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Goal-Directed Management of Pediatric Shock in the Emergency Department

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Early recognition and treatment of pediatric shock, regardless of diagnostic category, saves lives. This article emphasizes the early recognition of tachycardia, prolonged capillary refill, and hypotension at triage, and sets out a time-sensitive 3-step process, which includes establishment of emergency vascular access, goal-directed stepwise administration of fluid therapy, and infusion of epinephrine (in some cases with hydrocortisone) for reversal of shock within the first hour of arriving in the emergency department. Although the process outlined is straightforward, it requires thoughtful administrative preparation. Patients in shock must be recognized at triage and then quickly escorted to the resuscitation room, where a team approach is necessary to successfully attain all clinical goals within 1 hour. These time-sensitive goals include reversal of prolonged capillary refill and hypotension and an improved shock index. The goals and processes outlined in this article can be successfully accomplished in both community and tertiary-hospital emergency department settings with advanced planning and training.
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Shock is a state of acute energy failure in which there is not enough adenosine triphosphate (ATP) production to support systemic cellular function. Shock can be caused by lack of oxygen delivery (anemia, hypoxia, or ischemia); lack of glucose substrate delivery (glycopenia); or mitochondrial dysfunction (cellular dysoxia). Oxygen delivery is defined by the following equation: oxygen content ($1.36 \times \%$ hemoglobin $\times$ oxygen saturation $- .0003 \times Pa_{O_2}$) $\times$ flow (cardiac index [CI]). Anemic shock occurs when hemoglobin concentration is too low, hypoxic shock occurs when oxygen saturation is too low, and ischemic shock occurs when flow is too low. Glucose delivery depends on glucose levels, blood flow, and insulin for cells (eg, cardiac) with insulin-responsive glucose transportation. Glycopenic shock can be caused by hypoglycemia as well as by extreme insulin resistance.

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Although this definition of shock is logical and operationally sound, it is not very functional, because ATP measurements are not performed in patients. Therefore, the clinical state of the art is to use surrogate clinical signs and measures to diagnose and assess shock. These signs must identify the earliest stages of shock or preferably stages of pathology that occur before shock ensues. Anemia is identifiable by pallor, early compensatory tachycardia, and hemoglobin concentrations of less than 8 g/dL. Tachycardia increases cardiac output (CO) to maintain oxygen delivery despite decreased hemoglobin. Hypoxia is identified by early compensatory tachypnea and decreased Pa_{O_2}, less than 60 mm Hg. Hemoglobin remains adequately saturated until this threshold Pa_{O_2} is reached. Tachypnea causes a reduction in P_{CO_2}, which, according to the alveolar gas equation, results in a proportional increase in Pa_{O_2}. Ischemia is recognized in its earliest stages as tachycardia. Decreased flow occurs if stroke volume is decreased as a result of either hypovolemia or poor cardiac function. Flow under these conditions can be maintained by increased heart rate (CO = heart rate [HR] $\times$ stroke volume [SV]). Glycopenia

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is identified in its earliest stages by mild hypoglycemia or hyperglycemia. Implementation of therapies that reverse anemia, hypoxia, ischemia, and glycopenia before ATP deficiency occurs can prevent shock.

Shock can be diagnosed and assessed by progression of these clinical signs. Anemic shock occurs with reduced hemoglobin levels, less than 6 g/dL, and is recognized clinically by increasing heart rate to more than 98th percentile for age, altered mental status, and tachypnea. Ischemic shock is recognized as persistent tachycardia with prolongation of capillary refill to longer than 2 seconds when the systemic vasculature vasoconstricts to maintain perfusion pressure and blood flow to the central organs, including the brain and kidney. If flow continues to decrease, hypotension ensues with reduced blood flow to the brain and altered mental status. In its final stages, shock can be recognized by the presence of anion gap acidosis. At present, an anion gap of more than 16 mEq/L is the most commonly used surrogate marker for ATP depletion and energy failure. When oxygen delivery is inadequate, anaerobic metabolism occurs through glycolysis. Pyruvate is transformed to lactate, and lactic acid causes an anion gap. Glycopenic shock can be diagnosed as an anion gap larger than 16 mEq/L in the presence of hypoglycemia (inadequate substrate), hyperglycemia (insulin resistance), or euglycemia (inadequate substrate + insulin resistance). When glucose use is inadequate, an anion gap of more than 16 mEq/L is caused by organic acid intermediates produced by catabolism of protein and/or fat to fuel the Krebs cycle.

Blood infusion will increase hemoglobin and should reverse tachycardia and tachypnea in patients with anemic shock. Fluid administration and inotropic support should improve stroke volume and reverse tachycardia and reduce capillary refill to less than 2 seconds in patients with ischemic shock. Glucose administration as 10% dextrose at maintenance with use of insulin to correct hyperglycemia should attain euglycemia and resolve the anion gap in patients with glycopenic shock.

Shock, Severity of Illness Scores, and Outcomes

Shock commonly contributes to mortality in ill children. Abnormalities in physiologic parameters that represent clinical signs of shock are among the most robust predictors of death in the pediatric risk illness severity and mortality score and pediatric logistic organ dysfunction score. In the pediatric risk of mortality score (PRISM), tachycardia (>150 beats per minute for children, >160 for infants), tachypnea (>50 breaths per minute for children, >60 for infants), Pa_{O_2}/fraction of inspired oxygen (<300 mm Hg), glucose (<60 or >250 mg/dL), and bicarbonate (<16 mEq/L) all predict increased mortality. In the pediatric logistic organ dysfunction score (PELOD), hypotension (systolic blood pressure [SBP] <65 mm Hg in neonates, <75 mm Hg in infants, <85 mm Hg in children, <95 mm Hg in adolescents) and decreased mental status (Glasgow coma scale score, 7-11) predict mortality. Abnormalities in serum creatinine (≥140 μmol/L in less than 7 days of age, ≥55 μmol/L for 7 days-1 year of age; ≥100 μmol/L for 1-12 years of age; ≥140 μmol/L for older than 12 years) and prothrombin time (<60%) or international normalized ratio (INR) (≥1.4) also predict mortality. Prolonged shock and ATP depletion longer than 1 hour causes increased serum creatinine level when renal tubular cells lose their orientation and are shed into the tubules where obstruction then leads to acute renal dysfunction and failure. Prolonged low-flow shock states also cause intravascular coagulation with consumption of prothrombotic factors and ensuing prolongation of the prothrombin time.

