnesses are the cause in most of these patients. Some other causes include bleeding, thermal injury, and inappropriate diuretic use.

Signs and symptoms of hypovolemic shock include tachycardia, tachypnea, and signs of poor perfusion, including cool extremities, weak peripheral pulses, sluggish capillary refill, skin tenting, and dry mucous membranes. Orthostatic hypotension may be an early sign. As the body's ability to compensate reaches its limit, hypotension develops, along with additional signs of hypoperfusion and end-organ damage. At this stage, the clinical findings include weak central pulses, poor urine output, mental status changes, and metabolic acidosis.

Cardiogenic Shock

Cardiogenic shock refers to failure of the heart as a pump, resulting in decreased cardiac output. This failure may be due to depressed myocardial contractility, arrhythmias, volume overload, or diastolic dysfunction. Depressed myocardial contractility may be seen with primary neuromuscular disorders or may be acquired in any number of settings, such as infection, following exposure to a toxin, or when a patient suffers a metabolic derangement such as severe hypocalcemia or hyperkalemia. Myocardial ischemia due to inadequate coronary perfusion occurs with a number of congenital cardiac lesions as well as with dysrhythmias that may compromise cardiac output severely.

Hypoplastic left heart syndrome, aortic stenosis, and coarctation of the aorta are three life-threatening congenital lesions that obstruct outflow from the left heart. Systemic outflow and coronary perfusion in these conditions depend on right-to-left flow from the pulmonary artery to the aorta via a patent ductus arteriosus. Tricuspid atresia, pulmonary atresia, and tetralogy of Fallot are three cyanotic congenital lesions that obstruct outflow from the right heart. In these lesions, adequate pulmonary blood flow depends on a left-to-right shunt

across a patent ductus arteriosus. Infants born with ductal-dependent congenital heart disease often present within the first 2 weeks after birth, by which time the ductus arteriosus has closed.

Infants born with congenital lesions resulting in significant left-to-right shunts (eg, ventricular septal defects, truncus arteriosus, and anomalous left coronary artery from the pulmonary artery [ALCAPA]) typically present between 6 weeks and 3 months of age as pulmonary vascular resistance (PVR) falls. This change in resistance results in a steal phenomenon whereby blood preferentially flows to the pulmonary bed and away from the systemic bed, leading to inadequate cardiac output. In the case of ALCAPA, as PVR falls, blood flows to the pulmonary bed and away from the myocardium. Coronary ischemia develops, resulting in poor contractility, diminished cardiac output, and life-threatening dysrhythmias.

Other types of dysrhythmias (eg, supraventricular tachycardia) infections causing myocarditis or pericarditis, and congenital cardiomyopathies can present at any time and should be part of the differential diagnosis for any child presenting with signs of poor perfusion.

Infants and children who have cardiogenic shock often present with lethargy, poor feeding, tachycardia, and tachypnea. They typically appear pale and have cold extremities and barely palpable pulses. In the case of critical coarctation of the aorta, the infant may have absent femoral pulses and a significantly lower BP in the lower extremities compared with the right upper extremity. Oliguria is present.

Initially, it may be impossible to differentiate cardiogenic shock from septic shock. Findings more specific to cardiogenic shock include a gallop rhythm, rales, jugular venous distension, and hepatomegaly. Chest radiography reveals cardiomegaly and pulmonary venous congestion. Unlike other forms of shock in which central venous pressure (CVP) is low, in cardiogenic shock, CVP is elevated above 10 cm H_2O. Although it is imperative to obtain electrocardiography and echocardiography immediately if there is any suspicion of cardiogenic shock, empiric treatment for possible septic or cardiogenic shock should not be delayed.

Two noncardiac conditions that can lead to cardiogenic shock are bilateral pneumothoraces and cardiac tamponade. Both prevent diastolic filling of the heart, which leads to decreased SV and poor CO. These disorders should be suspected in the patient presenting with signs of poor perfusion accompanied by a narrow pulse pressure and, in the case of tamponade, muffled heart tones on auscultation.

