Sepsis and Septic Shock

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KEYWORDS

- Systemic inflammatory response syndrome (SIRS)
- Sepsis
- Septic shock
- Early goal-directed therapy
- Vasopressors
- Children

KEY POINTS

- Every physician who cares for children is challenged by the difficult tasks of recognizing and managing sepsis and septic shock.
- Early recognition and therapy are the cornerstones of acute care of the septic child. The rapidity and appropriateness of therapy administered in the initial hours significantly affects outcome.
- Septic shock in children is less frequently associated with hypotension than it is in adults. Children are more likely to present with a clinical syndrome referred to as cold shock, in which systemic vascular resistance is high and cardiac output is low. Clinically, these children have tachycardia (although neonates may present with bradycardia), pale, cyanotic, or mottled extremities, and prolonged capillary refill time (>3 seconds). Blood pressures may be normal, low, or high.
- Management of sepsis and septic shock includes respiratory support, aggressive fluid resuscitation, vasopressor therapy, and early antibiotic therapy. The goal is reversal of tissue hypoperfusion.
- The ideal choice of vasopressor agents in children with septic shock depends on the clinical appearance and hemodynamic status of the child.
- Mortality from sepsis in children is significantly lower than in adults.

INTRODUCTION

Infectious diseases have been a leading cause of death throughout the history of the human race, but only recently have we begun to understand their effects on the body. Ancient Greek and Roman philosophers viewed sepsis as a sort of biological decay.¹ It was not until the seventeenth and eighteenth centuries that the germ theory of disease ushered in eras of infection control and modern microbiology. The discovery of antibiotics during the first half of the twentieth century finally armed physicians with a specific weapon to fight infection. As we continue to unravel the mysteries of sepsis and septic shock, more recent research and innovation have focused on the molecular mechanisms and hemodynamics of sepsis and septic shock.¹
Even now, every physician who cares for children is challenged by the difficult tasks of recognizing and managing sepsis and septic shock. In its most fundamental definition, sepsis is a clinical syndrome characterized by systemic inflammation and tissue injury. It represents a clinical continuum of severity, usually triggered by infection, resulting in a cascade of biochemical and pathophysiologic events. If left unabated, microbial toxins together with a dysfunctional host immune response can quickly wreak havoc, resulting in tissue damage, shock, organ failure, and death.

Early recognition and appropriate therapy are the cornerstones of acute care of the septic child. Similar to the severely injured patient, the rapidity and appropriateness of therapy administered in the initial hours affects the outcome. Early goal-directed sepsis management has led to one of the greatest reductions in sepsis-related morbidity and mortality over the past 50 years.2

DEFINITIONS

The 1992 joint statement from the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) introduced the term systemic inflammatory response syndrome (SIRS) to describe the nonspecific inflammatory process in adults that develops in response to significant physiologic insults, such as infection, trauma, burns, and other disease processes.3 SIRS has since become part of the common medical vernacular.

The original criteria for SIRS contain several clinical signs and laboratory values that are specific to adults and, therefore, are not entirely useful in pediatric populations. In 2005, the International Pediatric Sepsis Consensus Conference (IPSCC) made several modifications and published pediatric-specific definitions based on expert opinion.4 These definitions are listed in Box 1.

Three major differences are noted in the pediatric definitions. Because children are more likely to present with tachycardia or tachypnea unrelated to SIRS, temperature or leukocyte abnormalities must be present. Second, age-appropriate numeric values for normal vital signs, based on consensus expert opinion, were agreed on (Table 1). Bradycardia was added as a criterion for SIRS in the newborn age group.

Sepsis, as defined by the 1992 ACCP/SCCM Consensus Conference and accepted unaltered for children by the 2005 IPSCC, is SIRS with an infectious source.3,4 Infection may be of bacterial, viral, fungal, or rickettsial origin. The diagnosis of infection may be supported by positive culture, tissue stain, or PCR testing, clinical examination, radiologic imaging, or other laboratory test findings (see Box 1). Severe sepsis is defined as sepsis plus the presence of cardiovascular dysfunction, ARDS, or 2 or more organ dysfunctions. The definitions of organ dysfunctions are modified for children and listed in Box 2.