Low CO (<2 L/min/m^2) also predicts mortality, and it can be assessed clinically by a capillary refill longer than 2 seconds, a cold toe temperature, a wide arteriovenous oxygen difference ($AVDO_2$), or by more direct measures of CO. Parr and colleagues [1] examined CO using the Fick-dilution indocyanine green dye injection technique in infants less than 6 months of age requiring cardiac surgery. They showed that mortality risk increased in this population when the CI was less than 2 L/min/m^2. Inotropic support followed by afterload reduction with nitroprusside and volume loading was effective in improving CO in these children [2]. Capillary refill shorter than 2 seconds was a clinical sign that CI was more than 2 L/min/m^2 in this population. Children with septic shock appear to require a higher CO than children with isolated cardiogenic shock. Pollack and colleagues [3] demonstrated that best outcomes are observed in these patients when the CI is between 3.3 and 6 L/min/m^2 in children with septic shock. Ceneviva and colleagues [4] demonstrated that children with septic shock could have any of 3 cardiovascular derangements: high CO (>5.5 L/min/m^2) and low systemic vascular resistance (SVR; <800 dyne · sec/cm^5), low CO (<3.3 L/min/m^2) and low SVR, or low CO and high SVR (>1200 dyne · sec/cm^5). They found that the use of vasopressors, inotropes and vasopressors, or inotropes and vasodilators, respectively, returned the CO to the favorable range. Similar to Parr et al [1], they found that patients with low CO had the highest risk of mortality.

Time-Sensitive Reversal of Clinical Signs of Shock Improves Outcomes

Time-sensitive early reversal of clinical signs of shock improves outcomes in patients. A recent adult study by Rivers and colleagues [5] demonstrated the importance of early goal-directed therapies that maintain not only blood pressure but also oxygen delivery. These investigators randomized adults presenting to the emergency

department in shock to therapies directed at achieving normal blood pressure in one group and therapies directed to normal blood pressure and a superior vena cava oxygen ($SVCO_2$) saturation of more than 70% (equivalent to a mixed venous oxygen saturation of 62%) in the other group, using packed red blood cell transfusion for patients with a hemoglobin level of less than 10 g/dL (to reverse anemic shock) and then fluids and inotropic support (to reverse ischemic shock) if the $SVCO_2$ saturation remained less than 70%. Mitochondria usually extract oxygen according to metabolic need. Oxygen delivery to mitochondria depends on oxygen-carrying capacity (percent hemoglobin), oxygen provided (oxygen saturation of hemoglobin plus oxygen dissolved in plasma), and CO. If the percentage of hemoglobin and arterial oxygen saturation are normal, only CO determines oxygen delivery. As CO decreases, and metabolic demands remain the same, the mitochondria extract more oxygen to maintain the same oxygen consumption and subsequent energy production. When this happens, the oxygen saturation of blood returning to the heart decreases. In a healthy child, the $SVCO_2$ saturation is 75%. Rivers and colleagues [5] observed that patients in the first group attained a normal blood pressure but an $SVCO_2$ saturation of only 65%, whereas those in the second treatment group maintained blood pressure and an $SVCO_2$ saturation of more than 70%. This was attained with more blood transfusion, fluid resuscitation, and inotrope use. This combination of blood pressure and oxygen delivery–directed therapy resulted in a 50% reduction in mortality as well as reversal of prothrombin time abnormalities. Resuscitation efforts directed to maintenance of blood pressure and CO improved outcome and also reversed coagulopathy.

In a second analysis of this study, the authors evaluated patients who had shock (defined as tachycardia and decreased $SVCO_2$ saturation) without normal or high blood pressure. Interestingly, these patients had higher mortality rates than patients with hypotension. When patients with tachycardia, $SVCO_2$ saturation of less than 70%, and normotension were evaluated according to treatment arms, those who received therapies directed to improving $SVCO_2$ saturation to more than 70% received more fluids and more inotropes. These patients had a reduction in the development of multiple organ failure and mortality compared with the patients not treated to maintain an $SVCO_2$ saturation of more than 70%. The authors called adult shock without hypotension "cryptic shock." Ischemic shock without hypotension can be represented by the following equation: decreased CO = normal or high mean arterial pressure (MAP) − central venous pressure (CVP)/increased SVR. Reversal of normotensive ischemic shock reduces organ failure and mortality.

Emergency departments place central lines for measurement of $SVCO_2$ saturations less frequently in children than in adults. Therefore, Han et al [6] and Orr and colleagues [7] examined early goal-directed therapy for neonatal and pediatric septic shock and "all-comer" shock in community hospital emergency departments, using prolonged capillary refill of longer than 2 seconds as a surrogate marker of decreased CO according to the report recommended by Parr et al [1] rather than decreased $SVCO_2$ saturation. Mortality and neuromorbidity increased in ascending order with tachycardia alone, hypotension with normal capillary refill, prolonged capillary refill without hypotension, and prolonged capillary refill with hypotension. Reversal of these clinical signs in the emergency department reduced mortality and neuromorbidity by more than 50%. Each hour that went by without reversal of hypotension or reduction in capillary refill to less than 2 seconds was associated with a 2-fold increased odds ratio of death from multiple organ failure.

The importance of reversing glycopenia was documented by van den Berghe [8] and colleagues in the adult surgical intensive care unit setting. These investigators gave all patients 10% dextrose at maintenance rates to meet glucose requirements. They then randomized patients to strict euglycemic control with insulin to maintain glucose levels between 80 and 120 mg/dL or to usual practice. Patients treated with insulin had a decreased serum glucose/glucose infusion rate ratio (45 vs 75) compared with those not treated with insulin and experienced a 50% reduction in mortality (3% vs 7%). All improvement in outcome was attributed to reduction in deaths from septic shock and multiple organ failure.

