HHS Public Access

Author manuscript

Minerva Pediatr. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

Minerva Pediatr. 2015 April ; 67(2): 141–158.

Initial resuscitation and management of pediatric septic shock

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Abstract

The pediatric sepsis syndrome remains a common cause of morbidity, mortality, and health care utilization costs worldwide. The initial resuscitation and management of pediatric sepsis is focused on 1) rapid recognition of abnormal tissue perfusion and restoration of adequate cardiovascular function, 2) eradication of the inciting invasive infection, including prompt administration of empiric broad-spectrum antimicrobial medications, and 3) supportive care of organ system dysfunction. Efforts to improve early and aggressive initial resuscitation and ongoing management strategies have improved outcomes in pediatric severe sepsis and septic shock, though many questions still remain as to the optimal therapeutic strategies for many patients. In this article, we will briefly review the definitions, epidemiology, clinical manifestations, and pathophysiology of sepsis and provide an extensive overview of both current and novel therapeutic strategies used to resuscitate and manage pediatric patients with severe sepsis and septic shock.

Keywords

sepsis; septic shock; resuscitation; management; critically ill children

Introduction

Sepsis is a common clinical syndrome that complicates severe infection. Characterized by immune dysregulation, systemic inflammatory response, microcirculatory derangements, and end–organ dysfunction, sepsis is a major cause of morbidity and mortality among children.[1,2] This article will briefly review the definitions, epidemiology, clinical manifestations, and pathophysiology of sepsis and provide a more extensive overview of current and novel therapeutic strategies used to manage pediatric patients with sepsis.

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Conflicts of interest: The authors report no conflicts of interest.

Congresses: None

Definitions

Working criteria to define sepsis and sepsis-associated organ failure have existed in the adult literature since a consensus conference published its recommendations in 1992.[3] In 2005, consensus definitions were published for pediatric systemic inflammatory response syndrome (SIRS) and the sepsis continuum to standardize enrollment into observational studies and clinical trials for children.[4] Although these definitions may also help to guide clinical practice, they should not supplant a clinical concern for sepsis in absence of meeting the defined cut-points discussed below.

Pediatric SIRS is defined as the presence of at least two abnormalities in temperature, heart rate (bradycardia or tachycardia), respiratory rate, or leukocyte count, one of which must be abnormal temperature or leukocyte count (Table 1). Unlike in adults, pediatric normal values for heart rate, respiratory rate, and leukocyte count vary substantially with age and thus the consensus conference identified age-specific criteria for the SIRS criteria (Table 2). Recently, new thresholds for heart rate and respiratory rate have been proposed for pediatric SIRS based on normative values from a systematic review of observational studies, reflecting the challenge of using concrete cut-points to distinguish normal from abnormal physiology.[5] Sepsis is defined as SIRS in the presence of a suspected or known invasive infection. Severe sepsis is defined as sepsis with the presence of one of the following - cardiovascular dysfunction, acute respiratory distress syndrome (ARDS), or two or more other organ dysfunctions. Septic shock is defined as sepsis and cardiovascular organ dysfunction (Table 1). Table 3 lists the criteria used to define cardiovascular and other organ dysfunctions.

Epidemiology

Pediatric severe sepsis accounts for over 75,000 hospitalizations with an estimated 8–10% mortality and $4.8 billion in healthcare costs in the United States.[1,2,6] Several recent studies have demonstrated that the prevalence of pediatric severe sepsis is on the rise.[7,8] Hartman et al. reported an 81% increase in the number of children hospitalized with severe sepsis between 1995 and 2000 and an increase of 45% between 2000 and 2005.[2] The population-based incidence also increased from 0.56 per 1,000 children in 1995 to 0.89 per 1,000 children in 2005.[2]

Sepsis is the tenth leading cause of death in the United States.[1] The overall case-fatality rate for all cases of pediatric severe sepsis requiring hospitalization was estimated at 8.9% in 2005, a decrease from 10.3% in 1995.[2] The highest mortality rates occur in infants less than 1 year-old.[2] However, for children requiring admission to a pediatric intensive care unit for severe sepsis or septic shock, mortality rates up to 10–25% have been reported.[7–9]

Clinical Manifestations

The clinical presentation of septic shock in children is more variable than in adult patients. Although most adults and some adolescents typically exhibit “warm shock” – a state of low systemic vascular resistance (SVR) and normal or increased cardiac output (CO)--neonates and young children more commonly present with “cold shock” -- a state of elevated SVR

and low cardiac output with cold extremities and delayed capillary refill. This important developmental difference reflects the inability of infants and young children to increase heart rate and cardiac stroke volume to the same extent as adults. Consequently, vasoconstriction resulting in "cold shock" is the predominant response to a decrease in cardiac output in pediatric septic shock, with hypotension manifesting as a relatively late finding in young children.[10]

Microbiology

A wide array of infectious pathogens has been implicated in pediatric sepsis, although bacteria, including gram-positive and gram-negative organisms, remain the most common.[2] *Staphylococcus* and *Streptococcus* species are the most frequently identified bacteria, with *Meningococcus*, *Haemophilus influenza*, *Pseudomonas*, *Escherichia Coli*, and *Klebsiella* species also commonly identified.[2] Viral pathogens, such as respiratory syncytial virus, influenza, parainfluenza, and adenovirus, can manifest as severe sepsis or septic shock, although these viruses tend to cause lower mortality rates than bacterial sepsis.[2] Fungal infections, particularly *Candida* species, can lead to sepsis especially in patients with known risk factors, including indwelling mechanical devices, immunocompromised conditions, and malignancies.[2] The most common site of infection in children is respiratory, followed by bacteremia, abdominal, device related, genitourinary, and central nervous system infections.[2] The proportion of patients without a documented pathogenic organism or clear source of infection, often referred to as "culture-negative sepsis", occurs in up to 40–50% of cases.[2]

Pathophysiology

The pathophysiology of sepsis is complex and has been previously reviewed in detail. In brief, the systemic manifestations of severe sepsis and septic shock are largely attributable to a dysregulated immune response to an invasive infection.[11] Although the initial inflammatory response may be an appropriate and protective reaction to a pathogen, the resulting systemic immuno-inflammatory cascade leads to generalized vascular dysfunction, increased microvascular permeability, and polyclonal leukocyte activation remote from the site of the initial infectious insult.[11] Release of both pro- and anti-inflammatory mediators ultimately leads to the cellular metabolic derangements and progressive multiple organ dysfunction characteristic of the sepsis syndrome.[11]