Distributive or Neurogenic Shock

Distributive shock is caused by derangements in vascular tone that lead to end-organ hypoperfusion. This outcome is seen with anaphylaxis, an immunoglobulin E-mediated hypersensitivity reaction in which mast cells and basophils release histamine, a potent vasodilator, and there is massive production of other potent vasodilators, including prostaglandins and leukotrienes. Spinal cord trauma and spinal or epidural anesthesia also can cause widespread vasoplegia due to loss of sympathetic tone. This situation sometimes is referred to as neurogenic shock. Unlike other forms of shock, patients who experience neurogenic shock exhibit hypotension without reflex tachycardia. Finally, septic shock in some children presents with vasoplegia.

Septic Shock

In 1992, the American College of Chest Physicians and the Society of Critical Care Medicine formally defined sepsis and its related syndromes. They introduced the important concept of a systemic inflammatory response syndrome (SIRS), whereby the body responds to various insults (infection, trauma, thermal injury, acute respiratory distress syndrome) with overwhelming inflammation resulting in hypo- or hyperthermia, tachycardia, tachypnea, and either an elevated or depressed white blood cell count. When SIRS is triggered by an infection, it is defined as sepsis, and when this condition is associated with organ dysfunction, it is referred to as severe sepsis. Septic shock in the pediatric population is characterized by sepsis accompanied by tachycardia and signs of inadequate perfusion. (1)

The host response to infection is one of the primary determinants of whether an individual develops septic shock. Endotoxin released by gram-negative rods and antigens presented by various other pathogens set in motion in the host an inflammatory cascade resulting in the activation of lymphocytes and the release of proinflammatory cytokines such as tumor necrosis factor, interleukin-1 (also known as endogenous pyrogen), and interleukin-6. These cytokines activate other proinflammatory cytokines and mediators of sepsis, including nitric oxide (a potent vasodilator), platelet-activating factor, prostaglandins, thromboxane, and leukotrienes. Overproduction of these mediators disrupts the delicate balance between pro- and anti-inflammatory factors and can lead to unchecked inflammation and septic shock.

"Cold" versus "warm" shock refers to the two primary clinical presentations of septic shock. "Cold" shock describes the pattern of signs and symptoms seen with

low CO and high SVR. This clinical picture includes tachycardia, mottled skin, cool extremities with prolonged capillary refill, and diminished peripheral pulses. Blood pressure may be normal. Most septic children have this presentation. In contrast, most adults and some children present in "warm" shock due to high cardiac output and low SVR. This scenario includes tachycardia, plethora, warm extremities with flash capillary refill, bounding pulses, and a widened pulse pressure. The previously noted patterns may interchange in the same patient, during the same illness. Therefore, frequent clinical assessment is required. The pattern of shock in neonates typically is more one of persistent pulmonary hypertension with right ventricular failure.

Treatments
Airway
Regardless of the cause of shock, initial resuscitation must be guided by the ABCs (airway, breathing, circulation). Supplemental oxygen should be administered immediately. Intubation is indicated for the patient whose mental status is altered, who is unable to protect his or her airway, or who has impending respiratory failure. In addition, early intubation should be considered to decrease metabolic demands, help regulate ventilation and temperature, and if needed, allow for the administration of sedation and analgesia for invasive procedures. Positive-pressure ventilation also is a powerful tool to decrease afterload to the left heart of the patient presenting in cardiogenic shock.

Patients suffering shock may develop acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). ALI and ARDS are marked by increasingly poor oxygenation ($PaO_2/FiO_2 < 300$ in ALI and $PaO_2/FiO_2 < 200$ in ARDS) and ventilation, despite escalating ventilatory support and worsening bilateral infiltrates on chest radiograph without signs of left-sided heart failure. It is important to recognize ALI or ARDS and respond appropriately with a lung-protective strategy of ventilation.