Administration of glucose prevents hypoglycemia, and administration of insulin for hyperglycemia guarantees delivery of the glucose into the organs with insulin-dependent glucose transporters, especially the cardiovascular system. Using anion gap acidosis as a surrogate marker of energy failure, Lin and colleagues [9] reported that elevated serum glucose/glucose infusion rate ratio predicted anion gap acidosis in children with shock. Use of insulin to decrease the serum glucose/glucose infusion rate ratio resolved anion gap acidosis in these patients.

Physiology and Pathophysiology

The Stress Response

The stress response is common in illness. Also referred to as the fight-or-flight response, it is dominated by central and sympathetic nervous system activation. The central nervous system releases adrenocorticotropic hormone, which in turn stimulates the adrenal glands to release cortisol. The sympathetic system releases epinephrine and norepinephrine. Cortisol facilitates the actions of these 2 catecholamines. Epinephrine and norepinephrine increase CO by increasing heart rate and stroke volume. These catecholamines also increase blood pressure. Epinephrine increases heart rate and contractility, whereas norepinephrine increases contractility and systemic vascular tone. To fuel these increased energy needs, glucagon is also released. It

increases glucose delivery to the Krebs cycle through activation of glycogenolysis and gluconeogenesis.

The Shock Response

The shock response occurs when the stress is no longer from fight or flight but instead from an acute decrease in oxygen delivery and/or ATP production. Severe and acute hemorrhage, hypovolemia from diarrhea, or cardiac and vascular dysfunction from sepsis, toxins, or drugs, causes the brain to orchestrate the immediate life-preserving shock response. This is somewhat similar to the stress response but more pronounced. Catecholamine and cortisol levels are higher. For example, cortisol levels can reach 30 μg/dL during stress but 150 to 300 μg/dL during shock. The angiotensin/aldosterone–antidiuretic hormone/vasopressin system is also activated to preserve intravascular fluid. The catecholamine surge induces tachycardia, and the angiotensin/aldosterone–antidiuretic hormone/vasopressin surge causes oliguria. Glucagon is also released. In concert with higher cortisol and catecholamine levels, this hormone induces hyperglycemia through gluconeogenesis but also inadvertently through insulin resistance. This shock response attains short-term survival in patients, but medical interventions are frequently needed to attain long-term survival in most. Understanding and use of physiologic principles is required to achieve long-term survival in these patients.

Cardiovascular Physiology

The cardiovascular system can be viewed similarly as follows: CO = MAP − CVP/SVR. This equation explains important pathophysiologic principles of shock. First, it guides us in the management of blood pressure. Mean arterial pressure − CVP is more important than MAP alone. According to the equation, one can theoretically have a normal MAP but no forward flow (eg, CO), for example, if the CVP is equal to MAP. When one uses fluid resuscitation to improve blood pressure, the increase in MAP must be greater than the increase in CVP. If the increase in MAP is less than the increase in CVP, the perfusion pressure is reduced. Cardiovascular agents, not more fluid, are indicated to improve blood pressure in this scenario.

This equation also guides us in management of CO or blood flow. Cardiac output can be decreased when MAP − CVP is decreased, but it can also be decreased when MAP − CVP is normal and when vascular resistance is increased. Perfusion pressure can be maintained, even in a low CO state, by increased vascular resistance (see Figure 1). Hence, patients with normal blood pressure can have inadequate CO because systemic vascular tone is high. Cardiac output can be improved in these patients with the use of inotropes, vasodilators, and volume loading.

Frank and Starling are given much deserved credit for popularizing basic principles that influence stroke volume (CO = heart rate [HR] × stroke volume [SV]).

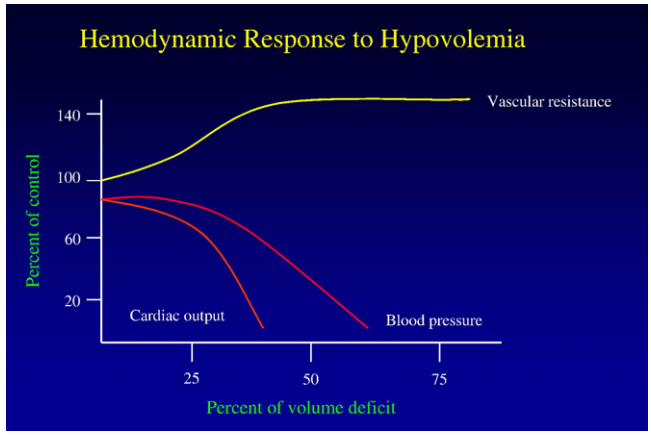

Figure 1 Systemic vasoconstriction can maintain MAP and perfusion pressure despite hypovolemia and reduced CO, so shock must be recognized as tachycardia and prolonged capillary refill before hypotension occurs.

Frank noted that cardiac muscle fibers contract more vigorously when stretched as long as the fiber is not overstretched. Starling illustrated Frank's important principle with a useful curve that plots stroke volume (y axis) against ventricular end-diastolic volume (see Figure 2). Stroke volume moves up along the curve as end-diastolic filling increases to a point where the ventricle is overfilled, and then stroke volume falls off again. Inadequate preload is defined as the end-diastolic volume below which maximum stroke volume is attained. Congestive heart failure occurs when preload or end-diastolic volume goes above this optimal range. Cardiac dysfunction is represented by downward and rightward displacement of the curve. This curve can be used to demonstrate the therapeutic principles of volume loading, inotropes, and vasodilators. Patients who have inadequate stroke volume despite adequate volume loading have reduced contractility. This is represented by a flattened Starling curve. Inotropic therapy improves the Starling curve, moving it upward and to the left. Stroke volume will be greater for any given end-diastolic volume in patients treated with inotropic therapy compared with those left untreated. Patients with severe cardiac dysfunction shock require addition of a vasodilator to improve the Starling curve, moving it further upward and to the left. Concomitant volume loading is often required to move these patients up and along their new and improved Starling curve because vasodilator therapy often reduces preload.

