Abstract:
Septic shock is a significant source of morbidity and mortality in children. Adhering to evidence-based guidelines for treatment for children with septic shock can lead to better outcomes. Initiation of treatment should begin promptly after recognition of shock in the emergency department. Elements of best practices include rapid administration of intravenous fluid for resuscitation and antibiotics in the first hour. Fluid resuscitation should be titrated to clinical and biochemical end points. If fluid resuscitation is not sufficient to reverse shock, an ionotrope or vasopressor infusion should be initiated. Steroids should be administered in patents known to be at high risk for adrenal insufficiency. All of these interventions should be achieved in the emergency department, ideally within the first hour after recognition of shock.

Keywords:
pediatric septic shock; emergency department; systemic inflammatory response syndrome

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Management of Pediatric Septic Shock in the Emergency Department

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In recent decades, there have been many advances in the treatment and prevention of septic shock in children. However, the burden of septic shock in children in the United States has been increasing. During the decade from 1995 to 2005, a study of severe pediatric sepsis in 7 US states noted an 81% increase in cases.[1] At the same time as the incidence has increased, mortality due to pediatric sepsis has decreased to less than 10%.[1–3] In the United States in 2005, the estimated health care costs associated with pediatric septic shock were nearly 5 billion dollars.[1]

In the emergency department (ED), septic shock must first be recognized. *Systemic inflammatory response syndrome* (SIRS) is defined as fever or leukocytosis in addition to tachycardia or tachypnea, or both fever and leukocytosis.[4] *Sepsis* is defined as SIRS due to a proven or suspected infection. Finally, *pediatric septic shock* is defined as sepsis with cardiovascular dysfunction. Metabolic acidosis, hypotension, elevated lactate, oliguria, prolonged capillary refill (>5 seconds), or cool extremities (>3°C difference between core and peripheral temperature) qualify as cardiovascular dysfunction.[4] Hypotension may be a late manifestation of shock in children, so hypotension is confirmatory of shock but is not required to make the diagnosis. This is in contrast to the adult definition of septic shock, which requires hypotension.[5] Clinicians must have a high index of suspicion for shock in children and search for the signs of cardiovascular dysfunction in all patients who have SIRS.

The management of sepsis has evolved greatly over the past few decades. Early, goal-directed therapy (EGDT) and effective broad-spectrum antibiotics have greatly improved outcomes. Evidence-based guidelines have made it possible for providers to deliver a common standard of care.[5,6] This article will review the initial resuscitation of children with septic shock.

PHYSIOLOGY OF SEPTIC SHOCK

Septic shock is characterized by insufficient oxygen and substrate delivery to tissues to meet their metabolic demands. This deficit in oxygen delivery leads to shunting of energy containing compounds into the less efficient anaerobic pathway. Lactic acid is a by-product of anaerobic metabolic and therefore is often used as a marker for hypoperfusion. Eventually, cell death may occur from lack of adenosine triphosphate, if shock is not corrected.

Shock is the result of cardiovascular dysfunction leading to tissue hypoperfusion. The function of the cardiovascular system is described by the classic equation $Q = P/R$, where Q is flow, P is pressure, and R is resistance. When clinically applied to the patient in shock, the equation can be transformed to CO = (MAP – CVP)/SVR, where CO is cardiac output, MAP – CVP is mean arterial pressure minus central venous pressure, and SVR is systemic vascular resistance.

Septic shock can be classified as cold or warm shock based on clinical findings.[7–9] Children in cold septic shock have cool extremities, delayed capillary refill, and poor pulses. Children with cold septic shock have low CO with elevated SVR in an attempt to maintain perfusion pressure. Conversely, warm shock is due to vasodilation and low SVR. Patients with warm shock have an increased CO and clinically are characterized by flash capillary refill, warm extremities, and bounding pulses. Historically, it was thought that most children with septic shock present with low CO and high SVR shock or cold shock.[8] More recently, it has been shown that community-acquired septic shock usually does present as cold shock; however, hospital-acquired or central line–associated septic shock is most frequently warm shock.[7,9] Children's hemodynamics can progress over time; they may switch from one shock state to another.[7,8] Clinicians must follow examination findings closely to monitor for these changes. Septic shock in adults presents differently; most adults present with warm septic shock.[10]

EARLY, GOAL-DIRECTED THERAPY

Early, goal-directed therapy consists of titration of therapies to clinical and biochemical end points. It is considered the standard of care for adults and children with septic shock and should be initiated immediately after diagnosis in the ED.