Initial Resuscitation

The initial resuscitation of the child with suspected severe sepsis or septic shock requires several key components and current sepsis guidelines recommend a protocolized approach.[12] For a patient with suspected sepsis—that is, SIRS with concern for an invasive infection—a rapid assessment of perfusion should focus on heart rate, blood pressure, capillary refill, quality of peripheral and central pulses, and mental status. In patients with signs of impaired perfusion, intravenous access should be promptly obtained in order to begin rapid administration of fluids and parenteral antibiotics. Initial evaluation and resuscitation should occur irrespective of patient location (emergency department, intensive care unit, general ward), even if it is clear that transfer to a higher level of care will be

needed. In addition, a comprehensive laboratory evaluation, including a complete blood count, electrolytes, renal and liver function tests, coagulation panel and fibrinogen, lactate, and blood and other indicated cultures and microbiological specimens, should be obtained. Fluid resuscitation should continue with the goal to restore tissue oxygen delivery within the first 6 hours (but as soon as possible), as indicated by clinical and laboratory parameters.

Fluid Resuscitation

Since septic shock commonly manifests as intravascular hypovolemia due to reduced fluid intake superimposed on vascular dysfunction and microvascular leak, rapid fluid resuscitation remains the cornerstone of current resuscitative therapy. Pediatric guidelines recommend a 20 ml/kg intravenous bolus of a crystalloid solution (either 0.9% normal saline or Lactated Ringer's (LR)) over 5 minutes.[12,13] If intravenous access cannot be established within 5 minutes, intraosseus access should be considered if appropriate expertise to obtain central venous access is not immediately available.[14] Reassessment of perfusion should be performed following the fluid bolus and additional fluid should be administered in repeated 20 ml/kg boluses until perfusion has improved or signs of fluid overload develop. Carcillo et al. showed that administration of at least 40ml/kg of fluid in the first hour was associated with a lower mortality in pediatric septic shock.[15] Fluid resuscitation was not associated with increased risk of ARDS or cardiogenic pulmonary edema in this study.[15] Moreover, in a study of 91 pediatric patients presenting to community hospitals with septic shock, reversal of shock with rapid fluid resuscitation (median time of 75 minutes) was associated with a 9-fold increased odds of survival, whereas delays in the initiation of resuscitation increased the odds of death by 1.53 per hour.[16]

In resource-limited settings, rapid fluid resuscitation may have a different benefit-to-risk profile. The Fluid Expansion As Support Therapy (FEAST) trial evaluated use of fluid resuscitation in 3141 children in sub-Saharan Africa.[17] This study included children between 60 days and 12 years of age who presented with a severe febrile illness (classified as impaired consciousness and/or respiratory distress) and impaired perfusion (defined as delayed capillary refill ≥ 3 seconds, weak pulses, or severe tachycardia).[17] Subjects were randomized to receive 20–40 ml/kg of normal saline, 20–40 ml/kg of 5% albumin, or no fluid bolus. Mortality was significantly higher at 48 hours in the albumin (10.6%) and normal saline (10.5%) groups compared to the non-bolus group (8.7%, p=0.003).[17] However, the subset of children who presented with severe hypotension (systolic blood pressure of <50 mm Hg in children younger than 12 months of age, <60 mm Hg in children 1 to 5 years of age, and <70 mm Hg in children older than 5 years of age) were not randomized to a non-bolus group and received either normal saline or albumin.[17] Although a large proportion of the subjects in this trial had malaria and severe anemia, thereby limiting the generalizability of this study to developed countries,[17] the FEAST trial suggests that rapid fluid resuscitation may not be the best therapeutic strategy for all children in settings with limited ability to provide advanced ventilation and hemodynamic support. It is important to note that for patients with severe hypotension due to sepsis (who were excluded from the "no bolus" group in the FEAST trial), the World Health Organization (WHO) guidelines continues to recommend rapid fluid resuscitation as initial therapy.[18]

Fluid Selection

Isotonic saline is commonly used as the initial crystalloid in fluid resuscitation, but some evidence suggests that balanced fluids such as LR solution or PlasmaLyte™ may be preferable in patients with septic shock. [19,20] Isotonic saline contains a higher chloride content than normal blood values and the ensuing hyperchloremic metabolic acidosis that can result has been associated with renal injury and increased mortality in adult sepsis.[19,20] A retrospective propensity-matched analysis of 53,448 adults with vasopressor-dependent septic shock either treated with isotonic saline alone or isotonic saline in combination with balanced fluids demonstrated that increasing utilization of balanced fluids was associated with a step-wise reduction in in-hospital mortality.[20] However, some reports suggest that the relative hypotonicity of LR can increase intracranial pressure in susceptible patients or induce microvascular thrombosis due to a calcium-mediated activation of the coagulation system.[21,22] Currently, both adult and pediatric sepsis guidelines recommend use of crystalloids as initial resuscitation fluid without specifying a specific type.[12,13] In the absence of direct data comparing different crystalloid preparations, it is our practice to use any readily available crystalloid for initial resuscitation but to consider switching to a more balanced solution, such as LR, if arterial pH falls below 7.20 or serum chloride rises greater than 110 mEq/L.

The use of colloid fluids in the initial resuscitation and management of pediatric septic shock remains controversial. On the one hand, colloids may increase blood oncotic pressure and thus restore intravascular volume more efficiently than crystalloid resuscitation.[23] However, the capillary leak inherent in septic shock may result in further extravasation of administered colloids, thereby exacerbating interstitial edema, at least in the earliest phases of resuscitation. Several large studies have compared the use of colloids and crystalloids in critical illness.[24–27] In the Saline versus Albumin Fluid Evaluation (SAFE) study, 6997 critically ill adults were randomized to receive either 4% albumin or normal saline with no difference in mortality, development of organ failure, ICU or hospital length of stay, days of mechanical ventilation, or days of renal-replacement therapy.[24] However, in a subanalysis of patients with severe sepsis, subjects randomized to the albumin group trended towards a lower relative risk of 28 day mortality as compared to saline (0.87, 95% CI 0.74, 1.02; p=0.09). [24] The Albumin Italian Outcome Sepsis (ALBIOS) study evaluated 1818 patients who met clinical criteria for severe sepsis and were treated with either crystalloid fluid alone or crystalloid fluids plus 20% albumin to achieve a serum albumin level of more than 30 g/L.[25] The addition of albumin to crystalloids was found to be safe, but did not result in higher survival, improvement in organ dysfunction, or shorter length of stay.[25] The Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial evaluated 2857 critically ill patients who required fluid resuscitation for hypovolemia and were treated with either colloids or crystalloids.[26] The use of colloids versus crystalloids did not reduce 28-day mortality (primary outcome), though 90-day mortality was lower in the colloid group (relative risk 0.92, 95% CI 0.86, 0.99).[26] Until further data are available, we support current guidelines that recommend crystalloid therapy for initial resuscitation but acknowledge that the addition of colloids such as 5% albumin is a reasonable option for children with