Access
Obtaining rapid vascular access with at least two wide-bore peripheral intravenous lines is critical to the timely treatment of circulatory shock. Obtaining such access can be challenging because most patients present with cool, poorly perfused extremities. If sufficient percutaneous venous access cannot be obtained quickly, the Neonatal Resuscitation Program and Pediatric Advanced Life Support (PALS) guidelines recommend placement of an umbilical venous catheter (neonates only) or intra-

osseous needle (infants and children). (2) Central venous access provides more stable, long-term access and should be obtained in patients who have fluid-refractory shock and who require titration of vasopressors and inotropes. In addition, a central venous catheter enables the clinician to monitor CVP. This measurement can be helpful for diagnosing cardiogenic shock and guiding the clinician during volume administration in all forms of shock.

Sedatives and Analgesics
Many of the sedating medications used for intubation and other invasive procedures in children have properties that may exacerbate shock. Benzodiazepines, opioids, and propofol can decrease the BP and must be used judiciously. Etomidate has been shown to induce adrenal insufficiency. The 2007 updated clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock from the American College of Critical Care Medicine (ACCM) recommend against the use of etomidate and for the use of atropine and ketamine for children (experience with ketamine use in neonates was insufficient to recommend its use in this age group). (3)

Fluid Therapy
Rapid volume resuscitation is the single most important intervention to help restore adequate organ perfusion in patients presenting with various forms of hypovolemic shock. Volume resuscitation should occur early and be goal-directed. The American Heart Association and PALS guidelines recommend an initial rapid bolus of 20 mL/kg of isotonic fluid followed by immediate reassessment and titration of additional fluid administration to goals of normal BP and perfusion (capillary refill <2 seconds, 1 mL/kg per hour urine output, normal mental status) or until signs of fluid overload occur (rales, increased work of breathing, gallop rhythm, hepatomegaly, CVP increases without additional hemodynamic improvement). Patients may require up to 200 mL/kg of isotonic fluid within the first hour, particularly in cases of vascular paralysis, to restore adequate perfusion.

The 2007 ACCM clinical practice guidelines for treatment of neonatal and pediatric septic shock recommend further that volume resuscitation beyond the first hour be titrated not only to signs of improved perfusion and normal blood pressure, but to an age-appropriate perfusion pressure (approximately 55 to 65 mm Hg), a mixed venous saturation greater than 70%, and a cardiac index greater than 3.3 L/min/m^2 and less than 6.0 L/min/m^2. The Figure provides an algorithm for goal-directed management of hemodynamic support in septic shock based on these guidelines.
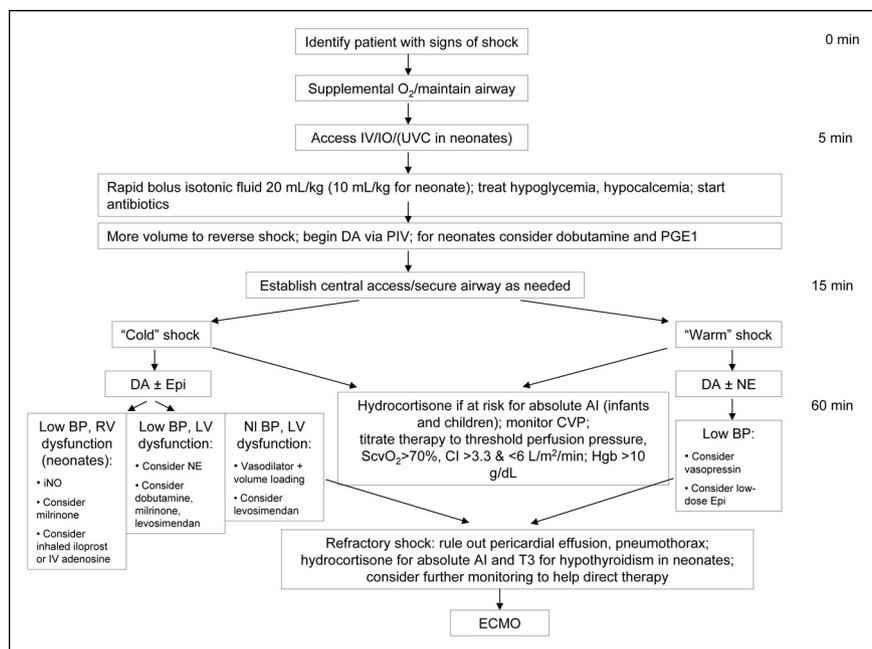
Figure. Algorithm for goal-directed management of hemodynamic support in septic shock. Adapted from the 2007 ACCM clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock. AI=adrenal insufficiency, BP=blood pressure, CI=cardiac index, CVP=central venous pressure, DA=dopamine, Dobut=dobutamine, ECMO=extracorporeal membrane oxygenation, Epi=epinephrine, IV=intravenous, iNO=inhaled nitric oxide, IO=intraosseous, LV=left ventricle, NL=normal, PGE1=prostaglandin E1, RV=right ventricle, ScvO$_2$=mixed venous oxygen saturation, UVC=umbilical venous catheter

