Circulatory Shock in Children: An Overview

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Objectives

After completing this article, readers should be able to:

1. Review the basic underlying pathophysiology of circulatory shock in children.
2. Characterize the physiologic derangements that occur with the different types of circulatory shock.
3. Discuss the clinical and laboratory manifestations of the acute respiratory distress syndrome and disseminated intravascular coagulation.
4. Review the general supportive measures used for initial stabilization of patients who have circulatory shock.
5. Describe some of the new therapeutic modalities directed at reversing the immunologic abnormalities that are part of the pathogenesis of circulatory failure.

Introduction

For the myriad practitioners who come into contact with critically ill children, the term "shock" has acquired a unique lexicon. For example, a call to our pediatric intensive care unit from a community emergency department physician was highlighted by the comment: "I have a lethargic 3-month-old who looks 'shocky' to me." A frantic page from one of our residents led to this exchange: "We have a 2-year-old down here who is developing diffuse petechiae—she really looks 'septic'." A 16-year-old admitted for worsening respiratory distress and an increasing oxygen requirement underwent echocardiography, which was read by the cardiologist as a "moderate-size pericardial effusion with no evidence of either right atrial compression or cardiac tamponade." Are these physicians talking about different pathophysiologic entities in their respective patients? Not really. Each simply is describing one of the protean manifestations of a diverse and complex syndrome: circulatory shock.

The primary function of the cardiovascular system is to provide oxygen and other substrate to the cells. Inextricably linked to this function is the timely and effective removal of the end products of a wide variety of metabolic processes. Circulatory shock or cardiovascular failure ensues when systemic oxygen and nutrient supply become acutely inadequate to meet the metabolic demands of the body's organ systems. The resulting anaerobic state inefficiently generates intracellular adenosine triphosphate, causing accumulation of lactic acid, an objective indicator of the functional status of the circulatory system. The effects of impaired perfusion are reversible for a period of time, but ultimately reach a point of irreversible disruption of essential biochemical processes necessary to maintain cellular integrity. This malfunction of the energy-dependent cell membrane pumps leads to intracellular edema and acidosis and eventually cell death. On a macroscopic level, this state of global hypoxemia causes multisystem organ failure and ultimately the patient's demise.

The pathophysiologic pathway to cardiovascular failure results from impairment of cardiac output (CO), systemic vascular resistance (SVR), or both. It can be caused by a variety of direct-acting or systemic insults. CO is the product of heart rate and stroke volume. Stroke volume is determined by left ventricular filling pressure and myocardial contractility. SVR represents the impedance to left ventricular ejection (afterload) as well as the "tone" of the peripheral vasculature. In the lexicon of "shock," a predominance of vasoconstriction is classified as "cold shock" and predominant vasodilation comes under

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the rubric of "warm shock." The early recognition and management of the various types of circulatory failure are crucial to restoring adequate tissue perfusion before irreparable end-organ damage and a bradycardic/asystolic cardiac arrest occurs.

This article reviews basic cardiovascular physiology in children, attempts to characterize the pathophysiologic derangements that occur with different types of circulatory shock, and examines a therapeutic regimen that comprises both general supportive measures as well as some of the newer, more specific agents being developed to reverse the immunologic and coagulation abnormalities that are being recognized increasingly as key players in the pathogenesis of circulatory failure.

Pathophysiology of Shock

A common pediatric axiom is "children are not small adults." This statement is particularly cogent when discussing total body water distribution and the compensatory cardiovascular responses of children during states of progressive circulatory insufficiency. Signs and symptoms of shock that are easily discerned in adults may remain subtle in children, leading to delays in recognition and underestimation of the severity of shock states. Although children's greater percent of total body water might be assumed to protect them from cardiovascular collapse, increased resting metabolic rate, increased insensible water loss, and decreased renal concentrating ability actually make children more susceptible to organ hypoperfusion. The early signs and symptoms of volume depletion can be subtle in children, but as the disease progresses, the physical findings become more impressive compared with an adult who has a similar degree of hypovolemia.

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The compensatory cardiovascular responses of the child to states of decreased ventricular preload, impaired myocardial contractility, and alterations in vascular tone differ from those of adults. In the pediatric patient, CO is more dependent on heart rate than on stroke volume due to the lack of ventricular muscle mass. Tachycardia is the child's principal means of maintaining an adequate CO in conditions of decreased ventricular preload, impaired myocardial contractility, or congenital heart disease categorized by an anatomic left-to-right shunt. Stroke volume is determined by ventricular filling (preload), the impedance to ventricular ejection (afterload), and intrinsic pump function (myocardial contractility).