The relationship between afterload and stroke volume is best viewed in a modified compliance curve. As afterload or aortic diastolic pressure increases, stroke volume decreases. A heart with normal function can tolerate increased aortic diastolic pressures fairly well. However, the heart with decreased contractility does not tolerate increased afterload at all. This explains the salutary effect

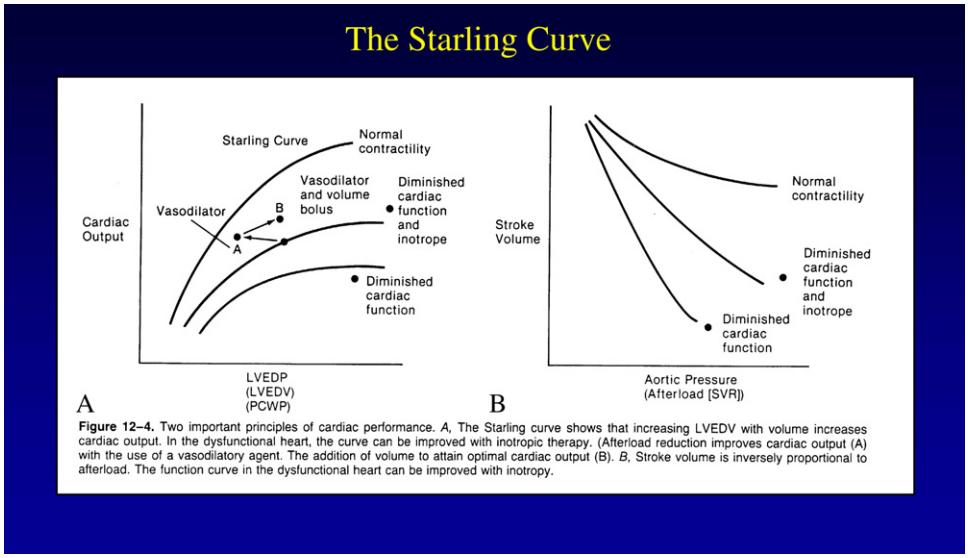

Figure 2 The Starling curve and ventricular compliance curves predict physiologic response to fluid, inotrope, vasopressor, and vasodilator therapies. Epinephrine at 0.05 μg/kg/min is the first-line inotrope in the first hour of resuscitation. It can be given peripherally until central intravenous access is attained (if given peripherally, it must be given with a faster volume infusion to get it to the heart in time).

of vasodilator therapy on the Starling curve. Afterload reduction with vasodilator therapy decreases aortic diastolic blood pressure and improves stroke volume, particularly in the poorly contracting heart. However, it is important to note that diastolic pressure is an important determinant of coronary artery perfusion pressure. Two thirds of the cardiac cycle is spent in diastole. Tachycardia, a reduced diastolic blood pressure, or increased wall stress, can reduce coronary filling. The use of vasodilator therapies should be directed to reducing wall stress (afterload reduction) without causing tachycardia or diastolic hypotension.

Coagulation Physiology

During homeostasis, blood is in an endogenously anticoagulated state. However, in prolonged states of low-flow shock, thrombosis and hypofibrinolysis occur. This occurs in part because of stasis, endothelial cell ATP depletion, and endothelial cell activation mediated by systemic inflammation. The activated endothelium is procoagulant and antifibrinolytic and causes consumption of both procoagulant and anticoagulant proteins in platelet and fibrin thrombi. This is the mechanism by which patients who die from shock commonly have thrombosis and bleeding. Prolonged prothrombin time is directly related to time to resuscitation and indirectly to the amount of fluid resuscitation administered. Rapid reversal of shock with fluid resuscitation, inotropes, and vasodilators reverses and prevents systemic disseminated intravascular coagulation and bleeding. In circumstances where resuscitation is delayed, replenishment of anticoagulant proteins such as protein C may be helpful. In the face of life- or limb-threatening thrombosis, fibrinolytic therapies can be effective to restore blood flow.

Goal-Directed Therapy

Clinical Goals

Resuscitation to clinical goals is the first priority. Patients should be resuscitated to normal mental status, normal pulse quality proximally and distally, equal central and peripheral temperatures, capillary refill of less than 2 seconds, and urine output of more than 1 mL/kg/hr. Twenty percent of blood flow goes to the brain, and 20% of blood flow goes to the kidney; therefore, clinical examination of function in these 2 organs is quite useful. These 2 organs control blood flow with autoregulation and are dependent on perfusion pressure (MAP − CVP) to maintain perfusion. Endotoxemia, cirrhosis, aminoglycosides, cisplatin, tacrolimus, and cyclosporine A induce preglomerular vasoconstriction. In these children, higher perfusion pressures are required to perfuse the kidney and maintain urine output. Distal pulse quality, temperature, and capillary refill reflect systemic vascular tone and CO. Normal capillary refill and toe temperature assure a CI of more than 2 L/min/m^2. Fluid resuscitation should be monitored using clinical findings such as palpation of the liver edge, rales being heard on auscultation, increasing tachypnea, or a wet cough, as indications to stop fluid resuscitation and begin inotrope therapy.

Hemodynamic and Oxygen Use Goals

Normal heart rate for age and normal perfusion pressure for age are the initial hemodynamic goals before central

access is attained. Fluid resuscitation can be monitored by observing effects on heart rate and MAP − CVP. The heart rate will decrease, and MAP − CVP will increase, when fluid resuscitation is effective. The heart rate will increase, and MAP − CVP will decrease, if too much fluid is given. The shock index (HR/SBP) can be used to assess the effectiveness of fluid and inotrope therapy as well. As stroke volume is increased by therapy, heart rate will decrease, and SBP will increase. The shock index will decrease. If stroke volume does not improve with resuscitation, heart rate will not decrease, SBP will not increase, and shock index will not improve.

In patients with superior vena cava central venous catheters, an oxygen saturation of more than 70% should be used as a goal. If less than 70% and anemic, the child should be transfused to achieve a hemoglobin of more than 10 g/dL. If central venous oxygen saturation is less than 70% without anemia, inotropes and vasodilators can be used to improve CO until the central venous saturation is more than 70%. The $AVDO_2$ can also be calculated with a hemodynamic goal of 3% to 5%. If it is wider than 5%, CO should be increased with therapy until the $AVDO_2$ returns to the normal range. The $AVDO_2$ is most accurate when the central venous catheter is located in the pulmonary artery. Cardiac output can be measured using the PiCCO (Philips Medical Systems, Bothell, Wash), femoral artery thermodilution, pulmonary artery catheter, or Doppler echocardiography. The goal is a cardiac index (CI) of more than 2 L/min/m^2 in cardiogenic shock and between 3.3 and 6 L/min/m^2 in septic shock.