Fluid resuscitation in infants and children who have cardiogenic shock should be approached carefully because these patients may be hypo-, hyper-, or euvolemic. In the euvolemic or hypervolemic patient, volume loading the failing heart may exacerbate pump failure and contribute to pulmonary congestion. Frequent clinical assessment is required during initial fluid resuscitation for patients who have potential cardiogenic shock. Ideally, a central venous line should be placed to monitor CVP and to assist in adjusting therapy.

Antibiotics

Broad-spectrum antibiotics based on age should be administered within the first hour of presentation when sepsis is suspected. Because it can be difficult to differentiate septic shock from cardiogenic shock in the neonate, this age group always should be treated with antibiotics. Appropriate specimens for blood, urine, and cerebrospinal fluid cultures should be obtained before antibiotic administration, although difficulty obtaining samples should not delay administration.

Crystalloid Versus Colloid

The 2007 ACCM clinical practice guidelines for treatment of neonatal and pediatric septic shock recommend either isotonic crystalloid or 5% albumin for volume resuscitation in the first hour. Beyond the first hour, the guidelines recommend crystalloid for patients who have Hgb values greater than 10 g/dL (100 g/L) and packed red blood cell transfusion for those whose Hgb values are less than 10 g/dL (100 g/L). In addition to restoring circulating volume, packed red blood cells also serve to increase oxygen-carrying capacity. Fresh frozen plasma administered as an infusion is recommended for patients who have a prolonged International Normalized Ratio.

Cardiovascular Support

In cases of fluid-refractory shock and cardiogenic shock, cardiovascular agents are necessary. The choice of agent depends largely on the underlying cause and the clinical presentation of shock. Selection of an appropriate agent is based on its known effects on inotropy, chronotropy, SVR, and PVR. The Table provides a summary of cardiovascular medications used in shock.

The 2007 ACCM guidelines recommend temporary instillation of cardiovascular agents through a peripheral intravenous line until central access can be obtained.

INOTROPIC AGENTS. Dopamine, dobutamine, and epinephrine work on beta$_1$ receptors in the myocardium to increase cytoplasmic calcium concentration and enhance myocardial contractility. Dopamine is considered first-line therapy for patients who have fluid-refractory, hypovolemic, or septic shock. However, infants younger than 12 months of age may not respond effectively to dopamine, in which case epinephrine should be considered. Epinephrine also should be added for children experiencing dopamine-refractory hypovolemic or septic shock, defined as persistent hypotension despite at least 60 mL/kg volume and dopamine infusing at 10 mcg/kg per minute. For patients who have cardiogenic shock, early inotropic support rather than large-volume resusci-