In addition to CO, the primary regulator of blood pressure is SVR. Children maximize SVR to maintain a normal blood pressure, even with significant decreases in their CO. Increases in SVR are due to peripheral vasoconstriction mediated by the sympathetic nervous system and angiotensin. As a result, blood flow is redistributed from nonessential vascular beds such as the skin, skeletal muscles, kidneys, and splanchnic organs, to the brain, heart, lungs, and adrenal glands. Such regulation of vascular tone, either endogenously or exogenously via vasoactive medications, can normalize blood pressure independent of CO. Therefore, in pediatric patients, blood pressure is a poor indicator of cardiovascular homeostasis. The evaluation of heart rate and end-organ perfusion, including capillary refill, the quality of the peripheral pulses, mentation, urine output, and acid-base status, is more valuable than blood pressure in determining a child's circulatory status.

The relationship between heart rate, stroke volume, and SVR are of paramount importance, particularly when deciding whether to use volume resuscitation, vasopressors, or an inotropic agent as the initial therapeutic approach to the patient in circulatory failure. Although there are an almost inexhaustible number of potential causes for circulatory shock in children, the choice narrows if the clinician uses a purely physiologic classification. The more common situation, exemplified by hypovolemic or cardiogenic shock, is manifested by the presence of a low CO and compensatory elevated SVR. The second scenario, seen in distributive shock, is characterized by the presence of an elevated CO and diminished SVR. The presentation of sepsis in newborns and children is more variable than in adults and can include any combination of hemodynamic abnormalities. Table 1 outlines the hemodynamic changes and treatments of various forms of shock, which are described in more detail in the text.

The shock syndrome, when unresponsive to therapeutic interventions, is characterized by a series of increasingly ominous clinical and physiologic changes, including steadily deteriorating respiratory, hematologic,

Table 1. Pathophysiology, Signs and Symptoms, and Treatment of the Various Forms of Shock

Type of Shock	Pathophysiology	Signs and Symptoms	Treatment
Hypovolemic	↓ CO, ↑ SVR intravascular ± interstitial volume loss	↑ HR, ↓ pulses, delayed CR, hyperpnea, dry skin, sunken eyes, oliguria BP normal until late	Repeat boluses of 20 mL/kg crystalloid as indicated Blood products as indicated for acute blood loss
Septic	↑ CO, ↓ SVR (classic adult, 20% pediatric)	↑ HR, ↓ BP, ↑ pulses, delayed CR, hyperpnea, MS changes, third-spacing, edema	Repeat boluses of 20 mL/kg crystalloid; may need >60 mL/kg in first hour Consider colloid if poor response to crystalloid Pharmacologic support of BP with dopamine or norepinephrine
	↓ CO, ↑ SVR (60% pediatric)	↑ HR, normal to ↓ BP, ↓ pulses, delayed CR, hyperpnea, MS changes, third-spacing, edema	Repeat boluses of 20 mL/kg crystalloid; may need >60 mL/kg in first hour Consider colloid if poor response to crystalloid Pharmacologic support of CO with dopamine or epinephrine
	↓ CO, ↓ SVR (20% pediatric)	↑ HR, ↓ BP, ↓ pulses, delayed CR, hyperpnea, MS changes, third-spacing, edema	Repeat boluses of 20 mL/kg crystalloid; may need >60 mL/kg in first hour Consider colloid if poor response to crystalloid Pharmacologic support of CO and BP with dopamine or epinephrine
Distributive	Anaphylaxis: ↑ CO, ↓ SVR	Angioedema, rapid third-spacing of fluids, ↓ BP, respiratory distress	Repeat boluses of 20 mL/kg crystalloid as indicated Pharmacologic support of SVR with norepinephrine or phenylephrine
	Spinal Cord Injury: normal CO, ↓ SVR	↓ BP with normal HR, paralysis with loss of vascular tone	Pharmacologic support of SVR with norepinephrine or phenylephrine Fluid resuscitation as indicated by clinical status and associated injuries
Cardiogenic	↓ CO, normal to ↑ SVR	Normal to ↑ HR, ↓ pulses, delayed CR, oliguria, JVD, hepatomegaly BP normal until late in course	Pharmacologic support of CO with dobutamine, milrinone, dopamine Judicious fluid replacement as indicated clinically