In a seminal 2001 study by Rivers et al,[11] 263 adults with septic shock were randomized to EGDT or current standard of care. Those in the EGDT arm had therapies titrated to CVP, MAP, and mixed venous saturation (SvO_2) goals. Patients who were randomized to EGDT had a mortality of 30.5% compared with 46.5% for standard of care ($P = .009$). The benefits of EGDT protocols have been reproduced many times in adults with septic shock.[12,13]

Studies have also shown benefits from EGDT in children with septic shock.[14–17] Adherence to American College of Critical Care Medicine/Pediatric Advanced Life Support (ACCM/PALS) guidelines (Figure 1) has been shown to be associated with significant decreases in mortality.[14,17] Han et al[14] in a retrospective study showed that when resuscitation of septic children was consistent with ACCM/PALS guidelines for EGDT, there was a increase of greater than 6-fold in odds of survival, after adjusting for severity of illness, compared with patients whose management was not consistent with EGDT.

FLUID RESUSCITATION

The first intervention of EGDT, after recognition of shock, is immediate and aggressive fluid resuscitation. Early and aggressive fluid resuscitation involves multiple goals. Intravenous access must be obtained quickly, ideally within the first 5 minutes of recognition of shock. An initial fluid bolus of 20 mL/kg should given be as rapidly as possible. When the fluid bolus is complete, the patient should be immediately reassessed for clinical signs of reversal of the shock state. The clinical end points to target are normal mental status, age-appropriate heart rate and blood pressure, capillary refill less than 3 seconds, palpable distal pulses, and urine output greater than 1 mL/kg/hr.[6] Adequate fluid resuscitation routinely requires 40 to 60 mL/kg in the first 15 to 60 minutes, but may require greater than 100 mL/kg for some children in septic shock. Patients should receive fluid boluses until the clinical markers of shock are corrected or the decision is made that the patient is fluid replete, and other forms of resuscitation are appropriate.

Children who receive aggressive fluid resuscitation in the first hour have significantly better