Table. **Cardiovascular Medications for the Treatment of Shock**

Medication	Site of Action	Clinical Effects	Uses in Shock
Dopamine	$\beta < \alpha$ (at higher doses), D_1, D_2	↑ inotropy, ↑ HR, ↑ SVR, ↑ PVR	• Hypovolemic shock (temporizing measure only during volume expansion) • Septic shock (all forms) • Cardiogenic shock
Dobutamine	$\beta_1 >> \beta_2$	↑ inotropy, ↑ HR, ↓ SVR, ↓ PVR	• Cardiogenic shock • Septic shock with ↓ CO, ↑ SVR
Epinephrine	$\beta > \alpha$	↑ inotropy, ↑ HR, ↑ SVR	• Septic shock with ↓ CO, ↓ SVR • Cardiogenic shock • Anaphylactic shock
Norepinephrine	$\alpha >> \beta$	↑ SVR, ↑ inotropy, ↑ HR	• Hypovolemic shock (temporizing measure only during volume expansion) • Distributive shock • Septic shock with ↑ CO, ↓ SVR
Milrinone	PDE III inhibitor	↑ inotropy, ↓ SVR, ↓ PVR, ↑ lusitropy	• Cardiogenic shock with stable BP • Septic shock with ↓ CO, ↑ SVR
Phenylephrine	$\alpha_1 > \alpha_2$	↑ SVR	• Septic shock with ↑ CO, ↓ SVR
Vasopressin	V_1, V_2	↑ SVR	• Distributive shock • Septic shock with ↑ CO, ↓ SVR
Prostaglandin E1	PGE1	Dilation of ductus arteriosus	• Cardiogenic shock in neonate with suspected ductus-dependent lesion
Nitroprusside	arteries>veins	↓ SVR, ↑ coronary perfusion	• Cardiogenic shock
Inhaled nitric oxide	pulmonary vessels	↓ PVR	• Cardiogenic shock with PHTN, RV failure
Levosimendan, enoximone	cardiac troponin C, ATP-dependent potassium channels in cardiac myocytes	↑ inotropy, ?cardioprotection	• Experimental use in cardiogenic shock

ATP=adenosine triphosphate, BP=blood pressure, CO=cardiac output, HR=heart rate, PDE=phosphodiesterase, PGE=prostaglandin E, PHTN=pulmonary hypertension, PVR=pulmonary vascular resistance, RV=right ventricle, SVR=systemic vascular resistance

tation is required. Dopamine, dobutamine, and epinephrine are acceptable therapies.

VASOPRESSORS. All of the previously discussed inotropic agents also have vasoactive properties that must be considered when selecting an appropriate agent and titrating the dose. At higher doses, for example, dopamine and epinephrine have increasing alpha-adrenergic effects, leading to peripheral vasoconstriction and increased SVR. Dobutamine, on the other hand, causes peripheral and pulmonary vasodilation due to beta$_2$-adrenergic effects. This effect may be deleterious in the patient who has low CO and low SVR but beneficial in the child presenting with low CO and high SVR or the neonate experiencing acute cardiac failure and pulmonary hypertension.

Phenylephrine is a pure alpha-agonist used to achieve systemic vasoconstriction in distributive shock and septic shock presenting with high CO and low SVR. Norepi-

nephrine is a more potent vasoconstrictor used in the same setting. At higher doses, norepinephrine also acts on beta receptors, exerting inotropic and chronotropic effects. Both drugs should be avoided in cardiogenic shock due to their powerful effect of increasing afterload.

Arginine-vasopressin and its synthetic analog, terlipressin, have been investigated for their potential use in vasodilatory shock refractory to first-line catecholamine agents. Given the limited pediatric experience with these agents for the treatment of catecholamine-refractory vasodilatory shock, no recommendation can be made at this time, and their use should be considered on a case-by-case basis. (4)

VASODILATORS. Nitroprusside is a pure vasodilator used to decrease afterload and improve coronary perfusion in neonates and children who have cardiogenic shock. Its use is limited by the need for adequate perfu-

sion pressure, which sometimes is attained by the concomitant use of dopamine or epinephrine.

Prostaglandin E1 is a potent vasodilator that relaxes smooth muscle in the ductus arteriosus to maintain patency. It should be initiated immediately in cases of suspected cardiogenic shock presenting within the first 2 weeks after birth until a ductal-dependent lesion has been ruled out by echocardiography. Prostaglandin E1 also may affect systemic vasodilation, and it may be necessary to add dopamine to maintain adequate systemic perfusion. In addition, prostaglandin E1 can cause apnea, necessitating intubation and mechanical ventilation.