CO=cardiac output, SVR=systemic vascular resistance, HR=heart rate, BP=blood pressure, CR=capillary refill, MS=mental status, JVD=jugular venous distension

and hemodynamic abnormalities. Most prominently, these changes include the development of acute respiratory distress syndrome (ARDS), manifested by the patient's need for increasing amounts of oxygen and ventilatory support. Disseminated intravascular coagulation (DIC) results in an imbalance between the clotting and fibrinolytic pathways, with concomitant anemia and thrombocytopenia. Early on, homeostatic mechanisms such as elevations in heart rate and changes in SVR can compensate effectively for circulatory insufficiency. When regulatory mechanisms become overwhelmed, however, the patient may decompensate rapidly. The appearance of hypotension in an infant or young child is worrisome and often the harbinger of full cardiopulmonary arrest. Consequently, early recognition and aggressive treatment of shock states in the pediatric age group are crucial to a successful outcome. The neurologic sequelae in children following an asystolic event, even if circulation is restored, invariably are devastating.

Classification of Shock

Hypovolemic Shock

The most common form of circulatory failure in children is hypovolemic shock. Today, in developing countries,

Table 2. Common Causes of Hypovolemic Shock in Children

Hemorrhagic
• Gastrointestinal bleeding
• Surgery
• Trauma
• Hepatic or splenic rupture
• Major vessel injury
• Intracranial bleeding
• Long bone fractures
Nonhemorrhagic
• Vomiting/diarrhea
• Heat stroke/water deprivation
• Pharmacologic (eg, diuretics)
• Burns
• Nephrotic syndrome
• Pancreatitis
• Diabetes mellitus
• Diabetes insipidus

hypovolemic shock remains a major cause of mortality in children. Fortunately, in the United States, deaths have been decreasing steadily. Hypovolemic shock may be due to a variety of insults, the two major categories being hemorrhagic and nonhemorrhagic (Table 2).

Regardless of etiology, the final common pathway to circulatory insufficiency is diminished intravascular volume. This volume reduction results in decreased systemic venous return and ventricular filling pressure (preload), yielding decreased stroke volume. Children suffering hypovolemic shock due to fluid and electrolyte losses have both intravascular and interstitial depletion. Clinical findings include sunken eyes, a sunken anterior fontanelle, dry mucous membranes, poor skin turgor, delayed capillary refill, and cool extremities. In contrast, patients afflicted with hypovolemic shock due to increased capillary permeability, such as with burns, have intravascular hypovolemia in the setting of interstitial euvolemia or hypervolemia. Their clinical presentation tends to be dominated by signs of decreased end-organ perfusion, such as mental status changes, decreased urine output, and cool, but often swollen, distal extremities. They do not exhibit classic signs of dehydration. Once again, hypotension is a late finding and may not occur until intravascular volume has decreased by 30% to 40%, reflecting failure of the child's compensatory increase in heart rate and SVR.

Septic Shock

Septic shock, with an annual incidence of 0.56 cases per 1,000 children, can present with a variety of hemodynamic abnormalities. The classic adult presentation of high CO and low SVR (warm shock) is seen in only 20% of septic pediatric patients. Up to 60% of patients have decreased CO and elevated vascular resistance (cold shock); others have a decrease in both CO and SVR. In 1992, sepsis was defined by a consensus conference of the Society of Critical Care Medicine and the American College of Chest Physicians as the systemic response to infection. (1) Severe sepsis is associated with hypotension, hypoperfusion, or organ dysfunction. Septic shock is defined as sepsis with hypotension despite adequate fluid resuscitation, combined with perfusion abnormalities (lactic acidosis, oliguria, altered mental status). Sepsis may be caused by bacterial, viral, or fungal agents. The systemic inflammatory response syndrome (SIRS) is a widespread inflammatory response that may be caused by systemic infection or some other severe insult, such as trauma, that presents similarly with hyper- or hypothermia, increased heart rate and respiratory rate, and increased white blood cell count with a left shift.

Susceptibility to infection depends on the patient's age and pre-existing medical conditions, such as immunologic disorders, neoplastic disease, neurodevelopmental disorders, cardiac disease, and the presence of indwelling catheters of any type. The incidence of sepsis is highest in infants (5.16 cases per 1,000 population annually), particularly newborns. The implementation of antepartum treatment for group B streptococcal (GBS) infection has reduced the incidence of early-onset GBS disease dramatically. Implementation of vaccines, such as against *Haemophilus influenzae* type b, has reduced significantly the number of patients who have invasive disease caused by these organisms. Further immunization programs may continue to alter the microbiologic etiology of sepsis.