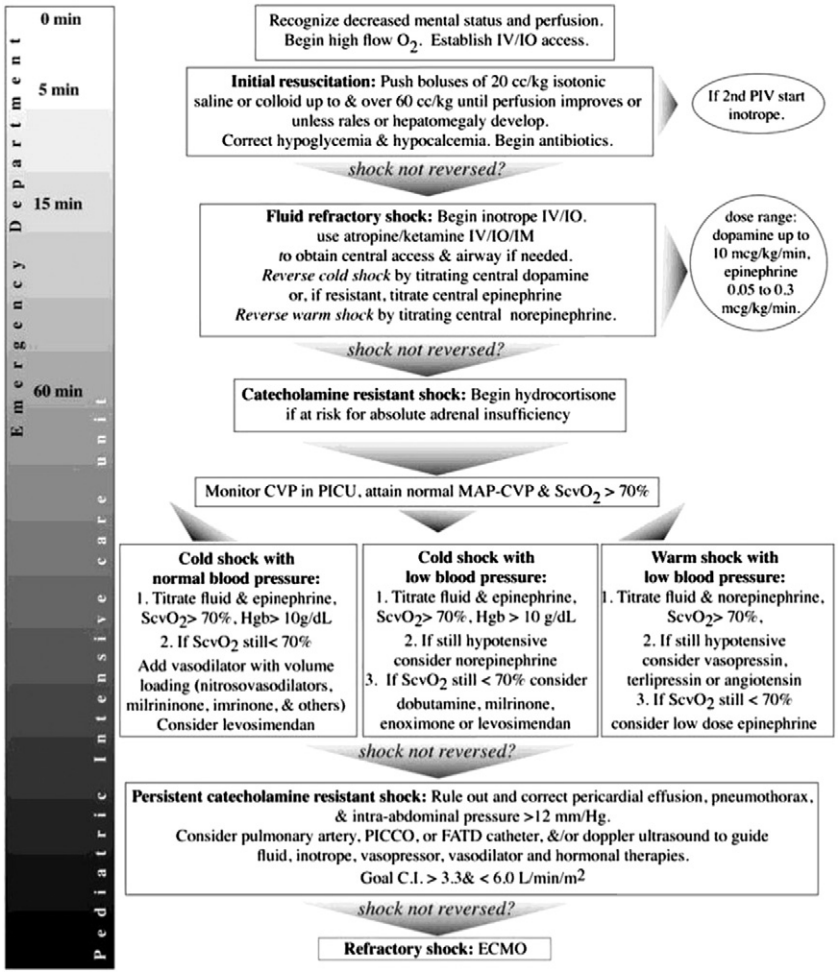

Figure 1. ACCM/PALS algorithm for the management of pediatric septic shock. Initial resuscitation in the ED in the first 60 minutes is focused on fluid resuscitation and initiation of first-line cardiovascular drug. Abbreviations: CVP, central venous pressure; MSP, mean arterial pressure; ScvO2, central venous oxygen saturation; FATD, femoral artery thermodilution; CI, cardiac index; ECMO, extracorporeal membrane oxygenation.

mortality outcomes than those who receive less fluid in the first hour or delayed fluid resuscitation.[18,19]

Clinicians may worry that high-volume fluid resuscitation can lead to respiratory distress. In a retrospective study, in which some children were resuscitated with greater than 100 mL/kg, the volume of fluid given was not associated with an increased risk of respiratory distress due to cardiogenic pulmonary edema.[18]

The volume of fluid resuscitation should be determined by clinical response rather than a predetermined limit, frequent monitoring of clinical signs of shock should include assessments for signs of heart failure. Increased work of breathing, crackles on lung examination, and hepatomegaly are common signs of heart failure in children. Heart failure can be secondary to sepsis or the patient may be in cardiogenic shock rather than septic shock.

Although several studies have demonstrated the benefits of EGDT fluid resuscitation for pediatric septic shock, a study that compared one fluid bolus to no fluid bolus in African children with septic shock demonstrated increased mortality in the group that received a fluid bolus.[20] This finding has put into question the previous decades of research supporting EGDT. Undoubtedly, there are key differences in the patient population in this study and that in developed nations. In addition, it is worth noting that the patients did not receive ACCM/PALS guideline therapy; they only received the first few minutes of resuscitation, the initial fluid bolus. These differences make it difficult to draw definitive conclusions from this study for patients in EDs in developed countries.

The decision of when to stop resuscitation with fluid and initiate a cardiovascular infusion can be difficult. The adult Surviving Sepsis Guidelines

suggest titrating fluid resuscitation to a CVP of 8 to 12 mm Hg.[5] Pediatric guidelines do not specify CVP goals.[6] However, if a patient in septic shock has a central venous line, CVP should be monitored to help with titration of fluid resuscitation. Central venous pressure is helpful for monitoring the progress of fluid resuscitation. A low CVP, less than 5 mm Hg, which does not increase after fluid bolus(es) indicates that the venous capacitance is not yet met and more fluid resuscitation will be beneficial for the patient. Central venous pressure can be intermittently or continuously measured. A patient with adequate or elevated CVP but still in shock will most benefit from a vasopressor or ionotrope. If the CVP is known, the clinician can also calculate the organ perfusion pressure of most organs (MAP – CVP). In certain clinical situations, the CVP may be elevated, in which case a higher MAP will be required in order to maintain an adequate organ perfusion pressure.

Resuscitation Fluid Options

Current recommendations for fluid resuscitation state that isotonic fluids should be used. Crystalloids, such as normal saline and lactated Ringers, or 5% albumin are acceptable resuscitation fluids.[6] Resuscitation fluid should be isotonic to blood to promote intravascular volume expansion. However, the type of resuscitation fluid used for patients in septic shock has been an active area of research. Some believe that colloids may be superior to crystalloid because of the potential to remain longer in the intravascular space.