The clinical definition of septic shock in children is more nebulous than in adults. Contrary to adults, children commonly do not develop hypotension until late in the clinical course of septic shock.5 Therefore, the 2005 IPSCC agreed on a definition of pediatric septic shock that includes the presence of severe sepsis with signs of cardiovascular dysfunction, defined as, despite 40 or more mL/kg fluid resuscitation, any of 1 of the following criteria: hypotension, a need for vasoactive agents, or 2 or more other signs of organ hypoperfusion (see Box 2).4

These definitions are useful for standardization of the diagnoses but may be less relevant in the clinical arena. Clinical suspicion for sepsis is more sensitive and should always supersede reliance on the presence of all components of the consensus criteria.6
According to the World Health Organization, more than two-thirds (68%) of the estimated 8.8 million deaths in children younger than 5 years worldwide in 2008 were caused by infectious diseases. The big 4 killers are pneumonia, diarrhea, malaria, and measles. Most of these deaths occur in the developing countries of Asia and sub-Saharan Africa. This situation makes infection, often culminating in severe sepsis and septic shock, the most common cause of death in infants and children in the world.

Among resource-rich countries, large-scale epidemiologic data in children with severe sepsis and septic shock are limited. Furthermore, because childhood immunization programs are constantly altering the microbiological landscape, the data that do

**EPIDEMIOLOGY**

According to the World Health Organization, more than two-thirds (68%) of the estimated 8.8 million deaths in children younger than 5 years worldwide in 2008 were caused by infectious diseases. The big 4 killers are pneumonia, diarrhea, malaria, and measles. Most of these deaths occur in the developing countries of Asia and sub-Saharan Africa. This situation makes infection, often culminating in severe sepsis and septic shock, the most common cause of death in infants and children in the world.

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exist may not be applicable to current pediatric populations in most of the developed world. With this caveat, it has been estimated that more than 42,000 children develop severe sepsis each year in the United States.\textsuperscript{9} Infants are at highest risk, with rates 10 times that of older children. Low-birth-weight and very-low-birth-weight children make up nearly one-fourth of the pediatric severe sepsis population. Similarly, a recent

<table>
<thead>
<tr>
<th>Box 2</th>
<th>Organ dysfunction criteria</th>
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<tr>
<td><strong>Cardiovascular</strong></td>
<td>Despite administration of isotonic intravenous fluid bolus 40 or more mL/kg in 1 hour</td>
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<tr>
<td>• Decrease in blood pressure (BP) (hypotension) less than the fifth percentile for age or systolic BP less than 2 standard deviations less than normal for age or</td>
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<tr>
<td>• Need for vasoactive drug to maintain BP in the normal range (dopamine &gt;5 ( \mu \text{g/kg/min} ) or dobutamine, epinephrine, or norepinephrine at any dose) or</td>
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<tr>
<td>• Two of the following:</td>
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<tr>
<td>o Unexplained metabolic acidosis: base deficit greater than 5.0 mEq/L</td>
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<tr>
<td>o Increased arterial lactate greater than 2 times upper limit of normal</td>
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<tr>
<td>o Oliguria: urine output less than 0.5 mL/kg/h</td>
<td></td>
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<tr>
<td>o Prolonged capillary refill: greater than 5 seconds</td>
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<tr>
<td>o Core to peripheral temperature gap greater than 3(^{\circ})C</td>
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<td><strong>Respiratory</strong></td>
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<tr>
<td>• Paco(_2) (partial pressure of carbon dioxide, arterial) greater than 65 torr or 20 mm Hg over baseline Paco(_2) or</td>
<td></td>
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<tr>
<td>• Proven need for more than 50% Fio(_2) to maintain saturation (\geq92)% or</td>
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<tr>
<td>• Need for nonelective invasive or noninvasive mechanical ventilation</td>
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<tr>
<td><strong>Neurologic</strong></td>
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<td>• Glasgow Coma Scale 11 or greater or</td>
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<tr>
<td>• Acute change in mental status with a decrease in Glasgow Coma Scale 3 points or more from abnormal baseline</td>
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<td><strong>Hematologic</strong></td>
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<td>• Platelet count greater than 80,000/mm(^3) or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients) or</td>
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<td>• International normalized ratio greater than 2</td>
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<td><strong>Renal</strong></td>
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<td>• Serum creatinine level 2 times or greater than the upper limit of normal for age or 2-fold increase in baseline creatinine</td>
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<td><strong>Hepatic</strong></td>
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<td>• Total bilirubin level 4 mg/dL or greater (not applicable for newborn) or</td>
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<tr>
<td>• Alanine aminotransferase level 2 times upper limit of normal for age</td>
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multicenter study in Columbian pediatric intensive care units estimated that more than half of all admissions for sepsis were children younger than 2 years.10 Beyond infancy, children with underlying chronic diseases account for about one-half of all cases.9,10 In the United States, respiratory infections and primary bacteremia are the most common infections leading to sepsis. Bacteremia predominates in neonates, and respiratory illnesses are more common among older children.9,11 No specific cause is found in most children presenting to US-based emergency departments with undifferentiated sepsis.11