Distributive Shock

Distributive (vasodilatory) shock occurs because of a loss of SVR, resulting in abnormal distribution of blood flow within the microcirculation, or functional hypovolemia. Cardiac contractility is increased initially, although CO eventually may be compromised by the lack of preload. Causes include anaphylactic and neurogenic (injury to the central nervous system [CNS]) shock.

ANAPHYLACTIC SHOCK. Anaphylactic shock is an immediate, life-threatening systemic reaction to an allergic stimulus. The stimulus may be a food, medication, or

exposure such as a bee sting, which precipitates an immunoglobulin E-mediated hypersensitivity response with massive release of cytokines from mast cells and basophils. Patients in anaphylactic shock may have respiratory distress from angioedema in addition to hypotension and hypoperfusion caused by rapid loss of vascular tone and third-spacing of intravascular volume.

NEUROGENIC SHOCK. Neurogenic shock is a rare and usually transient disorder that follows an acute injury to the CNS. The clinical presentation is unique and results from the generalized loss of sympathetic vascular and autonomic tone. Cardiac contractility usually is preserved, although CO eventually may be compromised due to the lack of venous return and preload. Consequently, the physical examination reveals hypotension in the absence of tachycardia.

Cardiogenic Shock

Cardiogenic shock in children may result from either impaired myocardial contractility, dysrhythmias, or redirected blood flow caused by congenital anatomic heart lesions in which myocardial contractility may be impaired. Congenital heart defects that present with shock are those that have left ventricular outflow tract obstruction and, rarely, those that have large left-to-right shunts. Neonates born with hypoplastic left heart syndrome may have diminished CO as the natural drop in pulmonary vascular resistance "steals" ductal-dependent right ventricular-to-systemic blood flow. Coronary insufficiency leading to decreased contractility ensues. Volume overload to the left side of the heart may result from left-to-right intracardiac shunts as in ventricular septal defect, patent ductus arteriosus, or endocardial cushion defect. However, these lesions are more likely to present with chronic heart failure. Arterial-venous malformations in neonates, when the shunt is large, may be profoundly symptomatic. Decreased myocardial contractility occurs most commonly in critical coarctation or stenosis of the aorta or in diseases of the myocardium such as myocarditis, cardiomyopathy, ischemic myocardial injury, and following cardiopulmonary bypass.

Treatment

Recognition and aggressive treatment of the various types of shock, beginning in community offices or hospitals and continued en route to a specialized pediatric intensive care unit, improve outcomes for patients. Provision of oxygen, stabilization of the airway, and establishment of vascular access are immediate goals, followed rapidly by fluid resuscitation. Supplemental oxygen should be administered to all patients, with oxygenation measured by pulse oximetry. Intubation may be required for airway stabilization when mental status changes occur to prevent imminent respiratory failure or to decrease the work of breathing and oxygen consumption.

Two large-bore peripheral intravenous catheters should be established. If peripheral access is not readily obtained, intraosseous (IO) access may be established quickly and reliably in patients of any age. In older patients, an IO needle may be placed in the distal tibia or the sternum. Subsequently, a central venous line may be required for vasoactive infusions, for central venous pressure monitoring, and to provide a more stable form of vascular access. If a child has a central venous catheter already in place (as in an oncology patient), it should be used for resuscitation.

Vigorous fluid resuscitation restores perfusion and prevents end-organ damage in hypovolemic and septic shock. Boluses of 20 mL/kg of isotonic crystalloid or colloid should be administered rapidly and repeated until perfusion improves. Patients may require 60 mL/kg or more within the first 30 to 60 minutes; often, 100 to 200 mL/kg is needed in the first few hours of resuscitation. In the absence of acute tubular necrosis or other intrinsic renal disease, urine output of 1 to 2 mL/kg per hour may be the best indicator of adequate organ perfusion. Serum calcium and blood glucose concentrations should be measured and corrected if low. Fluids should be limited only if primary cardiac dysfunction is highly suspected as the cause of the patient's shock. Blood products may be indicated for cases of hemorrhagic shock or for patients in septic shock who have evidence of DIC.