It is not clear based on current literature if albumin or other colloids offer any benefit over crystalloids. The SAFE trial of nearly 7000 adults in intensive care units, not just for septic shock, showed no mortality or morbidity benefit of 4% albumin or normal saline for resuscitation.[21] The CRISTAL trial enrolled 2857 adults with shock; there was no difference in 28-day mortality between crystalloids and colloids, but use of colloids was associated with a 90-day mortality benefit.[22] However, there was no difference in the subgroup of patients with septic shock. It is important to note that this study included multiple different crystalloids and colloids. When broken down by specific fluids in septic patients, there were no significant differences in mortality.[22] There have been no large-scale studies in children with septic shock comparing colloids vs crystalloids.

There may be a benefit of colloid fluids in some specific patient populations. Maitland et al[23] showed a reduction in mortality from 18 to 3.6% (P = .013) in children with malarial septic shock when resuscitated with 4.5% albumin vs saline in a randomized controlled trial. Studies on dengue fever and septic shock in India have not shown benefit with colloids.[24,25]

Albumin carries a substantial cost; so much research has been done on synthetic starch colloids. Resuscitation of adults with starches has been shown to increase mortality, renal dysfunction, and need for continuous renal replacement therapy.[26–28]

Even 0.9% normal saline as a resuscitation fluid has recently been called into question. Normal saline, when compared with balanced crystalloid solutions for resuscitation, has been shown to cause more acute kidney injury, decreased renal perfusion, increased transfusions, increased infections, and increased acidosis in certain patient populations.[29–31] The question of normal saline vs balanced crystalloid solutions, which more closely imitate serum electrolyte concentrations, has not been evaluated by a prospective randomized trial in pediatric septic shock.

ANTIBIOTICS

Appropriate antibiotics should be initiated within 1 hour of recognition of septic shock.[5] Whenever possible, blood and any other clinically appropriate cultures should be obtained prior to administering antibiotics. However, inability to obtain cultures should not delay timely antibiotic administration. Delay in delivery of antibiotics has been associated with increased mortality in adults.[32,33] The odds of survival decreased by an average of 7.6% for every hour antibiotics were delayed through the first 6 hours of medical care in one study.[32] No similar study has been done in children, but in a study of pediatric patients with pneumonia requiring ventilation, longer lengths of mechanical ventilation, intensive care unit stay, and hospital stay were all found to be independently associated with delays in antibiotic administration.[34]

Children with septic shock should receive broad-spectrum antibiotics; first-line therapy is a third-generation cephalosporin and vancomycin. A third-generation cephalosporin (such as ceftriaxone) has good gram-positive and gram-negative coverage. Adding vancomycin covers both methicillin-resistant *Staphylococcus* and cephalosporin-resistant *Streptococcus pneumoniae*. This first-line treatment can be added to or adjusted depending on patient risk factors (Table 1).

CARDIOVASCULAR INFUSIONS

Many children with septic shock will respond to fluid resuscitation. However, some children will not

TABLE 1. Risk factor specifics to consider when choosing empiric antibiotics for pediatric septic shock.

Risk Factor	Pathogen(s)	Antibiotic
Neonate <4 wk old	*Listeria*	Ampicillin
Intra-abdominal source	Anaerobes	Add metronidazole or replace cephalosporin with pipercillin-tazobactam
Neutropenia or hospital-acquired	*Pseudomonas*	Fourth-generation cephalosporin, pipercillin-tazobactam, or meropenem instead of third-generation cephalosporin
Suspicion of herpes virus	Herpes	Acyclovir

reach clinical goals of age-appropriate heart rate and blood pressure and capillary refill less than 3 seconds with fluid alone. An ionotrope or vasopressor should be initiated for these patients. The first infusion should be started through peripheral access if central venous access is not available. Central access is preferred because of risk of tissue damage from peripheral intravenous catheter infiltration. However, a central venous catheter may not be easily or readily obtained, and delay in initiation of ionotropes is associated with increased mortality.[35] Pure vasopressors such as norepinephrine, phenylephrine, or vasopressin should not be infused in a peripheral intravenous whenever possible.