Inhaled nitric oxide is a selective pulmonary vasodilator that may be considered in the treatment of cardiogenic shock involving right ventricle failure. This agent works via second messenger cGMP to relax vascular smooth muscle and produce vasodilation. With the advent of inhaled nitric oxide therapy to treat neonates who have cardiogenic shock due to persistent pulmonary hypertension, many patients now can recover without the need for extracorporeal membrane oxygenation (ECMO) support.

INODILATORS. Milrinone is a phosphodiesterase III inhibitor that has gained popularity in the treatment of cardiogenic shock due to its positive inotropic and lusitropic effects as well as its ability to reduce systemic and pulmonary afterload through vasodilation. This agent works by preventing the breakdown of cAMP, leading to an increase in intracellular calcium.

Levosimendan and enoximone are two of the newest inodilators being investigated for their use in cardiogenic shock due to their dual action as positive inotropes as well as coronary and systemic vasodilators. Unlike milrinone, these agents work by increasing myocyte sensitivity to calcium rather than by increasing intracellular concentrations of calcium. They mediate vasodilation through activation of adenosine triphosphate-dependent potassium channels in vascular smooth muscle. Activation of these channels in cardiomyocytes also may have a cardioprotective effect following an ischemic insult to the heart. (5) To date, research in children has been limited, but there have been reports of decreased demand for catecholamine infusion and improved myocardial contractility with the addition of levosimendan in neonates and children experiencing acute heart failure. (5)(6)

Corticosteroids

The 2008 Surviving Sepsis Campaign guidelines recommend consideration of stress-dose corticosteroids (hydrocortisone 50 mg/m² per 24 hours) in pediatric patients who have catecholamine-resistant septic shock and suspected or proven adrenal insufficiency. (7) In children, absolute adrenal insufficiency is considered at a random cortisol concentration less than 18 mcg/dL (496.6 nmol/L). An increase of less than 9 mcg/dL (248.3 nmol/L) following cosyntropin (synthetic derivative of corticotropin) stimulation test is considered relative adrenal insufficiency, and treatment is debatable. In neonates, adrenal insufficiency is defined as a peak cortisol value less than 18 mcg/dL (496.6 nmol/L) following cosyntropin test or basal cortisol value less than 18 mcg/dL (496.6 nmol/L) in an appropriately volume-loaded patient requiring epinephrine. In addition to patients known to have pituitary or adrenal abnormalities, patients at risk for adrenal insufficiency include those who have a history of corticosteroid use within the last 6 months and those suffering severe septic shock accompanied by purpura fulminans and Waterhouse-Friderichsen syndrome. Indications for possible corticosteroid use are the same according to the 2007 ACCM guidelines, although the suggested dose of hydrocortisone ranges from 2 mg/kg per day for stress coverage to 50 mg/kg per day to reverse shock. The data to support these recommendations are weak, and a randomized, controlled study is needed.

Corticosteroids also should be administered to patients who have distributive shock caused by anaphylaxis or spinal trauma. In addition, antihistamines may help prevent additional mast cell degranulation in anaphylactic shock.

Glycemic Control

Children presenting in shock often have a number of metabolic derangements, including hyper- or hyponatremia, hypocalcemia, and hypoglycemia. These disorders should be suspected and treated promptly. However, persistent hyperglycemia often is seen beyond the initial resuscitation of shock and has been associated with increased severity of illness and increased mortality in hospitalized patients. Tight glycemic control (<150 mg/dL [8.3 mmol/L]) in critically ill adults has been advocated. However, to date no pediatric studies have analyzed the effects of tight glycemic control with insulin. Due to a lack of data and the known risk of hypoglycemia in children dependent on intravenous glucose, the 2008 Surviving Sepsis Campaign guidelines and 2007 ACCM parameters make no recommendations beyond the use of maintenance fluid containing 10% glucose.