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Patients who have sepsis and remain hypotensive or poorly perfused despite aggressive fluid resuscitation and those who develop signs of pulmonary edema from fluid resuscitation require vasoactive medications. Careful as-

Table 3. Vasoactive Medications

Agent (dose range)	Site of Action	Clinical Effect
Dopamine (3 to 20 mcg/kg per min)	Beta, increasing alpha with increasing dose	Inotrope, vasoconstriction, chronotrope, increases PVR
Dobutamine (1 to 20 mcg/kg per min)	$Beta_2$>$beta_1$	Inotrope, vasodilation ($beta_2$), decreases PVR
Epinephrine (0.01 to 1.0 mcg/kg per min)	Beta>alpha	Inotrope, chronotrope, vasoconstriction
Norepinephrine (0.01 to 1.0 mcg/kg per min)	Alpha>beta	Vasoconstriction, increases SVR, inotrope, chronotrope
Phenylephrine (0.1 to 0.5 mcg/kg per min)	Alpha	Vasoconstriction, increases SVR
Amrinone (1 to 20 mcg/kg per min) Milrinone (0.25 to 1.0 mcg/kg per min)	Type III phosphodiesterase inhibitor	Inotrope, chronotrope, vasodilator
Nitroprusside (0.5 to 10 mcg/kg per min)	Vasodilator, arterial>venous	Decreases afterload
Vasopressin (0.0003 to 0.008 U/kg per min)	V_1 vascular receptor	Vasoconstriction, vasodilation of circle of Willis, stimulation of cortisol secretion

PVR=pulmonary vascular resistance, SVR=systemic vascular resistance

sessment of the child's hemodynamic status is required because children in septic shock can present with various combinations of increased or decreased CO and SVR. Vasoactive medications should be chosen based on the desired cardiac and peripheral vascular effects (Tables 1 and 3). Adrenal insufficiency should be suspected in children who display catecholamine-resistant hypotension, who have a history of CNS abnormality or steroid use, or who present with purpura fulminans. Hydrocortisone 50 mg/m^2 can be administered as an initial bolus, followed by a similar daily dose divided every 6 hours. Neonatal shock often is complicated by persistent pulmonary hypertension, which may result in right ventricular failure. Because of these differences from adults, the American College of Critical Care Medicine published guidelines for the hemodynamic support of children and newborns with septic shock. (2) These recommendations are summarized in Figs. 1 and 2.

As other measures are applied, the source of sepsis should be identified and treated as quickly as possible. The history and physical examination may reveal potential sources and should guide microbiologic evaluation and antimicrobial coverage. Whenever possible, cultures of appropriate body fluids or sites should be obtained, and aerobic and anaerobic blood cultures always should be obtained. Empiric broad-spectrum antimicrobial coverage should be chosen based on suspected sources and organisms and can be narrowed as results of cultures and sensitivities become available.

Because septic shock remains a significant cause of morbidity and mortality for patients of all ages, numerous alternative and experimental strategies, specifically those aimed at modulating the inflammatory and coagulation cascades, are being explored.

Patients in anaphylactic shock who have hypotension and hypoperfusion due to rapid loss of vascular tone and third-spacing of intravascular volume are treated with fluid and vasopressor resuscitation, as described previously. Additionally, antihistamines and steroids may slow the release of mediators and help reverse symptoms. The offending agent should be sought and further exposure prevented. Treatment of neurogenic shock consists of pharmacologic support of vascular tone and volume resuscitation, as indicated by perfusion status and the presence of any additional traumatic injuries.

Cardiogenic shock requires a careful assessment of volume status prior to initiation of fluids because patients may present with hypo-, hyper-, or euvolemia. Because of the availability of a wide and ever-expanding array of inotropic and vasoactive agents that have differing mechanisms of action (Table 3), treatment of cardiogenic shock requires a thorough understanding of the underlying pathophysiology. In children, this information is obtained best and most easily by echocardiography and serial clinical examinations.

Crystalloid Versus Colloid

Crystalloid solutions used in the resuscitation of shock in pediatric patients include 0.9% normal saline and lactated Ringer solution. The advantages of crystalloid include availability, low cost, and lack of exposure to blood products. Colloid solutions include 5% albumin, dextran, hydroxyethyl starch, and blood products. These solutions contain large molecules that are relatively imperme-