When choosing the appropriate ionotrope or vasoactive infusion, the clinician must consider all aspects of the patients' cardiovascular system. Cardiovascular drug infusions are selected based on the patient's cardiovascular pathophysiology and the drug effects on the vasculature (vasoconstriction or vasodilation), heart rate (chronotropy), and contractility (ionotropy).

According to guidelines, dopamine and epinephrine are the empiric first-line options for septic shock in children (Figure 1). However, choice of which ionotrope or vasopressor infusion to use can be tailored to each patient's cardiovascular status. Children who present with clinical signs of cold shock will benefit most from increased ionotropy. Dopamine and epinephrine both increase ionotropy, through β-adrenergic receptors in the heart. Conversely, children who have clinical signs of warm septic shock due to vasodilation and low SVR require vasoconstriction to reverse shock. In this case, norepinephrine is an appropriate drug. Norepinephrine mainly exerts its effects on α-adrenergic receptors in the peripheral vasculature, leading to vasoconstriction (Table 2). Adult guidelines for treatment of septic shock call for norepinephrine as the first-line therapy because of adults' propensity for presenting with warm septic shock.[5,10]

TABLE 2. Physiological effects of common first-line cardiovascular infusions.

Drug	Chronotropy	Ionotropy	Vasoconstriction
Epinephrine	+++	+++	+++
Norepinephrine	+	+	++++
Dopamine	++	++	(High dose) ++

Vasopressin is a pure vasoconstrictor that functions independently from catecholamine receptors. It can be used for catecholamine-resistant septic shock. Vasopressin has shown physiological benefits of increased urine output and improved MAP.[36] However, evidence of its benefit on other clinically important outcomes in septic shock is lacking.[37]

Vasodilatory infusions do rarely have a role in septic patients with cold shock, elevated SVR, and low CO. Milrinone, a phosphodiesterase inhibitor, causes vasodilation, thereby reducing afterload on the heart, in addition to ionotropy and luisotropy (improved cardiac relaxation). Milrinone does not have a role in the acute resuscitation of a child in septic shock.

ACCESS AND MONITORING

Central venous access allows for additional physiological and biochemical monitoring of children with septic shock. A central catheter will provide CVP and SvO_2 measurements. Mixed SvO_2 is best measured from a catheter with the tip at the junction of the superior vena cava and the right atrium.

Venous saturation is a reflection of both oxygen delivery and extraction. Oxygen delivery is described by the equation: $DO_2 = CO \times [(SaO_2 \times Hgb \times 1.36) + 0.003 \times PaO_2]$, where DO_2 is the delivery of oxygen, SaO_2 is arterial oxygen saturation, Hbg is hemoglobin concentration, and PaO_2 is arterial partial

pressure of oxygen. In a well, acyanotic child, SvO_2 should be approximately 75%, representing an oxygen extraction of 25%. A low SvO_2 (<70%) in a patient with septic shock represents a deficiency in delivery of O_2 or an excess in extraction of O_2. Most patients with septic shock and a low SvO_2 have a deficit in delivery of O_2. The above equation for oxygen delivery can help guide the clinician in management of patients in septic shock. A patient with a low SvO_2 can benefit from optimization of SaO_2 and hemoglobin. However, the most important factor is CO. Cardiac output may be enhanced through fluid resuscitation, vasopressors, ionotropes, or a combination of these therapies. Some causes of excess O_2 extraction are fever, seizures, agitation, or work of breathing. If present, these should be treated in order to decrease oxygen demand.

Normal SvO_2, obtained from an appropriately located central line, is one of the end points used to titrate therapies in EGDT.[6] In a Brazilian study by Oliveira et al,[17] children with sepsis were resuscitated according to ACCM/PALS guidelines with or without SvO_2-guided interventions. Venous saturation–guided therapy included fluid boluses and vasoactive medications to reach an SvO_2 level greater than 70%. The SvO_2-guided therapy group had a mortality of 11.8% vs 39.2% in the control group ($P < .003$).