Biochemical Goals

Many use lactate as a serum measure of anaerobic metabolism; however, lactate can be elevated by a number of conditions even in the absence of shock. These include metabolic disorders, lymphoproliferative disorders, liver failure, and sepsis. Lactate is most useful in the setting of preoperative and postoperative cardiogenic shock (although levels can be increased even in the absence of the low-flow state). For these patients, mortality risk increases as serum lactate levels rise above 2.0 mmol/L. When used as a hemodynamic goal, a level of less than 2.0 mmol/L is the target. Others use anion gap acidosis as a biochemical goal. Anion gap acidosis can be attributed to anaerobic metabolism in low-flow states and to organic acids in glycopenic states. The goal is an anion gap of less than 16 mmol/L. If patients have received bicarbonate, it will mask acidosis, but it will not mask the anion gap. Non–anion gap acidosis caused by the anion chloride is common in patients resuscitated with saline. The acidosis remains, although the anion gap has resolved, because the acidosis is caused by the administration of a strong anion (chloride) and not by energy failure. Troponin I levels can be used as a therapeutic marker for cardiac injury and dysfunction. Troponin I levels are increased with myocardial injury and become normal with resolution of myocardial injury. Creatinine clearance can be used as a therapeutic marker for renal dysfunction. Creatinine clearance will improve as renal hemodynamics improve.

Therapy

Fluids

Fluid therapy is the hallmark of shock resuscitation in infants and children. It is used to reverse the hypovolemic state and optimize the Starling curve to provide optimal flow and CO for any degree of contractility. Approximately 8% of the total blood volume is contained within the arterial side, 70% within the venous side, and 12% in the capillary beds. The total blood volume in a newborn is 85 mL/kg and 65 mL/kg in infants. Rapid resuscitation can restore circulating volume. Because of significant vasoconstricting abilities, hypotension is not seen until 50% of blood volume is lost. Therefore a rapid push of 30 to 40 mL/kg is required to restore intravascular volume. If the patient has capillary leak syndrome and if crystalloid resuscitation fluids are being used, quite-large volumes can be needed in the first hour (up to 200 mL/kg in septic shock).

Crystalloids and colloids can both be used to expand intravascular volume. Less colloids are needed than crystalloids because they redistribute to the extravascular space more slowly. In a large randomized controlled trial, albumin appeared to be most effective in patients with adult sepsis/septic shock compared with crystalloid [10]. In a randomized controlled trial in children with dengue shock, crystalloid and colloids performed equally well [11]. Some use crystalloid as their first-line fluid and follow with colloid if needed [12].

Rapid volume bolusing using a pushing technique not only restores intravascular volume, it also turns off expression of inflammation and coagulation genes. Rapid and aggressive volume expansion in the first hour improves survival in animal models and humans with shock. However, fluid administration in neonates and children should be judicious, with the potential for exacerbation of cardiogenic failure from cardiomyopathy or congenital heart disease. These children may be pushed off the Starling curve if too aggressively managed. Volumes of 10 mL/kg are recommended with monitoring of CVP/left atrial pressure/pulmonary artery occlusion pressure in these patients.

Blood

Blood is required in patients with anemic shock. Mitochondria cannot extract the last 20% of oxygen bound to hemoglobin. Under normal conditions, the mitochondria extract 25% of oxygen bound to hemoglobin. This is seen clinically by a mixed venous oxygen saturation of 75% in a healthy patient with an arterial blood oxygen saturation of 100%. In a child with 10 g/dL hemoglobin, only 8 g/dL is

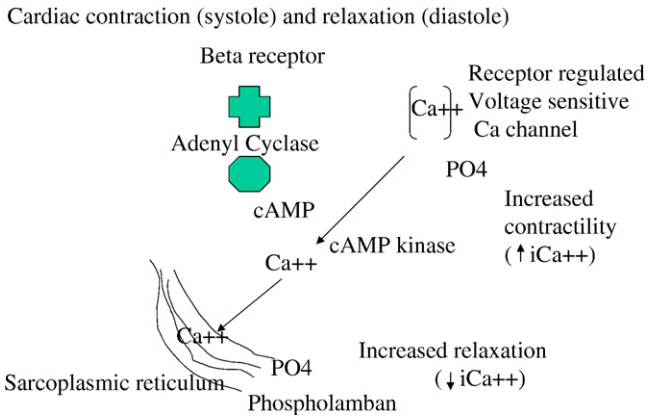

Figure 3 Inotropes such as epinephrine stimulate β-adrenergic receptors, which increase intracellular calcium during systole and reduce intracellular calcium during diastole. This is accomplished through the cAMP second messenger system. Type III phosphodiesterase inhibitors can potentiate these effects by preventing cAMP breakdown.

available for extraction (20% cannot be extracted), and 2.5 g/dL is used for oxygen extraction, leaving a surplus of 5.5 g/dL of hemoglobin. In states of hemolysis, hemolytic shock can occur when this surplus is lost or when the hemoglobin level drops below 5 g/dL. Mortality rates increase when the hemoglobin level drops below 6 g/dL. This is also true with hemorrhagic shock. Transfusion of blood is life saving in these circumstances. Whole blood is available in some parts of the world, and packed red blood cells are available in others. The usual hemoglobin concentration of packed red blood cells is 20 g/dL. Because the blood volume of the child ranges from 85 mL/kg in the newborn to 65 mL/kg in the child, 10 mL/kg of packed red cells should increase the hemoglobin concentration by approximately 2 g/dL.