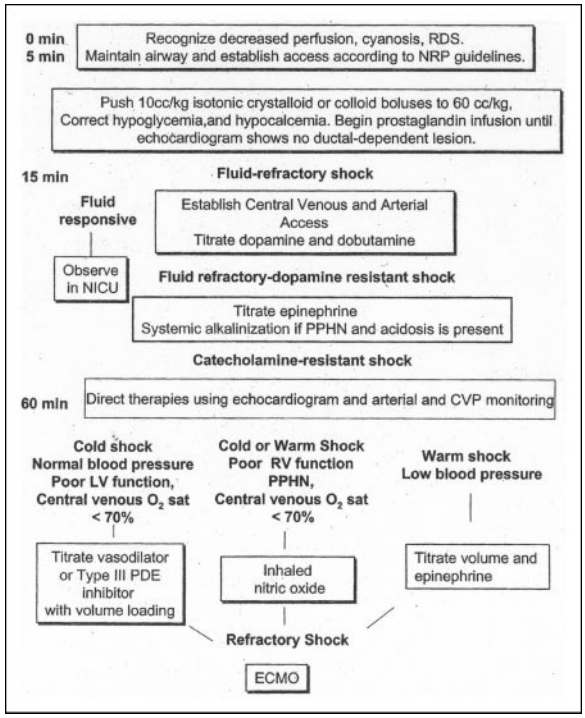

Figure 1. Recommendations for stepwise management of hemodynamic support with goals of normal perfusion and perfusion pressure (MAP-CVP) and pre- and postductal oxygen saturation difference less than 5% in near-term newborns who have septic shock. RDS=respiratory distress syndrome, NRP=Neonatal Resuscitation Program, NICU=neonatal intensive care unit, PPHN=persistent pulmonary hypertension of the newborn, CVP=central venous pressure, LV=left ventricular, RV=right ventricular, ECMO=extracorporeal membrane oxygenation, Type III PDE inhibitor=amrinone or milrinone. From Carcillo JA, Fields AI, Task Force Committee Members. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. *Crit Care Med.* 2002;30:1365–1378

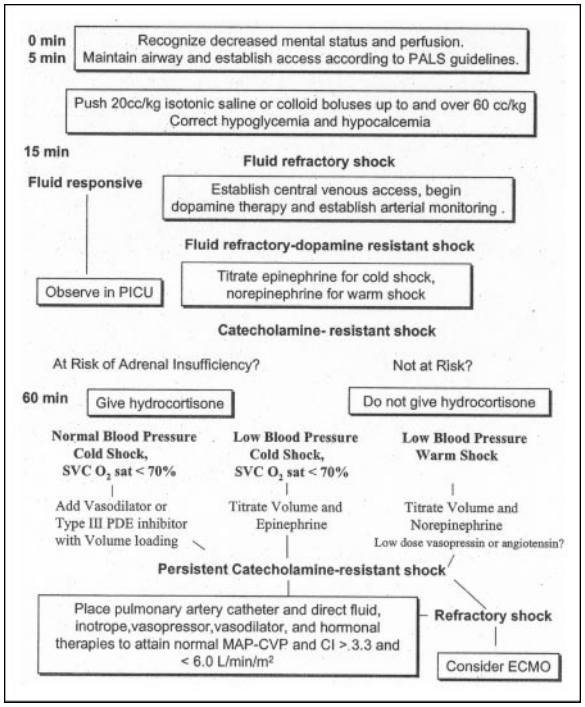

Figure 2. Recommendation for stepwise management of hemodynamic support with goals of normal perfusion and perfusion pressure (MAP-CVP) in infants and children who have septic shock. Proceed to next step if shock persists. PALS=Pediatric Advanced Life Support, PICU=pediatric intensive care unit, MAP=mean arterial pressure, CVP=central venous pressure, SVC=superior vena cava, CI=cardiac index, ECMO=extracorporeal membrane oxygenation, Type III PDE inhibitor=amrinone or milrinone. From Carcillo JA, Fields AI, Task Force Committee Members. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. *Crit Care Med.* 2002;30:1365–1378

able to the capillary membrane. This property leads to decreased extravasation and an increased percentage of the infused volume remaining intravascular. Studies in adults show that the same physiologic parameters can be achieved with either fluid, but up to three to seven times the volume may be required if crystalloid alone is used. This effect is not deleterious and actually may serve to replace extravascular losses, particularly in hypovolemic shock. In practice, unless the child has an underlying process that contributes to loss of oncotic pressure, the initial 40 to 60 mL/kg should be administered as crystalloid, followed by reassessment of interstitial volume status and consideration of colloid for additional fluid replacement.

Blood Product Replacement

Patients in shock may require transfusion of blood products to replace blood lost from trauma or active bleeding or abnormal blood component consumption, as in DIC. Ideally, blood product replacement is guided by laboratory values, and specific component therapy is provided. However, in the case of hyperacute volume loss, laboratory values may not reflect equilibration, and transfusion must be based on the patient's hemodynamic status and response to crystalloids. Crossmatched blood is preferable, but type-specific or O-negative packed red blood cells (RBCs) may be given if necessary.