Children who do not yet have central venous access can be managed by the clinical end points previously discussed. Capillary refill time of less than 2 seconds has been shown to have a good association with an SvO_2 level greater than > 70%, the positive predictive value is better than 95%, although it has a poor negative predictive value.[38] Therefore, correction of a prolonged capillary refill is likely to indicate an SvO_2 level greater than 70%. On the other hand, failure to correct capillary refill to less than 2 seconds does not necessarily equate to a low (<70%) SvO_2.

Arterial access allows for more precise measurement of respiratory function and closer monitoring of blood pressure and arterial lactate levels. Arterial access also permits frequent blood draws with significantly less infectious risk than a central venous catheter. Patients who are on a vasoactive drug at more than a low dose typically have an arterial catheter placed for monitoring.

MECHANICAL VENTILATION

Most patients with septic shock do not require intubation. However, there are indications for intubation in children with septic shock. Practically, intubation may be necessary for the insertion of central access in patients who are not cooperative or too unstable to receive sedation without adequate airway protection. Intubation may also be required for respiratory failure due to primary lung disease (ie, pneumonia) or secondary lung disease (ie, acute respiratory distress syndrome). Rarely, mental status may be so impaired from sepsis that intubation is indicated for airway protection.

The primary benefit of intubation and mechanical ventilation in septic shock is to unload the work of breathing of the respiratory apparatus. When respiratory distress is present, the respiratory apparatus may account for as much as 40% of O_2 consumption. By relieving the work of breathing through mechanical ventilation, more O_2 is available for the metabolic work of the vital organs, thereby improving the balance of oxygen delivery vs oxygen demand.

Intrathoracic pressures change significantly with intubation owing to a transition from negative pressure breathing to positive pressure breathing. Initially, this may cause hypotension. Increased intrathoracic pressure causes a decrease in venous return to the right ventricle; downstream, this leads to a decrease in left ventricular end diastolic volume. An underfilled left ventricle will lead to a decreased stroke volume. Cardiac output is the product of heart rate and stroke volume. Patients with sepsis are already tachycardic and therefore have little reserve to further increase heart rate to improve CO if stroke volume decreases. This will result in decreased CO and hypotension. Children should be adequately fluid resuscitated before intubation whenever possible. The second effect of positive intrathoracic pressure with mechanical ventilation is improved left ventricular ejection by a decrease in afterload. The decreased afterload will lead to an increased stroke volume, which will increase CO and ultimately oxygen delivery to tissues.

Sedation and analgesic medications for intubation of patients with septic shock should be chosen with caution. Several medications including propofol, opioids, benzodiazepines, and inhalational anesthetics can cause vasodilation and/or depression of cardiac function. The hemodynamically neutral etomidate is generally contraindicated in sepsis because of the risk of adrenal suppression.[39–41] Ketamine, a central *N*-methyl-D-aspartate receptor blocker with analgesic and sedative properties, is a good choice in hypotensive patients because it is sympathomimetic.[41–43] However, there are some data indicating that ketamine causes myocardial depression.[44]

STEROIDS

There are several situations when stress dose steroids are clearly indicated as part of the

treatment of pediatric septic shock. Patients who are currently on systemic steroids, have a recent history of systemic steroid use, have previously documented adrenal or pituitary dysfunction, or present with purpura fulminans should all be given stress dose steroids. Outside these indications, there is much debate about the use of stress dose steroids in septic shock.