**MICROBIOLOGY**

Overall, *Staphylococcus aureus* is the most common infecting organism in children with severe sepsis in the developed world (17.5%).9 Among blood culture isolates, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and group B *Streptococcus* predominate among previously healthy children. In children with chronic medical problems, coagulase-negative *Staphylococcus* species is most common.9 Urinary tract infections leading to severe sepsis are most commonly caused by gram-negative bacilli, including *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, and *Proteus mirabilis*.11 Meningococcal infections are rare and even less common among children with comorbidities. Fungal infections, on the contrary, are significantly more common among children with underlying chronic illnesses, especially human immunodeficiency virus (HIV).9 Herpes simplex virus in neonates may cause either disseminated or central nervous system disease and may be clinically indistinguishable from bacterial infections.

Before widespread immunization, *Haemophilus influenzae* serotype b (Hib) was a leading cause of invasive infection and sepsis in children younger than 5 years. Since routine Hib vaccination during infancy in the United States, the rates of Hib-invasive infection has declined to approximately 1 per 100,000 population.12 With the subsequent widespread implementation of pneumococcal vaccination programs within the last 2 decades, the incidence of invasive pneumococcal infections has similarly decreased significantly.13 Both of these pathogens continue to exert a huge burden on pediatric populations worldwide.

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### Table 1

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Heart Rate (Beats/Min)</th>
<th>Respiratory Rate (Breaths/Min)</th>
<th>Leukocyte Count ( \times 10^3/\text{mm}^3 )</th>
<th>Systolic BP (mm Hg)</th>
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<tbody>
<tr>
<td>0 d to 1 wk</td>
<td>&gt;180</td>
<td>&lt;100</td>
<td>&gt;50</td>
<td>&lt;34</td>
</tr>
<tr>
<td>1 wk to 1 mo</td>
<td>&gt;180</td>
<td>&lt;100</td>
<td>&gt;40</td>
<td>&gt;19.5 or &lt;5</td>
</tr>
<tr>
<td>1 mo to 1 y</td>
<td>&gt;180</td>
<td>&lt;90</td>
<td>&gt;34</td>
<td>&gt;17.5 or &lt;5</td>
</tr>
<tr>
<td>2–5 y</td>
<td>&gt;140</td>
<td>NA</td>
<td>&gt;22</td>
<td>&gt;15.5 or &lt;6</td>
</tr>
<tr>
<td>6–12 y</td>
<td>&gt;130</td>
<td>NA</td>
<td>&gt;18</td>
<td>&gt;13.5 or &lt;4.5</td>
</tr>
<tr>
<td>13 to &lt;18 y</td>
<td>&gt;110</td>
<td>NA</td>
<td>&gt;14</td>
<td>&gt;11 or &lt;4.5</td>
</tr>
</tbody>
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A more thorough discussion on specific pediatric infections, including urinary tract infections, community-acquired pneumonia, and so forth, is presented in the article on infectious disease emergencies elsewhere in this issue.