Inotropes

Inotropic agents are used to increase contractility and CO. Dobutamine is a β_1-adrenergic agonist with chronotropic and inotropic actions. It is considered to be a partial agonist. In adults, dobutamine is effective; however, there is an age-specific insensitivity to the agent in children. Perkin and coworkers [13] demonstrated that children younger than 2 years have reduced response to dobutamine. At a dose of more than 10 μg/kg/min, dobutamine can lead to significant afterload reduction and, at times, hypotension. This is thought to occur because dobutamine at this dose has some α_2 receptor effects that inhibit the release of norepinephrine from the presynaptic terminal. This, in turn, reduces vascular tone.

Epinephrine is the inotrope of choice for patients who fail dobutamine therapy (see Figure 3). Adults and children who are resistant to dobutamine therapy generally respond to epinephrine [14]. Epinephrine is the natural circulating neurohormone, which is produced to increase contractility during stress and shock. Epinephrine is a β_1-, β_2-, α_1-, and α_2-adrenergic agonist. At a lower dose (0.05 μg/kg/min) the β_s-adrenergic effect negates the α_1-adrenergic effect, giving nearly pure inotrope qualities. The α_1-adrenergic effects become more prominent as the epinephrine dose approaches and exceeds 0.3 μg/kg/min. Patients with heart failure and increased SVR may be harmed by higher epinephrine doses unless it is concomitantly administered with a vasodilator or inodilator.

Vasodilators

Vasodilators are used to reduce pulmonary or systemic vascular resistance and improve CO (see Figure 4). The nitrosovasodilators depend on release of nitrosothiols, nitric oxide donors, to activate soluble guanylate cyclase and release cyclic guanosine monophosphate. Nitroprusside is a systemic and pulmonary vasodilator. An accepted starting dose is 1 μg/kg/min. Nitroglycerin has somewhat selective dose-dependent effects. It is a coronary artery vasodilator at less than 1 μg/kg/min, a pulmonary vasodilator at 1 μg/kg/min, and a systemic vasodilator at 3 μg/kg/min. Inhaled nitric oxide is a selective pulmonary vasodilator, which can be started a 5 ppm. Prostaglandins are vasodilators that increase cyclic adenosine monophosphate (cAMP) levels. Prostacyclin can be started at 3 ng/kg/min. Prostaglandin E1 can be started at 0.1 μg/kg/min and is effective in maintaining an open ductus arteriosus in newborns with ductal-dependent congenital heart disease.

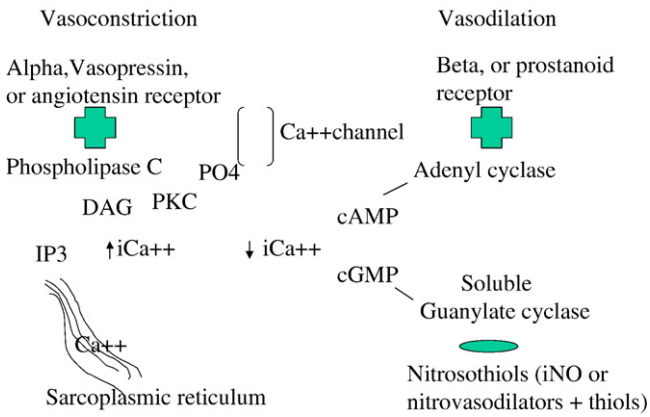

Figure 4 Vasoconstrictors and vasodilators stimulate opposing second messenger systems. α-adrenergic agonists, angiotensin, and vasopressin stimulate different receptors, which stimulate the production of inositol 1,4,4-triphosphate (IP3) and diacylglycerol (DAG), leading to increase in ionized calcium (iCa+) and contraction. β_2-agonists and vasodilator prostanoids stimulate cAMP production, and nitrosovasodilators and inhaled nitric oxide (iNO) stimulate guanosine monophosphate production. These second messengers decrease iCa+ and induce vasodilation. Types III and V phosphodiesterase inhibitors can potentiate the effect of vasodilators. PKC indicates protein kinase C.

Inodilators

The phosphodiesterase inhibitors (PDEIs) are an important class of drugs, which mediate inotropy and vasodilation by preventing hydrolysis of cAMP (type III PDEI, milrinone, amrinone, enoximone, or pentoxyfilline). When administered alone, this increase in cAMP improves contractility and diastolic relaxation and also causes vasodilation of pulmonary and systemic arterial vasculature. The interaction of PDEIs with concomitant inotropes, vasodilators, and even vasopressors can be used to therapeutic advantage in patients with shock (see Figure 3). For example, epinephrine can remain a potent, relatively pure inotrope at higher doses. For any given dose of epinephrine, type III PDEIs prevent breakdown of cAMP produced by β_1- and β_2-adrenergic stimulation. This increased intracellular cAMP inhibits the effects of α_1-adrenergic stimulation. Hence, vasoconstriction is less likely to occur at higher epinephrine doses. Norepinephrine can also become a more effective inotrope while maintaining vasopressor effectiveness when administered with a type III PDEI. The β_1 receptor production of cAMP is not hydrolyzed. Increased cardiac cAMP leads to improved contractility and relaxation. The α_1- and α_2-adrenergic effects remain the same because in the absence of β_2 stimulation, milrinone has a minimal effect on vasodilation compared with the norepinephrine mediated α-adrenergic vasoconstriction.

The major problem with presently used phosphodiesterase drugs is their relatively prolonged half-life compared with catecholamines and nitrosovasodilators. Although the latter agents are eliminated within minutes, PDEIs are not eliminated for hours. This half-life elimination is a more important consideration when organ failure exists. For example, milrinone is predominantly eliminated by the kidney, and amrinone is predominantly eliminated by the liver. When toxicities such as hypotension or tachyarrhythmias are observed, these drugs should be discontinued. Interestingly, norepinephrine has been reported as being an effective antidote for these toxicities. As mentioned, norepinephrine is an α_1-adrenergic agonist with β_1- but not β_2-adrenergic activity. It increases blood pressure (α_1-adrenergic effect) and CO (β_1-adrenergic effect) but does not exacerbate the vasodilatory effect of the PDEI (no β_2-adrenergic effect).

Isoproterenol is an important inodilator with β_1- and β_2-adrenergic activity. It is an important drug in the treatment of heart block, refractory status asthmaticus, and pulmonary hypertensive crisis with right ventricular failure. Levosimendan represents a new class of inodilators that sensitize calcium binding in the actin-tropomyosin complex, improving contractility, while also hyperpolarizing potassium channels, causing vasodilation.