persistent shock and hypoalbuminemia (serum albumin <3 mg/dL) despite 60ml/kg of saline or LR.[12]

Synthetic colloids, including dextrans, gelatin, and hydroxyethylstarch (HES), have also been used for colloid resuscitation. Although initially thought to be promising for the treatment of hypovolemia,[28,29] the use of HES—including newer formulations with a lower molecular weight and a lower substitution ratio (the number of hydroxyethyl groups per glucose molecule)--has been associated with increased mortality, coagulopathy, and acute kidney injury and thus is no longer recommended for use in septic shock.[26,27,30,31]

Antimicrobial Therapy

Administration of empiric broad-spectrum antimicrobial coverage is the second key component of the initial resuscitation and management of pediatric sepsis. Current guidelines recommend that empiric broad-spectrum antibiotics be administered within one hour of the recognition of septic shock.[12,13] While other on-going goals of resuscitation (e.g., fluid administration, central line placement, laboratory evaluation) can compete for the timely delivery of these medications, early antimicrobial administration requires equal prioritization as it has been shown to be associated with improved survival.[32–34] A retrospective study of 2,154 adult patients who received antimicrobial therapy after the onset of hypotension demonstrated that antibiotic delivery within the first hour resulted in improved survival. [32]. Patients who received antibiotics within the first hour had a survival rate of 79.9% and each hour delay in administration was associated with a 7.6% decrease in survival over the next 6 hours.[32] A retrospective analysis of 28,150 patients with severe sepsis and septic shock from 165 ICUs in Europe, US, and South America further demonstrated a linear increase in the risk of mortality for each hourly delay in antibiotic administration.[33] A retrospective observational study of 130 pediatric patients treated for severe sepsis or septic shock found a similar pattern of increased mortality in children, with more than a 3 hour delay from sepsis recognition to initial antimicrobial administration resulting in a 3.92 (95% CI, 1.27–12.06) increased odds of PICU mortality.[9] In that pediatric study, there was also an association between delayed antimicrobial administration of more than 3 hours with fewer organ failure-free days (16 vs 20 days, $p = 0.04$).[9]

Despite consistent reports of adverse outcomes with delays in antimicrobial administration, recent studies have shown that only 50–68% of septic shock patients received effective antimicrobial therapy within the first 6 hours of presentation.[32,35] In the pediatric study by Weiss et al, the median time from sepsis recognition to initial antimicrobial administration was reported to be 140 minutes (interquartile range, 74–277 minutes) and to first appropriate antimicrobial was 177 (90–550 minutes).[9] Several recent studies have now demonstrated that implementation of a bundled approach to resuscitation can improve adherence to guidelines, decrease time to therapy, and improve outcomes in pediatric septic shock.[36,37] For example, Cruz et al. showed that implementation of a sepsis resuscitation protocol in a pediatric emergency department decreased time from triage to administration of first antibiotic from a median of 130 to 30 minutes for children with severe sepsis or septic shock ($p<0.001$).[36]

Goal-directed Therapy and Monitoring

Goal-directed therapy with continuous monitoring of various clinical and laboratory parameters is recommended to guide the initial resuscitation and management of pediatric septic shock.[12,13] Although recent randomized trials have called into question the optimal approach to goal-directed therapy, we continue to recommend titration of resuscitative therapies toward progressive improvements in physiologic parameters.[38,39] A variety of clinical parameters, hemodynamic monitoring, and laboratory data can be used to assess a patient's response to fluid therapy, including heart rate, blood pressure, capillary refill, quality of central/peripheral pulses, mental status, and urine output (goal ≥ 0.5 mL/kg/hr). Other objective measures include central venous pressure (CVP), central venous oxygen saturation (ScvO2), and blood lactate.

Although infants may manifest bradycardia in severe shock, tachycardia is a common and sensitive—albeit non-specific—indicator of hypovolemia and shock. A decrease in heart rate in the patient with tachycardia for age (Table 2) in response to a fluid bolus can generally be taken to indicate an improvement in intravascular volume status. In pediatrics, other causes of tachycardia, including fever, anxiety, and non-septic cardiac dysfunction should also be considered, especially if heart rate does not improve with appropriate fluid resuscitation. Repeated bedside assessments of pulse quality, capillary refill, and mental status can also provide an indication of whether perfusion is improving with ongoing fluid resuscitation. The quality of distal pulses as poorly palpable, strong, or bounding and the quality of capillary refill as "flash" or prolonged (>2–3 seconds) can help classify the type of shock in a pediatric patient as "cold" or "warm" and can help guide additional therapy. A combined assessment of heart rate, capillary refill time, and systolic blood pressure by community hospital physicians has been shown to be a simple and reliable indicator of shock in children.[40]

In adults, a mean arterial pressure target of 65 mm Hg has been shown to preserve tissue perfusion,[41] but in children the optimal blood pressure target needs to be considered by age (see Table 4). Notably, these blood pressure goals serve more as a general guide than an absolute rule and comorbidities such as known pre-existing hypertension should cause a clinician modify recommended targets. In addition, while blood pressure provides a reasonable measure of macrovascular circulation and tissue perfusion, it should not be used in isolation. For example, it is not clear if minor degrees of relative hypotension are harmful if other parameters of perfusion, such as mental status, urine output, capillary refill, and lactate, are reassuring.