Packed RBC transfusions replace volume and oxygen-carrying capacity, and 15 to 20 mL/kg should increase hemoglobin by approximately 5 g/dL (50 g/L). If bleeding continues after the patient has received several

packed RBC transfusions, replacement of platelets and clotting factors should be initiated. Platelets given in a volume of 1 U/10 kg of body weight increase the platelet count by approximately 10^5. Fresh frozen plasma (FFP) is given at a dose of 10 to 20 mL/kg to maintain normal prothrombin and partial thromboplastin times. Cryoprecipitate is indicated only in cases of documented hypofibrinogenemia (fibrinogen <100 mg/dL [1.0 g/L]) because of its increased infectious risk as a multiple donor product.

Transfusion of blood products may be associated with complications, the most common of which are transfusion reactions, hypothermia, hypocalcemia, and hyperkalemia. Transfusion reactions may consist of fever, rash, or hypotension and are treated supportively and with discontinuation of that unit of blood product. Because hypothermia may result from transfusing large volumes of cold blood, blood should be warmed before being transfused. Hypocalcemia, which may decrease myocardial contractility, can result from chelation of calcium by the citrate contained in banked blood, particularly FFP. Ionized calcium levels should be measured and calcium repleted as indicated. Hyperkalemia may result from hemolyzed RBCs in banked blood, particularly in older units. Potassium levels should be monitored, particularly in patients receiving multiple units of packed cells or in those who have pre-existing renal disease or other risk factors.

Vasoactive Medications

Children who continue to show signs of shock and hypoperfusion despite adequate volume resuscitation should be treated with vasoactive medications (Table 3) to correct the specific cardiovascular abnormalities present. The pathophysiology of various shock states guides the choice of the appropriate pharmacologic agent(s) to improve cardiovascular function. Vasoactive medications should not be withheld when clinically indicated while waiting for central venous access.

Vasopressin

Catecholamines, as described previously, are first-line therapy for septic patients who require support of myocardial contractility or vascular resistance. The utility of these agents, however, may be limited by resultant tachycardia or decreased splanchnic flow. In such patients, vasopressin may play a role. The physiologic effects of vasopressin (antidiuretic hormone) include systemic vasoconstriction, but with vasodilation of the circle of Willis and the pulmonary vasculature at higher doses. In addition, vasopressin may be synergistic with other pressors, enhancing the sensitivity of the vasculature to catecholamines. Vasopressin also stimulates cortisol secretion by increasing adrenocorticotropic hormone production and release. Studies in adults suggest that the addition of vasopressin may be useful when standard vasoactive medications are ineffective or when catecholamine toxicity is present. No randomized, placebo-controlled trials are available to support the use of vasopressin in children specifically, but anecdotal reports suggest it may be safe and effective in the dose range of 0.0003 to 0.008 U/kg per minute. (3)

Recombinant Human Activated Protein C

Infection and other systemic insults result in the release of tumor necrosis factor-alpha (TNF-alpha) as well as interleukins from activated monocytes and other cells. These cytokines recruit and further activate other cells, resulting in the release of inflammatory mediators, which cause endothelial injury and activate the coagulation cascade. This series of events can result in SIRS, ARDS, and DIC. In DIC, the balance between the procoagulant and anticoagulant systems is altered in favor of coagulation, which results in fibrin deposition and further inflammation in an effort to limit microbial dissemination. Activated Protein C (aPC) is a critical endogenous regulator of coagulation and inflammation that has the following properties: (3)

- Antithrombotic: inhibits thrombin formation by inhibiting factors V and VIII
- Profibrinolytic: inhibits plasminogen activator inhibitor activity
- Anti-inflammatory: decreases TNF-alpha production and neutrophil endothelial action

Patients in severe shock display acquired deficiencies of aPC. Treatment of adults suffering severe sepsis with recombinant human-aPC (drotrecogin alfa [activated]) at a dose of 24 mcg/kg per hour for 96 hours resulted in a 19.4% reduced risk of death, with some increased risk of bleeding (3.5%). (4) An international, multicenter phase III trial of 83 pediatric patients who had severe sepsis documented similar deficiency of endogenous protein C. (5) The risk of bleeding in children treated with aPC was similar to that of adults (4.8% for all bleeding or 2.4% for serious bleeding). Because no placebo group was included, outcomes, particularly death, could only be compared with predicted mortality. A subsequent randomized, double-blind, placebo-controlled study in children was stopped for futility after a planned interim analysis showed lack of improvement with aPC versus placebo in time to resolution of organ failure (personal communi-

cation, Eli Lilly and Company, April 21, 2005). In addition, the rate of CNS bleeding was increased in the aPC group versus the placebo group, with three of the four intracranial hemorrhages occurring in patients age 60 days or less. At present, aPC is not indicated for use in children who have sepsis.