Hypothalamic-pituitary-adrenal axis dysfunction is common in sepsis and may be related to severity of illness and outcomes.[45,46] Adrenal insufficiency in septic shock has been diagnosed by a single cortisol level or by corticotropin stimulation test; neither test is ideal. A significant number of patients with high or normal cortisol levels still have adrenal insufficiency on corticotropin stimulation testing.[45,46] A single cortisol level less than 10 μg/dL or an increase of less then 9 μg/dL after corticotropin stimulation is generally considered diagnostic of adrenal insufficiency.[47]

Up to one-third of children with septic shock have laboratory evidence of adrenal insufficiency.[45,48] Patients with adrenal insufficiency require more fluid, higher doses, and longer duration of catecholamines.[45] Adrenal insufficiency is associated with more severe illness in children with septic shock, but not mortality.[48,49]

It is clear that relative adrenal insufficiency is associated with worse outcomes and is common in septic shock, but it is unknown whether administration of steroids in patients in septic shock improves outcomes. In one retrospective study, the use of steroids in pediatric septic shock was associated with a decreased dose of vasoactive infusions,[50] but there was no mortality benefit. There have not been any prospective randomized trials to study this question. The largest retrospective pediatric study did not show any mortality benefit.[51] Steroid administration in pediatric septic shock was associated with increased mortality in another retrospective cohort study.[52] However, it is likely that this finding was confounded by the fact that sicker patients were more likely to be given steroids. The adult data on mortality benefit of steroids in sepsis have been mixed.[53,54]

The current recommendation from the most recent Surviving Sepsis Guidelines suggests using steroids for fluid-resistant, catecholamine-resistant shock. Testing of adrenal axis function is not recommended.[5] The ACCM guidelines recommend obtaining a baseline cortisol before initiation of steroids.

Hydrocortisone is the steroid of choice for patients with septic shock because of its glucocorticoid and mineralocorticoid properties. Stress doses of hydrocortisone are commonly in the range of 50 to 100 mg/m^2, or 2 mg/kg if the patient's height is not available. The addition of fludrocortisone to hydrocortisone has been studied retrospectively and may shorten the duration of vasopressor use.[40]

BLOOD PRODUCTS

The use of packed red blood cells as a vascular volume expander in pediatric sepsis has not been extensively studied. In adult and pediatric studies that have shown improved outcomes with EGDT, packed red blood cells were transfused when Hgb level was less than 10 g/dL and SvO_2 was less than 70%, despite resuscitation, indicating at deficiency in oxygen delivery.[11,17] Once a patient is hemodynamically stable, the transfusion threshold should be an Hgb level less than 7 g/dL, unless there is another specific indication for transfusion.[55,56]

Fresh-frozen plasma, platelets, and cryoprecipitate are not indicated empirically in patients with septic shock with or without disseminated intravascular coagulation. Patients with evidence of disseminated intravascular coagulation with clinical bleeding may benefit from fresh-frozen plasma or cryoprecipitate. A coagulation panel including fibrinogen and D-dimers will help with this decision.

SUMMARY: ADHERENCE TO GUIDELINES AND OUTCOMES OF PEDIATRIC SEPSIS

When children present to the hospital with septic shock, ED clinicians have the crucial responsibility to recognize sepsis and initiate treatment in a timely manner, thereby reducing the morbidity and mortality associated with pediatric septic shock. Despite the existence of published guidelines and data to support the benefits of EGDT, there is room for improvement. Studies in both the United Kingdom and the United States have shown adherence to published guidelines for the treatment of septic shock to be poor at referring and pediatric hospitals.[14,15,57,58]

Implementation of pediatric septic shock protocols in pediatric EDs has significantly improved adherence to guidelines and the time to delivery of care, such as fluid boluses and antibiotics.[58,59] An association with between length of hospital stay and adherence to EGDT guidelines has also been shown.[58]

As evidence builds that adherence to guidelines and institutional protocols can improve outcomes for pediatric sepsis, the goals of sepsis management will also need to focus on improving long-term health of survivors of sepsis. Survivors of critical illness are at risk for developing functional, cognitive, and psychological derangements in the months

and years afterward.[60–62] The specific risks of long-term morbidity after pediatric sepsis are not yet well delineated. In a study of patients with severe sepsis, more than one-third of children who survived experienced a decline in global physical function during the first 28 days.[63] Future efforts to improve pediatric sepsis outcomes should include attention to prevention, detection, and treatment of the long-term morbidities of survivorship.

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