Central venous pressure (CVP), as a surrogate for right atrial pressure, reflects cardiac preload and is commonly used in patients with septic shock to guide adequacy of fluid resuscitation. Current early goal-directed therapy guidelines recommend targeting a CVP of 8–12 mm Hg for patients with spontaneous ventilation in septic shock and 12–15 mm Hg for patients requiring positive-pressure ventilation.[12] However, the use of CVP to guide fluid resuscitation can be limited because CVP may be affected by factors other than volume, such as cardiac diastolic dysfunction, pulmonary hypertension, and increased intrathoracic pressure due to positive-pressure ventilation. These limitations have raised questions about

the overall benefit of using CVP to guide fluid resuscitation in septic shock. For example, a recent meta-analysis of 43 studies showed that CVP was unable to predict fluid responsiveness in critically ill adults.[42] However, while a pre-defined CVP target should not be the sole indication for continued fluid resuscitation, a low CVP (<5 mm Hg) generally indicates that an additional fluid bolus is unlikely to cause acute problems of fluid overload for a patient with other ongoing indices of abnormal perfusion and shock.

Central venous or mixed venous oxygen saturation (ScvO2 or SmvO2) can be used as a continuous or intermittent measure to assess the global balance of oxygen delivery and consumption in a patient with septic shock. Since central venous catheters have largely replaced the use of pulmonary arterial catheters, ScvO2 is now more commonly measured than SmvO2. ScvO2 is ideally measured from a catheter with its tip at the superior vena cava-right atrial junction. Measurements taken from a femoral catheter with its tip in the inferior vena cava are thought to be less reliable due to variability in splanchnic oxygen utilization. An $ScvO_2$ <70% indicates that tissue oxygen extraction is increased from normal, suggesting inadequate oxygen delivery due to either low cardiac output, decrease arterial oxygen content, or both. Such a finding should prompt efforts to further improve oxygen delivery either through additional fluid administration, vasoactive therapy, or an increase in arterial blood oxygen content (i.e., increase inspired oxygen or red blood cell transfusion if hemoglobin is <10 g/dL). Although $ScvO_2$ may also be low if metabolic demand is high (e.g., fever in sepsis), an $ScvO_2$ <70% is evidence that oxygen delivery is lower than oxygen demand, and thus the shock state remains.

In the landmark trial of early goal-directed therapy in adult septic shock by Rivers et al, an ScvO2 >70% was targeted and this value remains the recommended target in current pediatric shock guidelines.[43] A pediatric trial repeated this work in children with severe sepsis or fluid refractory shock, evaluating patients with ScvO2 targets >70% for 72 hours compared to standard therapy, and found a reduction in mortality from 39.2% to 11.8% (p=0.002) along with fewer new organ dysfunctions.[44] Furthermore, a pediatric prospective cohort trial evaluated the effect of intermittent ScvO2 monitoring on 120 children with fluid refractory septic shock.[45] Children who had intermittent ScvO2 monitoring performed at 1, 3, and 6 hrs had significantly lower in-hospital mortality (33% versus 55%, p=0.02) and a reduction in the number dysfunctional organs (2 versus 3, p<0.001).[45]

An important limitation of $ScvO_2$ is the need for central venous access, making this laboratory value difficult to obtain in many children who may not otherwise require such an invasive procedure. In addition, continuous ScvO2 measurements require a specialized catheter that may not be available in all centers. A recent prospective cohort study of adult patients diagnosed with severe sepsis at three different hospitals found that mean arterial pressure and central venous pressure were still the most important hemodynamic variables in initial hemodynamic resuscitation and that low post-resuscitation SvO_2 was not associated with a worse outcome.[46] Other studies have failed to show an advantage of using ScvO2 over other markers such as lactate in predicting in-hospital mortality.[47,48] Thus, we recommend monitoring ScvO2 when central venous access is obtained for other indications and interpreting ScvO2 in combination with other markers of oxygen delivery and perfusion.

Lactate is a commonly used surrogate for tissue hypoxia since it is produced as a byproduct of anaerobic metabolism. However, because blood lactate levels are also dependent on hepatic metabolism, hyperlactatemia is not specific for impaired oxygen delivery.[49] Nonetheless, prior studies have found that initial lactate correlates with increased mortality[47,50] and lactate clearance of 10% or more during the early hours of sepsis resuscitation predicts survival.[47,51] On the other hand, in a recent study of 123 adult patients with vasopressor-dependent septic shock, 45% were found to be “non-lactate expressers” (defined as a lactate <2.4 mmol/L), but mortality remained high at 20% in these patients.[52] In pediatrics, hyperlactatemia appears to be less common overall than in adults with septic shock. Thus, while hyperlactatemia has been associated with increased risk of organ dysfunction, need for resuscitative therapies, and has been independently associated with in-hospital mortality,[53,54] the absence of an elevated lactate should not slow ongoing aggressive resuscitative efforts in children with other indices of altered perfusion.

Current pediatric sepsis guidelines recommend optimizing cardiac index to between 3.3–6.0 L/min/m^2.[12,13] However, accurate methods to measure cardiac output at the bedside of a critically ill patient remain a challenge. Several non- or minimally-invasive monitoring devices are now available to assess volume status, cardiac output, and tissue perfusion.[55] Bedside cardiac ultrasound to serially measure inferior vena cava diameter and collapsibility and right ventricular diameter has been associated with overall volume status and can predict clinical responsiveness to subsequent volume loading.[56] Although cardiac ultrasound is increasingly available, results are prone to variability in expertise. More objective devices are available that rely on pulse contour analysis to calculate cardiac output based on the relationship among blood pressure, stroke volume, arterial compliance, and SVR. However, these devices require placement of an arterial catheter.[55,57]. Other devices that measure bioimpedance—the change in voltage of a current applied across the thorax--can estimate cardiac output without an arterial catheter, though pediatric experience is limited.[57] Near-infrared spectroscopy (NIRS) measures venous-weighted oxyhemoglobin saturation in an underlying tissue bed (e.g., renal, splanchnic, brain) and displays a number (rSO_2) that varies with local oxygen delivery and extraction. A decrease in NIRS rSO_2 has been correlated with a fall in local tissue perfusion in animal models of shock and predicted fluid responsiveness in hypovolemia but their specific use to guide resuscitation in pediatric sepsis has not been adequately studied.[58–60]