Vasopressors

Phenylephrine is a pure α-adrenergic receptor agonist. Its primary role in children is for reversal of tetralogy of Fallot spells. Infants and children with tetralogy of Fallot have a thickened infundibulum, which tends to spasm and cause right-to-left blood flow through the ventricular septal defect. This spasm can be so severe that it prevents blood flow through the lung. Therapies used include oxygen and morphine to relax the infundibulum and knee-to-chest positioning to increase afterload and help generate left-to-right flow across the ventricular septal defect. When these maneuvers fail, phenylephrine is the drug of choice. Increased systemic arterial vasoconstriction leads to left-to-right shunting and perfusion of the lung. Because phenylephrine has no β-adrenergic effects, it does not increase heart rate. Hence, the heart is better able to fill. Also, the infundibular narrowing is not worsened by increased contractility.

Recently, there has been renewed interest in the use of 2 old vasopressors: angiotensin and vasopressin (see Figure 4). Angiotensin interacts with the angiotensin receptor and mediates vasoconstriction through the phospholipase C second messenger system. It has a relatively long half-life compared with catecholamines. Angiotensin also mediates blood pressure effects through increased aldosterone secretion. It is prudent to determine whether the use of angiotensin reduces CO in children with hypotension because it has no known inotropic effects. Vasopressin has been rediscovered as well. Unlike angiotensin, vasopressin is administered only in physiologic doses and is thought to improve blood pressure not only through interaction with the vasopressin receptor and the phospholipase C second messenger system but also by increasing release of adrenocorticotropic hormone and subsequent cortisol release. This vasopressor should also be used with caution because it can reduce CO in children with poor cardiac function.

Inovasopressors

Dopamine is the most commonly used dose-dependent inotrope/vasopressor. At a dose range of 3 to 10 μg/kg/min, the β_1-adrenergic receptor is stimulated. At doses of more than 10 μg/kg/min, the α_1-adrenergic receptor effect becomes predominant. As with dobutamine, there is age-specific insensitivity to the drug. Dopamine mediates much of its β_1- and α_1-adrenergic effects through release of norepinephrine from the sympathetic vesicles. Immature animals and infants less than 6 months of age do not have their full number of sympathetic vesicles. This has been proposed as one cause of reduced effectiveness of dopamine in this age group. Dopamine insensitivity can also be found in older children and adults, particularly those who have exhausted their endogenous catecholamine reserves.

Norepinephrine is effective for dopamine-resistant shock. It mediates its effects through the β_1-, α_1-, and

α_2-adrenergic receptors. Norepinephrine is always an inotrope, but its vasopressor qualities predominate even at a low dose of 0.01 μg/kg/min. Dopamine and norepinephrine have their greatest role in the maintenance of adequate perfusion pressure in children with shock. Renal function in particular can be improved by using these inovasopressors to increase blood pressure to the point where renal perfusion pressure is adequate.

Hydrocortisone

Hydrocortisone has also been rediscovered. Centrally and peripherally mediated adrenal insufficiency is increasingly common in the pediatric intensive care setting. Many children are being treated for chronic illnesses with steroids with subsequent pituitary-adrenal axis suppression. Many children have central nervous system anomalies and acquired illnesses. Some children have purpura fulminans and Waterhouse-Friderichsen syndrome. Others have reduced cytochrome P450 activity and production of cortisol and aldosterone. Interestingly, adrenal insufficiency can present with low CO and high SVR or with high CO and low SVR. The diagnosis should be considered in any child with epinephrine- or norepinephrine-resistant shock. The dose of hydrocortisone recommended in the literature is 50 mg/kg of hydrocortisone succinate followed by the same dose over 24 hours [16]. The dose recommended for stress is 2 mg/kg followed by the same dose over 24 hours. Central or peripheral adrenal insufficiency may be diagnosed in infants or children who require epinephrine or norepinephrine infusions for shock and who have a cortisol level of less than 18 mg/dL [15].

When considering the dose of hydrocortisone to be used for patients with shock, it is important to understand 2 concepts. First, hydrocortisone doses seem higher than they are because of relative glucocorticoid potency. Hydrocortisone must be multiplied by 6 to be glucocorticoid equivalent to methylprednisone and by 30 to be glucocorticoid equivalent to dexamethasone dosing. Neither methylprednisone nor dexamethasone has any mineralocorticoid effect; however, hydrocortisone has glucocorticoid and mineralocorticoid effects. This is the reason to use hydrocortisone, not methylprednisone or dexamethasone. Second, cortisol levels differ during stress and shock, so efforts to treat patients with adrenal insufficiency should be directed to achieving these levels. During surgical stress, cortisol levels increase to a 30 μg/dL range. However, during acute shock, cortisol levels can reach 150 to 300 μg/dL. Hydrocortisone infusion at 2 mg/kg/d (50 mg/m^2/d) attains cortisol levels of 20 to 30 μg/dL. Hydrocortisone infusion at 50 mg/kg/d attains cortisol levels of 150 μg/dL.

Glucose and Insulin

Glucose and insulin together function as an effective inotrope, increasing both cAMP and ATP production in the heart. The amount of glucose required to meet glucose delivery requirements is 10% dextrose at the maintenance intravenous fluid rate. The amount of insulin required can vary from 0 to more than 1 U/kg/hr, with higher concentrations of insulin required with greater insulin resistance. Higher insulin infusion rates can be associated with electrolyte abnormalities. Monitoring of phosphorous, calcium, magnesium, and potassium levels with appropriate replacement is recommended when using this therapy [16].

Atropine and Ketamine

Sedation for placement of invasive lines or for intubation can be required for patients with shock. Ketamine is not only the drug of choice for this indication, it is also an inovasopressor that turns off interleukin 6 production. Ketamine induces the endogenous release of norepinephrine. In experimental studies, ketamine improved survival from septic shock possibly because as an *N*-methyl-D-aspartic acid receptor antagonist, it turns off systemic inflammation and reverses myocardial suppression. In adults undergoing cardiopulmonary bypass surgery, ketamine infusion at 0.25 mg/kg/hr decreased systemic inflammation and improved cardiac function [17]. Ketamine allows safe anesthesia in adult septic shock. Atropine should be used in conjunction with ketamine to reduce bronchorrhea. The addition of a benzodiazepine may or may not be needed to reduce the incidence of reemergence.