Activated Protein C

Severe sepsis and septic shock often are accompanied by a significant disruption of the delicate balance between pro- and anticoagulants, leading to life-threatening disseminated intravascular coagulation. Uncontrolled coagulation ultimately consumes procoagulants, resulting in bleeding. Activated protein C is an anticoagulant that helps regulate coagulation and inflammation, and it has been found to be deficient in patients experiencing septic shock. Adult studies have shown that treatment with recombinant human activated protein C (rhAPC) reduces mortality with only a small increase in risk of bleeding. However, a large randomized, controlled trial of rhAPC in children was halted prematurely after interim analysis of the data from 474 enrolled patients revealed no difference in mortality. (8) Due to the inherent risk of bleeding and the absence of proven efficacy, the Surviving Sepsis Campaign guidelines recommend against the use of rhAPC in children who have septic shock.

Extracorporeal Life Support

Although ECMO has a definitive role in the treatment of cardiogenic shock refractory to maximum pharmacologic support, its role in the treatment of refractory septic shock has been less clear. Over the past decade, more centers have begun to use ECMO as rescue therapy for septic shock with circulatory collapse and multiorgan failure. The current ECMO survival rate for term newborns who have septic shock is 80%; that for older children is 50%. Based on limited retrospective data, the Surviving Sepsis Campaign guidelines and the ACCM parameters for support of pediatric and neonatal septic shock suggest that ECMO be considered only in cases of refractory septic shock or respiratory failure that cannot be managed adequately with conventional support.

References

1. SCCM/ESICM/ACCP/ATS/SIS. International sepsis definitions conference. *Crit Care Med*. 2003;31:1250–1256
2. American Heart Association (AHA) guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) of pediatric and neonatal patients: PALS. *Pediatrics*. 2006;117:e1005–e1028
3. American College of Critical Care Medicine. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med*. 2009;37:666–688
4. Meyer S, Gortner L, McGuire W, et al. Vasopressin in catecholamine-refractory shock in children. *Anesthesia*. 2008;63:228–234
5. De Luca L, Colucci WS, Nieminen MS, et al. Evidence-based use of levosimendan in different clinical settings. *Eur Heart J*. 2006;27:1908–1920
6. Namachivayam P, Crossland DS, Butt WW, Shekerdemian LS. Early experience with levosimendan in children with ventricular dysfunction. *Pediatr Crit Care Med*. 2006;7:445–448
7. Surviving Sepsis Campaign. International guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36:296–327
8. Nadel S, Goldstein B, Williams MD, et al. Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomized controlled trial. *Lancet*. 2007;369:836–843
9. Han YY, Carcillo JA, Dragotta MA, et al. Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. *Pediatrics*. 2003;112:793–799

Summary

- Based on strong research evidence (2), if sufficient peripheral access cannot be obtained quickly, placement of an intraosseous needle should be considered in the initial management of shock.
- Based on strong research evidence (9), fluid resuscitation for hypovolemic and septic shock should start immediately and the volume be titrated to attain specific goals indicating improved perfusion.
- Based on some research evidence and consensus (3), inotropic support should be administered through a peripheral intravenous line until central access can be obtained to avoid delay in restoration of adequate perfusion pressure.
- Based on weak research evidence and consensus (7), corticosteroid therapy is suggested only for patients who have catecholamine-resistant septic shock and suspected or proven adrenal insufficiency.
- Based on strong research evidence (8), rhAPC should not be used to treat children who have septic shock associated with disseminated intravascular coagulopathy.

PIR Quiz
Quiz also available online at http://pedsinreview.aappublications.org.

1. A 3–day–old girl presents with difficulty breathing and looking dusky for the past 6 hours. The infant was born after a normal vaginal delivery and weighed 3.2 kg at birth. Examination reveals a pale/grayish–looking child whose respirations are labored, accompanied by grunting. Rectal temperature is 36.0°C, respiratory rate is 80 breaths/min, heart rate is 160 beats/min, and blood pressure is 50/30 mm Hg. Peripheral pulses are poor but equal in all extremities. Chest auscultation reveals a gallop rhythm and normal breath sounds. Her abdomen is distended, and the liver is palpated 4 cm below the right costal margin. No improvement is noted after an intravenous bolus of 20 mL/kg saline, endotracheal intubation, and mechanical ventilation with 40% oxygen. Antibiotics are administered. Pulse oximetry shows 90% oxyhemoglobin saturation. Blood gas analysis shows pH of 7.12, Pco_2 of 60 torr, and Po_2 of 74 torr. Which of the following is the next *most* appropriate step?
   A. Administer sodium bicarbonate.
   B. Begin infusion of norepinephrine.
   C. Increase FiO_2 to increase oxyhemoglobin saturation above 95%.
   D. Initiate infusion of prostaglandin E1.
   E. Initiate inhaled nitric oxide therapy.