Conclusions

Shock is a pathophysiologic state of inadequate delivery of oxygen and substrate to the body tissues. Various insults causing a disturbance either in CO or SVC can lead to this impaired perfusion. Causes include the broad categories of hypovolemic, septic, distributive, and cardiogenic shock. The presentation of shock should be viewed as a continuum, and the earlier the recognition and intervention, the better the outcome for the patient. Early signs include tachycardia, tachypnea, poor skin perfusion with mottling or delayed capillary refill, and oliguria. Hypotension is a late and ominous finding in children who are in shock. Treatment involves stabilization of the airway, provision of oxygen and adequate ventilation, establishment of vascular access, and aggressive fluid resuscitation. Further treatments, including transfusion of blood products or support with vasoactive medications, should be guided by the evolving clinical situation. New experimental therapies aimed at modulating the immune response to systemic insult show promise, particularly in septic shock.

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

10. A 1-week-old boy presents with a history of poor feeding, lethargy, and rapid breathing for 1 day. Examination reveals a sick-appearing infant whose extremities are pale and mottled. His weight is 3 kg. His vital signs are: rectal temperature, 33°C (91.4°F); heart rate, 145 beats/min; respirations, 48 breaths/min; and blood pressure, 64/40 mm Hg. His pulses are equal in all extremities. His capillary refill time is 4 seconds. Multiple petechiae are noted on his trunk and extremities. His chest is clear to auscultation, his heart sounds are normal, and no abnormality is noted on his abdominal examination. Pulse oximetry on supplemental oxygen shows 100% saturation. Intravenous access is obtained. Of the following, the *most* appropriate next step in management is:

    A. Endotracheal intubation.
    B. Infusion of 60 mL 0.9% saline over the next 20 minutes.
    C. Infusion of 60 mL fresh frozen plasma over the next hour.
    D. Infusion of dopamine at 5 mcg/kg per minute.
    E. Lumbar puncture.

11. A 2-week-old girl presents with poor feeding and rapid respirations for 1 day. Examination reveals pale, cool, and mottled extremities. Her vital signs are: rectal temperature, 38°C (100.4°F); respirations, 60 breaths/min; heart rate, 130 beats/min; and blood pressure, 80/50 mm Hg. Her pulses are equal in all extremities. Her lungs are clear to auscultation. A gallop rhythm is heard. Her liver is 4 cm below the right costal margin. Chest radiography shows mild cardiomegaly. You diagnose circulatory shock. Compared with adults, which of the following is more important in infants to increase cardiac output?

    A. Decreasing afterload.
    B. Increasing blood pressure.
    C. Increasing heart rate.
    D. Increasing myocardial contractility.
    E. Increasing preload.

12. A 10-year-old boy is brought to the emergency department after being struck by an automobile while riding his bicycle. His Glasgow coma scale score is 13. He is intubated and manually ventilated at 20 breaths/min for ineffective respirations. His neck and spine are immobilized by a cervical collar and a rigid body board. His vital signs are: rectal temperature, 36.8°C (98.2°F); heart rate, 60 beats/min; and blood pressure, 70/40 mm Hg. His air entry is equal bilaterally, and heart sounds are normal. His abdomen is soft and nontender. No bruising is noted anywhere on his body. The capillary refill time is 1 second. Following appropriate intravascular expansion with normal saline over the next hour, his heart rate is 62 beats/min and blood pressure is 72/40 mm Hg. Which of the following is the *most* likely explanation for his persistent hypotension?

    A. Fat embolism.
    B. Myocardial contusion.
    C. Rupture of solid abdominal organ.
    D. Septic shock.
    E. Spinal cord injury.

13. A 10-year-old girl has been undergoing chemotherapy for acute myelogenous leukemia. She has an indwelling catheter for long-term vascular access. Over the last 12 hours, she has developed fever and shaking chills. In the emergency department, her vital signs are: oral temperature, 39.8°C (103.6°F); heart rate, 148 beats/min; respirations, 22 beaths/min; and blood pressure, 68/34 mm Hg. Her extremities are warm and well-perfused, with a capillary refill time of 1 second. Findings on the rest of the physical examination are unremarkable. After receiving 60 mL/kg 0.9% saline, her heart rate is 130 beats/min and blood pressure is 70/36 mm Hg. Appropriate antibiotic therapy has been instituted. Intravenous infusion of which of the following is the *most* appropriate next step in her management?

    A. Dopamine.
    B. Milrinone.
    C. Norepinephrine.
    D. Phenylephrine.
    E. Recombinant human activated protein C.