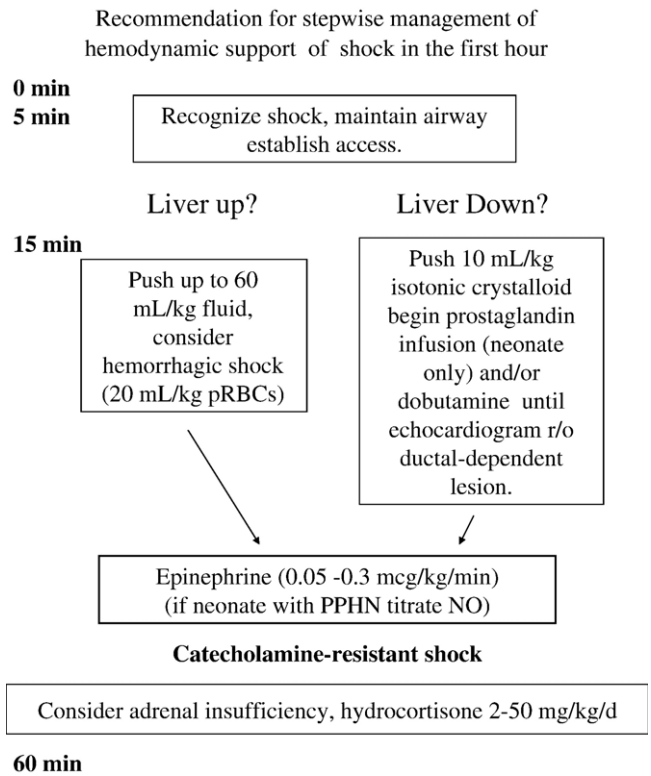

Figure 5 Early stepwise management of hemodynamic support for shock.

Table 1 The 10 steps: goal-directed management of pediatric shock in the emergency department.

1. Recognize shock at time of triage
   a. Hypotension alone with bounding pulses in warm shock
   b. Diminished peripheral perfusion alone (diminished peripheral compared with central pulses and capillary refill >2 sec) in compensated cold shock
   c. Combination of hypotension with diminished peripheral perfusion in decompensated cold shock
2. Transfer patient immediately to shock/trauma room and amass resuscitation team
3. Begin nasal oxygen and establish intravenous access using 90 sec for peripheral attempts
4. If unsuccessful after 2 peripheral attempts, consider intraosseus access
5. Palpate for hepatomegaly; auscultate for rales

6a. If liver is up and if no rales are present, push 20 mL/kg boluses of isotonic saline or 5% albumin up to 60 mL/kg in 15 min until improved perfusion or liver comes down or patient develops rales. Give 20 mL/kg pRBCs if unresponsive hemorrhagic shock [18]

6b. If liver is down, beware of cardiogenic shock, and give only 10 mL/kg bolus of isotonic crystalloid. Begin PGE_1 to maintain ductus arteriosus in all neonates

7. If capillary refill >2 sec and/or hypotension persists during fluid resuscitation, begin IO/peripheral epinephrine at 0.05 μg/kg/min
8. If at risk for adrenal insufficiency (eg, previous steroid exposure, Waterhouse Friderichsen, or pituitary anomaly) give hydrocortisone as bolus (50 mg/kg) and then as infusion titrating between 2 and 50 mg/kg/d
9. If continued shock, use atropine (0.2 mg/kg) plus ketamine (2 mg/kg) for sedation for central line placement. If mechanical ventilation is required, use atropine plus ketamine plus neuromuscular blocker (in skilled hands) for induction for intubation
10. Direct therapy to goals
    a. Capillary refill <3 sec (eg, ≤2 sec)
    b. Normal blood pressure for age
    c. Improving shock index (HR/SBP)

pRBC, packed red blood cells; PGE1, prostaglandin E1; IO, intraosseous.

Hypothermia

Hypothermia has been used for many years to allow cardiac surgery to be performed in neonates and children under low-flow or no-flow states. The rationale is that reduction in temperature reduces energy demands. Lower levels of ATP are required to provide vital cell function at lower levels of temperature. With each degree centigrade increase above 37°C, energy metabolism increases by approximately 10%. With each degree reduction, the relationship is different. At 35°C to 36°C, energy demands actually increase as shivering occurs. This temperature is met with a cardiovascular response, which includes vasoconstriction and increased blood pressure. At 34°C, energy demands normalize, but blood flow is increased in the brain. Below 33°C, energy demands decrease; however, below 30°C, ventricular arrhythmias and asystole become risk factors. During cardiopulmonary bypass, deep hypothermia, below 18°C, is required to reduce ATP requirements to levels that allow surgery. Maintenance of adequate hemoglobin concentrations and oxygen saturations are required to maintain higher oxygen content levels, and maintenance of normal temperature-corrected pH is required to maintain optimal cerebral blood flow. Glucose must also be delivered to meet ATP production demands.

In some patients with refractory shock, mild/moderate hypothermia may be helpful as a bridge to extracardiac mechanical support. If a patient is in refractory shock, and the decision is made to begin extracardiac mechanical support, there is little rationale to warm them above 34°C before commencing. Once on extracardiac mechanical support, warming can be done with the understanding that vasodilation will require volume loading of the patient.

Summary

Pediatric patients in shock must be recognized upon their presentation to the emergency department. The early recognition and expeditious treatment of shock will afford improved outcomes for these sick children. The time-sensitive goals for shock therapy include reversal of prolonged capillary refill (ie, capillary refill <2 seconds) and hypotension (normal blood pressure for age) and an improved shock index (ie, normal HR/SBP ratio for age). Anticipation in the form of advanced planning and staff training should allow timely recognition, effective therapeutic intervention, and reduced morbidity and mortality (Figure 5, Table 1).

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