2. A 3–month–old boy presents with difficulty breathing and looking dusky for the past 6 hours. The infant has had difficulty feeding and episodes of high–pitched cry several times a day for the past 2 weeks. Examination reveals a pale/grayish–looking child whose respirations are labored, accompanied by grunting. Rectal temperature is 36.0°C, respiratory rate is 50 breaths/min, heart rate is 160 beats/min, and blood pressure is 90/60 mm Hg. His extremities are cold, with a capillary refill time of 4 seconds. Chest auscultation reveals a gallop rhythm and bilateral wheezes. The liver is palpated 4 cm below the right costal margin. Chest radiograph shows moderate cardiomegaly and pulmonary congestion. Electrocardiography shows prominent Q waves; ST segment elevation; and inverted T waves in leads I, aVL, V5, and V6. Which of the following mechanisms is the *best* explanation for these manifestations?
   A. Closure of the ductus arteriosus.
   B. Decrease in pulmonary arterial pressure.
   C. Decreased ventricular lusitropy.
   D. Inflammation of cardiac myocytes.
   E. Pericardial tamponade.

3. A 12–year–old boy presents after being struck by a car while crossing a street. He is unresponsive, with a respiratory rate of 15 breaths/min, heart rate of 50 beats/min, and blood pressure of 76/36 mm Hg. Physical examination reveals bruises and abrasions across the neck, chest, and abdomen. Chest auscultation documents clear breath sounds with equal air entry bilaterally. Rapid sequence intubation is performed, followed by mechanical ventilation. Rapid intravenous infusion of 100 mL/kg 0.9% saline is administered over 1 hour. Repeat assessment shows a heart rate of 52 beats/min and blood pressure of 80/40 mm Hg. His extremities are warm with brisk capillary refill time. Which of the following is *most* likely associated with these findings?
   A. Abdominal solid organ injury.
   B. Adrenal insufficiency.
   C. Intracranial hemorrhage.
   D. Myocardial contusion.
   E. Sympathetic tone loss.

4. A 5–year–old girl presents with fever and decreasing responsiveness for 12 hours. She is obtunded and moaning incomprehensibly. Her rectal temperature is 40.0°C, respiratory rate is 26 breaths/min, heart rate is 136 beats/min, and blood pressure is 78/50 mm Hg. Her extremities are cool with prolonged capillary refill time. Multiple areas of ecchymosis and purpura are noted over her face, trunk, and extremities. After rapid sequence intubation, mechanical ventilation, intravenous fluid expansion with 0.9% saline (80 mL/kg), and administration of dopamine, epinephrine, and dobutamine, her blood pressure improves to 100/70 mm Hg. Her extremities, however, remain cold with poor perfusion. Which of the following is the next *most* appropriate therapy?
   A. Activated protein C.
   B. Arginine vasopressin.
   C. Hydrocortisone.
   D. Phenylephrine.
   E. 25% albumin.

Updated Information & Services	including high resolution figures, can be found at: http://pedsinreview.aappublications.org/content/31/8/311
References	This article cites 9 articles, 3 of which you can access for free at: http://pedsinreview.aappublications.org/content/31/8/311#BIBL
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Cardiovascular Disorders** http://pedsinreview.aappublications.org/cgi/collection/cardiovascular_disorders **Infectious Diseases** http://pedsinreview.aappublications.org/cgi/collection/infectious_diseases **Fluid and Electrolyte Metabolism** http://pedsinreview.aappublications.org/cgi/collection/fluid_electrolyte_metabolism **Critical Care** http://pedsinreview.aappublications.org/cgi/collection/critical_care
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: /site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: /site/misc/reprints.xhtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™