Inotropic and Vasopressor Initiation

Fluid resuscitation alone is frequently insufficient to restore a minimal organ perfusion pressure in septic shock. Fluid-refractory septic shock is defined as persistent shock despite at least 40–60 ml/kg of fluid resuscitation in the first hour. In these cases, inotropic or vasopressor therapy should be initiated, ideally within the first 60 minutes of resuscitation. Current pediatric guidelines recommend starting with a vasoactive agent with inotropic properties, such as dopamine or epinephrine, given the preponderance of “cold shock” in children.[13] However, in children with “warm shock”, a vasopressor agent such as norepinephrine, may be more appropriate to increase SVR.[13] Adequate fluid resuscitation should ideally be achieved or ongoing prior to initiation of vasoactive agents. A recent retrospective cohort study evaluating the use of fluid resuscitation and initiation of

vasoactive agents in 2,849 adult patients admitted with septic shock found the lowest mortality rates were associated with aggressive fluid administration and initiation of vasoactive agents within 1–6 hours of sepsis recognition rather than just early vasoactive agent administration alone.[61]

Commonly used vasoactive agents in pediatric septic include dopamine, epinephrine, norepinephrine, dobutamine, and phosodiesterase inhibitors. Different agents have varying effects on heart rate, myocardial contractility, and vascular tone, and should be selectively used based on the pathophysiologic parameters that require manipulation.[62] Dopamine is dose-dependent – at low doses it improves splanchnic perfusion and increases heart rate and cardiac contractility whereas at higher doses it increases systemic vascular resistance. Epinephrine also increases heart rate and cardiac contractility, but acts as a vasodilator at low doses (<0.1–0.3 mcg/kg/min) and a vasoconstrictor at doses >0.1–0.3 mcg/kg/min. Norepinephrine increases heart rate, cardiac contractility, and vasoconstricts; however, the effects of vasoconstriction are more potent than with dopamine.[13] In pediatrics, selection of the appropriate vasoactive agent should be driven by the clinical features of a patient's presentation with either low cardiac output and high systemic vascular resistance ("cold shock") or high cardiac output and low systemic vascular resistance ("warm shock"). Dopamine and epinephrine should be used to improve cardiac output in "cold shock," whereas norepinephrine should be preferentially used to increase SVR in patients with "warm shock." Often children have dynamic shifts from one hemodynamic state to another, so constant clinical monitoring and changes in agent may be necessary. Regardless of the physiology and choice of agent, peripheral inotropic support with epinephrine has been shown to be safe for short durations[63] and should be started for patients with fluid-refractory shock until central venous access is obtained.[13]

Other agents, such as dobutamine, milrinone, and vasopressin may have an adjunctive role in treatment of pediatric septic shock. Dobutamine increases heart rate and cardiac contractility, while decreasing SVR and can be used to improve perfusion in patients with normotension but decreased myocardial function. Milrinone, a phospodiesterase inhibitor, also improves cardiac contractility and decreases SVR, with the added benefit of improving cardiac lusitropy.[64] One small randomized control trial of milrinone in combination with catecholamines in pediatric patients with septic shock found improvement in cardiac index, stroke volume index, and oxygen delivery compared to placebo.[64] Vasopressin is an endogenously released hormone that can be administered in shock states to restore vascular tone in refractory cases of "warm" septic shock.[12] A recent multicenter, randomized, double-blind trial of low-dose vasopressin compared to norepinephrine in adult patients with septic shock found no difference in the 28-day or 90 day mortality rate or the rate of organ dysfunction.[65] A pediatric randomized control trial of vasodilatory shock evaluated the addition of low-dose vasopressin in addition to vasoactive infusions compared to placebo and did not find any benefit in time to vasoactive-free hemodynamic stability, mortality, organ failure-free days, or length of ICU stay.[66] Notably, in this pediatric trial, there was a concerning trend toward harm with 10 deaths (30%) in the vasopressin group versus only five (15.6%) in the placebo group (relative risk, 1.94; 95% confidence interval, 0.75–5.05; p=0.24).[66] Until further studies are available to determine the comparative efficacy of one vasoactive agent over another in pediatric septic shock are available, we recommend starting

dopamine or epinephrine for “cold shock” and norepinephrine for “warm shock” with close titration of inotropic and vasopressor agents based on the clinical and hemodynamic parameters noted above.

Corticosteroids

Children at risk for absolute adrenal insufficiency (AI) should be given stress-doses of hydrocortisone (50 to 100mg/m^2/24hrs) as soon as possible.[13] Risk factors for absolute AI include use of exogenous steroids for more than seven days in the past two weeks; hypothalamic, pituitary, or adrenal disease; and purpura fulminans. Current guidelines recommend that children with fluid-resistant, catecholamine-refractory septic shock, commonly defined as shock that persists despite 60 ml/kg of fluid and escalating doses of vasoactive infusions, also be treated with hydrocortisone (50 to 100mg/m^2/24hrs).[13] A normally functioning adrenocortical axis is necessary to survive critical illness. During times of stress or critical illness, patients with an intact axis will have elevated plasma cortisol levels reflecting the activation of this axis. However, in a state of relative adrenal insufficiency, an inappropriately low amount of cortisol is available to respond to a stressful stimulus and has been demonstrated to be common in patients with fluid-resistant, catecholamine refractory septic shock. [13,67]. Replacement with hydrocortisone should be continued until the patient becomes hemodynamically stable and no longer requires vasoactive infusions, though there is insufficient evidence to support a particular duration or weaning protocol.[13]

Although currently recommended in pediatrics, the evidence for steroid use in septic shock has been mixed. In the 1980’s and early 1990’s, several studies failed to demonstrate benefit to using high-dose glucocorticoids in adult sepsis.[68,69] However, this led to concern that some patients with *relative* adrenal insufficiency may benefit from low-dose corticosteroids therapy. In a randomized controlled trial by Annane et al, 300 adults with septic shock were evaluated for response to a seven day treatment with hydrocortisone and fludrocortisone compared to placebo.[70] Patients with *relative* adrenal insufficiency (as measured by less than 9 μg/dL cortisol increase following a a corticotropin stimulation test) who were treated with corticosteroids had decreased 28 day mortality compared to placebo (53% vs 63%, p=0.02) and had vasopressor therapy terminated more quickly without evidence of increased adverse events.[70] However, a follow-up randomized trial of 499 adults with septic shock who did not have a response to corticotropin failed to demonstrate a mortality benefit with steroid use, although time to shock resolution was faster in the corticosteroid group.[71] A recent retrospective multicenter propensity matched cohort study further showed that early administration of low-dose corticosteroid was not associated with decreased mortality, but did find a modest decrease in mortality in a subgroup of patients with the highest severity of illness treated with steroids compared to placebo (50.6% vs 55.8%, p=0.02).[72]

In pediatrics, a retrospective cohort study found no improvement in outcomes with steroid treatment in septic shock, with an association between steroid use and increased mortality (OR 1.9, 95% CI 1.7, 2.1).[73] In a risk-stratified analysis of a multi-center pediatric septic shock database, there did not appear to be a mortality benefit for corticosteroids even in patients with the highest severity of illness.[74] Although future studies of the role and

potential side effects of steroids are warranted, stress-dose hydrocortisone should be administered to those patients with known or suspected *absolute* adrenal insufficiency who present with sepsis and should be considered for patients with fluid-resistant, catecholamine refractory septic shock.[13]

Respiratory support

All patients with septic shock should be initially treated with supplemental oxygen to increase the oxygen content of the blood and optimize oxygen delivery. Further respiratory support including non-invasive modes and endotracheal intubation may be warranted in specific situations, including development of pulmonary edema, ARDS, and inadequate airway reflexes due to compromised mental status. Furthermore, in cases of refractory shock, sedation and neuromuscular blockade can eliminate work of breathing and reduce oxygen demand by the respiratory system, allowing for diversion of cardiac output to other organ systems.

Once endotracheal intubation is deemed necessary, many factors need to be considered in planning for the process of sedation and intubation. An approach that minimizes the risk of aspiration of gastric contents should be considered, especially for those patients in whom the last oral intake cannot be established. The pharmacological agents selected to induce sedation need to account for the possible exaggerated hemodynamic effects in a patient with sepsis who may already have some degree of hemodynamic instability. Agents such as ketamine, which maintain relative cardiovascular stability, are preferable agents for sedation with endotracheal intubation.[13] although in patients with prolonged shock who are “catecholamine deplete” are at risk for a ketamine-induced cardiovascular collapse. Etomidate is another agent that maintains cardiovascular stability, but also carries a significant risk of inhibiting cortisol formation and precipitating adrenal insufficiency. Several small retrospective studies have shown significantly lower cortisol levels and higher adrenocorticotropic hormone (ACTH) levels in patients sedated with etomidate and have reported an association between etomidate use and increased mortality in sepsis.[75,76] Consequently, current recommendations are to avoid the use of etomidate in pediatric septic shock. Use of high-dose benzodiazepines, barbiturates, and propofol can precipitate worsening hypotension and should be avoided if possible.[13] While use of a short-acting neuromuscular blocking agent can help to facilitate intubation, long-term neuromuscular blockade should also be avoided if possible due to risk of development of neuropathies and myopathies.[12]

Electrolyte Abnormalities

Pediatric patients with severe sepsis and septic shock are at risk of hypoglycemia, hyperglycemia, and hypocalcemia. These should be recognized by rapid testing and corrected if present.

Hypoglycemia is especially common in infants and young children in shock states because of their low glycogens stores.[13] Correction by an intravenous bolus infusion of dextrose should be done rapidly with subsequent monitoring to ensure return to euglycemia.[13] Hyperglycemia is also a common finding in children with septic shock and has been

identified as a risk factor for mortality in observational studies.[77] A randomized control trial of 700 critically ill pediatric patients compared conventional therapy, defined as blood glucose between 10 and 11.9 mmol/L (180 mg/dL and 215 mg/dL), to intensive glucose management, defined as 2.8–4.4 mmol/L (50–79 mg/dL) for infants aged 0–1 year and 3.9–5.5 mmol/L (70–99 mg/dL) for children aged 1–16 years.[78] The intensive glucose management group had decreased PICU length of stay (5.5 days vs 6.1 days, p=0.017) and decreased mortality (3% vs 6%, p=0.038) compared to the conventional group, although there were more episodes of hypoglycemia.[78] A recent multicenter randomized trial of 1369 critically ill children found no significant effect on mortality and ventilator free days with tight glycemic control (72 to 126 mg/dL) versus conventional glycemic control (<216 mg/dL), although severe hypoglycemia was again more common in the tight glycemic control group.[79] The Heart and Lung Failure-Pediatric Insulin Titration (HALF-PINT) study is an ongoing randomized control clinical trial comparing tight glucose control (80–110mg/dL) to conventional glucose control (150–180mg/dL) in critically ill pediatric patients, which may help clarify future glycemic goals (http://clinicaltrials.gov/NCT01565941). Currently, guidelines recommend insulin therapy to avoid hyperglycemia with targets of <180 mg/dL while also avoiding hypoglycemia.[12,13]

Calcium is critically important as an intracellular second messenger and regulator of cell functions such as excitation-contraction coupling in cardiac and smooth muscle. Ionized hyocalcemia is common in patients with septic shock.[80–82] Decreased secretion of parathyroid hormone (PTH) as well as resistance of PTH in bone and kidney during sepsis, low concentrations of vitamin D, increased levels of calcitonin, transfusion of blood containing citrate, and inflammation have all been implicated as potential mechanisms for hypocalcemia.[80–82]. Although there are not clear data that calcium supplementation improves outcomes in septic shock, without precipitating hypercalcemia, current guidelines recommend intravenous calcium gluconate (at a dose of 50–100mg/kg up to 2 grams) to correct ionized hypocalcemia.[12,83] However, since calcium administration may exacerbate cytokine release, increase free radical production, and promote cell death, excessive calcium supplementation and hypercalcemia should be avoided.[13]

Blood products

Blood oxygen content is determined by the amount of hemoglobin (Hgb) in the blood and, in addition to cardiac output, determines oxygen delivery to various tissues. In septic shock, blood transfusion is recommended to maintain a hemoglobin goal of 10 g/dL during the acute phase of resuscitation.[12,43] However, in the absence of cardiovascular instability and inadequate oxygen delivery, a lower hemoglobin level can be tolerated.[84–86]. In a study of transfusion parameters in children with sepsis after resolution of shock, patients randomized to a restrictive transfusion strategy (Hgb <7 g/dL) had no differences in organ dysfunction or mortality compared to the liberal transfusion group (Hgb <9.5g/dL) but had an overall decreased exposure to blood products.[86]

Disseminated intravascular coagulopathy (DIC) occurs frequently in patients with septic shock and is a strong predictor of mortality and organ failure.[87] Lab monitoring of coagulation factors (prothrombin time, partial thromboplastin time, fibrinogen) and platelet

counts as well as clinical monitoring for bleeding is important. Rapid recognition and resuscitation of shock often improves DIC in most cases, but in children who develop significant bleeding or purpura, replacement with FFP, cyropreciptiate, and platelets is recommended to improve INR, fibrinogen, and thrombocytopenia, respectively with target goals of INR < 1.5, fibrinogen >100 mg/dL, platelets > 50,000 per mm^3.

Activated protein C, a protein that promotes fibrinolysis and inhibits thrombosis and inflammation, has been a focus of study in children and adults with septic shock over the past decade. Low levels of activated protein C are found frequently in patients with sepsis and have been associated with an increased risk of death.[87] The prospective recombinant human activated protein C worldwide evaluation in severe sepsis (PROWESS) trial evaluated the administration of recombinant activated protein C versus placebo in 1690 adults with septic shock.[88] Patients treated with recombinant activated protein C exhibited a reduction in mortality from 30.8% to 24.7% (p=0.005), but there was an increased incidence of serious bleeding (3.5% vs 2%, p=0.06).[88] A pediatric trial, Researching Severe Sepsis and Organ Dysfunction in Children: a Global Perspective Trial (RESOLVE), investigated treatment with recombinant activated protein C versus placebo in 477 children with septic shock and found no difference in mortality.[89] Subsequently, the lack of a confirmatory 28- or 90-day mortality benefit in the PROWESS-SHOCK study of 1697 adults with septic shock led to the drug to be voluntarily withdrawn from the market.[90]

ECMO

Extracorporeal membrane oxygenation (ECMO) can be an effective rescue therapy for children with fluid-refractory/catecholamine resistant septic shock. ECMO is not a curative therapy in sepsis, but rather supports cardiopulmonary function to allow for the continuation of other treatment. Although septic shock was once thought to be a relative contraindication for ECMO, data now suggest a 50% and 80% survival to discharge in pediatric and neonatal patients, respectively, with septic shock following ECMO.[13] In addition, a recent retrospective case series of central cannulation of pediatric patients with septic shock reported 78% survival, suggesting that higher flow rates may provide incremental benefit over peripheral cannulation.[91] Thus, ECMO is a reasonable rescue therapy for children with refractory septic shock who cannot be supported by conventional therapies.

Novel Therapies

Many novel therapies have emerged for the treatment of refractory septic shock or special cases of septic shock, including plasma exchange, intravenous immune globulin (IVIG), and immunomodulatory strategies.

Plasma exchange, which functions to filter circulating inflammatory mediators, has been used to treat sepsis-induced multiple organ system failure in multiple small reports with conflicting results.[92] In children with thrombocytopenia-associated multiple organ failure (TAMOF), plasma exchange may have particular benefit.[93] TAMOF, defined as new-onset thrombocytopenia (platelet count <100,000/mm^3) and at least two organ dysfunctions, is a thrombotoic microangiopathic syndrome in critically ill children that has been associated with decreased disintegrin and betalloprotease with thrombospondin motifs -3

(ADAMTS-13) activity, thrombocytopenia, and multiple organ system failure. It is believed to represent a spectrum of disease that includes thrombotic thrombocytopenic purpura (TTP), secondary thrombotic microangiopathy (TMA), and disseminated intravascular coagulation (DIC). In a study by Nguyen et al., children with TAMOF randomized to plasma exchange had replenished levels of ADAMTS-13 activity and improved organ function compared to standard therapy ($p<0.05$).[93] Although there are no large studies to support the use of plasma exchange, we recommend that this novel therapy be considered for pediatric patients with septic shock who meet clinical criteria for TAMOF and fail to improve within 24 hours of initial therapy.

IVIG has been suggested as a potential adjuvant therapy for certain patients with sepsis as it is a known modulator of the inflammatory response that improves opsonization of bacteria, prevents activation of non-specific complement, and neutralizes endotoxin and other superantigens. Despite these theoretical benefits, however, the evidence of benefit from IVIG in sepsis has been limited. One prospective trial of 100 children with septic shock found that treatment with IVIG was associated with a significant reduction in mortality (72% vs 44%) and length of stay LOS (6 vs 9 days).[94] However, in a subsequent study of 3493 neonates with suspected or documented serious infection treated with IVIG or placebo, no differences in mortality were found.[95] At our institution, IVIG is not commonly used for children with septic shock unless there is concern for toxic shock syndrome or a primary or secondary immunodeficiency with low blood immunoglobin levels.

Secondary hemophagocytic lymphohistiocytosis (HLH) shares common features with severe sepsis and some cases of sepsis may well represent a spectrum of this disease process. In particular, children with septic shock, hyperferritinemia, and multiple organ dysfunction have been suggested to benefit from immunomodulatory therapies, including corticosteroids, plasma exchange, IVIG, and anakinra, that are less intense than typically used in primary HLH. For example, a recent multi-center cohort study evaluated 23 children with hyperferritinemia who met criteria for secondary HLH in the setting of sepsis and were treated with either plasma exchange, IVIG, and/or methylprednisolone or with a primary HLH protocol of dexamethasone or cyclosporine A and/or etoposide).[96] Patients treated with plasma exchange, IVIG, and/or methylprednisolone had improved survival (100%) compared to the primary HLH protocol (50%) ($p=0.002$).[96] While data remain limited, we recommend that clinicians consider secondary HLH in children with septic shock and multi-organ failure who demonstrate cytopenias, hyperferritenemia, splenomegaly, and/or persistent fevers.

Sepsis-associated immunosuppression has been associated with decreased survival in adult and pediatric patients.[97,98] Granuloyte-macrophage colony-stimulating factor (GM-CSF), an immune stimulating agent, has been shown to improve proliferation, differentiation, and function of neutrophils and monocytes/macrophages.[97] Use of low-dose GM-CSF in adult septic patients has been effective at restoring monocytic immunocompetence, shortening mechanical ventilation, and reducing length of stay.[97] A recent cohort study of pediatric patients with sepsis and MODS found that 34% exhibited laboratory evidence of immunoparalysis by day seven of illness, which was associated with an increased risk of hospital-acquired infection (RR 3.3, $p<0.05$) and death (RR 5.8, $p<0.05$).[98] In patients

treated with GM-CSF, laboratory markers of immunoparalysis improved and hospital-acquired infections were eliminated ($p<0.05$).[98]

Quality Improvement and Protocolized Therapy

In order to enhance early recognition and improve outcomes in sepsis, international efforts to standardize a protocolized approach to the management of severe sepsis and septic shock have led to the publication of treatment guidelines for both adult and pediatric patients.[12,13] In a study by Levy et al to evaluate the effect of these guidelines on outcome, bundles were distributed and utilized at a cohort of 165 sites with a total of 15,022 patients. Compliance of bundle use increased from 10.9% to 31.3% by the end of two years and unadjusted hospital mortality decreased from 37% to 30.8%.[35] In addition, a recent meta-analysis of eight trials of sepsis bundles found that use of sepsis bundles increased survival (odds ratio, 1.91; $p < 0.0001$) and decreased time to antibiotics ($p<0.0002$).[99]

Sepsis treatment protocols have also been utilized to help streamline and standardize care for the pediatric patients at several institutions. In a recent study performed in a pediatric emergency department at Texas Children's Hospital, an automated tool was established to improve early recognition of children with septic shock based on abnormal vital signs and decrease time to therapy.[36] Time from triage to first intravenous fluid bolus and antibiotic administration decreased following protocol initiation from 56 to 22 minutes ($p < 0.001$) and 130 to 28 minutes ($p <0.001$), respectively.[36] A second prospective cohort study at Children's Hospital Boston investigated the adherence to five time-specific goals in the management of pediatric septic shock. Only nineteen percent of patients had complete adherence to the five-component bundle, which included 60 ml/kg IV fluid, antibiotic administration, and administration of vasoactive agents within 60 minutes of sepsis recognition. However, for patients with 100% compliance, hospital length of stay was shorter by 57% ($p = 0.009$).[100] Following a quality improvement intervention, the same authors demonstrated a sustainable increase in adherence from 35% 100% for the five-component bundle and a decrease in mortality from 4.8% to 1.7%.[37]

Conclusions

Pediatric sepsis remains a common cause of morbidity and mortality worldwide. The management of children with suspected sepsis should focus on the rapid recognition of signs of abnormal perfusion, early and aggressive fluid resuscitation to restore cardiovascular function, and prompt antimicrobial delivery. Additional management with titration of vasoactive agents, respiratory support, correction of electrolyte abnormalities, consideration of low-dose corticosteroid replacement, and other adjunctive and novel therapies should be considered based on specific patient characteristics and response to fluid resuscitation. Efforts to standardize recognition, initial resuscitation, and ongoing management strategies have demonstrated improved outcomes in pediatric severe sepsis and septic shock.

Acknowledgments

Funding: Financial support was provided by the Division of Critical Care, The Children's Hospital of Philadelphia. Dr. Weiss is also supported by NIH K12HD047349-10.

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Table 1

Definitions of pediatric SIRS, sepsis, severe sepsis, and septic shock[1]

SIRS
The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count. • Core temperature of >38.5°C or <36°C • Tachycardia (HR > 2 SD above normal for age) or, for children <1 year old, bradycardia (HR <10th percentile for age). • Tachypnea (RR >2 SD above normal for age) • Leukocyte count elevated or depressed for age or >10% bands
Sepsis
SIRS in the presence of a suspected or known invasive infection.
Severe Sepsis Sepsis with one of the following • Cardiovascular organ dysfunction • Acute respiratory distress syndrome • Two or more other organ dysfunctions
Septic Shock
Sepsis and cardiovascular organ dysfunction

SIRS, systemic inflammatory response syndrome; HR, heart rate; SD, standard deviation, RR, respiratory rate)

[1]Adapted from Goldstein 2005

Table 2

Pediatric SIRS criteria[1]

Age	Heart Rate (HR)	Respiratory Rate (RR)	Leukocyte Count (Leukocytes x10^3/mm^3)
0 days to 1 week	>180, <100	>50	>34
1 week to 1 month	>180, <100	>40	>19.5 or <5
1 month to 1 year	>180, <90	>34	>17.5 or <5
2–5 years	>140	>22	>15.5 or <6
6–12 years	>130	>18	>13.5 or <4.5
13 to <18 years	>110	>14	>11 or <4.5

* Excludes premature infants.

SIRS, systemic inflammatory response syndrome

[1] Adapted from Goldstein 2005

Table 3

Consensus criteria for sepsis-associated organ dysfunction[1]

Organ System	Criteria for dysfunction
Cardiovascular	Hypotension (<5th percentile for age) despite >40ml/kg fluid bolus in 1 hr or Vasoactive requirement to maintain BP despite >40ml/kg fluid bolus in 1 hr or Two or more signs of abnormal perfusion (increased lactate, metabolic acidosis, decreased urine output (<0.5mL/kg/hr), capillary refill >5 sec)
Respiratory	PaO2/FiO2 <300 Hypercarbia (PaCo2 > 65 mm Hg or increase of ≥20 mm Hg from baseline) Required FiO2 >50% to maintain SpO2 ≥92% Need for non-elective invasive or non-invasive mechanical ventilation
Neurologic	Altered mental status defined as absolute GCS < 11 or decrease in GCS ≥3 from baseline
Hematologic	Platelet count <80,000/mm^3 or decline of 50% from baseline INR > 2.0
Renal	Serum creatinine ≥2 times upper limit of normal for age Two-fold increase from baseline serum creatinine
Hepatic	Total bilirubin >4mg/dL ALT more than 2 times the upper limit of normal for age

BP, blood pressure, GCS, glascow coma scale, ALT, alanine aminotransferase

[1]Adapted from Goldstein 2005

Table 4

Age-specific definition of hypotension[1]

Age	5th Percentile SBP (mm Hg)
0 days to 1 week	<59
1 week to 1 month	<79
1 month to 1 year	<75
>1 year to 5 years	<74
>5 years to 12 years	<83
>12 years to 18 years	<90

SBP, systolic blood pressure

[1] Adapted from Goldstein 2005