**RISK FACTORS**

Not every infection leads to SIRS, severe sepsis, septic shock, and death. In most cases, the child’s immune system and appropriate antimicrobial therapy are able to safely eliminate the offending pathogen and return the child to normal health. The tendency to develop severe sepsis and septic shock is likely more determined by the host response to infection rather than a function of the offending pathogen.\(^4\)

There are several risk factors that may contribute to an increased risk of severe sepsis and septic shock. Age is the single most important factor; neonates are at particularly high risk.\(^9,10\) Beyond infancy, children who have chronic medical problems such as chronic lung disease, congenital heart disease, neuromuscular diseases, and hematologic or oncologic diseases account for nearly half of all cases of pediatric sepsis. In addition, these children have increased mortality.\(^9,10\)

Other unique pediatric populations have an increased risk of sepsis. Sickle cell disease causes splenic dysfunction and impaired ability to combat encapsulated organisms. Host immunosuppression, caused by HIV/AIDS, malignancy, congenital immunodeficiencies, immunomodulating medications, asplenia, malnutrition, among other conditions, also increases the risk. Indwelling medical devices, such as catheters, and anatomic conditions such as congenital heart disease and urinary tract abnormalities predispose children to bacterial seeding and infection.

**DIFFERENCES BETWEEN PEDIATRIC AND ADULT SEPSIS PATHOPHYSIOLOGY**

The cardiovascular response to severe sepsis in children is complex and more variable than in adults. Systemic vascular resistance (SVR), cardiac contractility, and heart rate may each be affected to different degrees among patients with septic shock. In adults, SVR is almost universally decreased, whereas cardiac output (CO) is usually increased. The result is a distributive shock with hypotension, termed warm shock. Clinically, these patients have warm, well-perfused skin, bounding pulses, and brisk or flash capillary refill time. A few children (approximately 20%) present with signs of warm shock.

The more common cardiovascular response to severe sepsis in children, present in approximately 60% of cases, is an increase in SVR as a result of peripheral vasoconstriction. Consequently, blood flow is redistributed from the nonessential peripheral vascular beds such as the skin to more vital organs, including the brain, heart, kidneys, and lungs. It is also accompanied by a decrease in CO, either as a direct result of impaired cardiac contractility or as a secondary effect of high afterload. This clinical syndrome is referred to as cold shock. Peripheral pulses may be weak or absent; the extremities may appear cool, pale, or cyanotic; and capillary refill time is delayed. An important distinction is that BP is usually maintained and may be supranormal in children with cold shock.

Occasionally, both CO and SVR may be decreased in a child with septic shock. This situation may result in a clinical syndrome that is difficult to classify as either strictly warm or cold shock.

**CLINICAL FINDINGS AND RECOGNITION**

Recognizing sepsis early in the course of the disease is vital to curbing its natural progression to shock, organ failure, and death. Differentiating a benign, localized
infectious illness from sepsis in children is challenging. The clinical signs and symptoms of early sepsis may be subtle and easily missed. Carcillo and colleagues\textsuperscript{15} retrospectively reviewed the charts of more than 4000 children transferred from community emergency departments to a large, tertiary pediatric medical center, concluding that physicians failed to recognize and diagnose shock in more than three-quarters (76\%) of cases.

There is no single diagnostic tool or clinical decision rule that is both highly sensitive and specific in recognizing sepsis in its early stages. The best approach is a high level of clinical suspicion, combined with the clinical history, vital signs, and physical examination. Often, a parent may describe a vague change from baseline behavior, such as increased fussiness, decreased activity, or poor oral intake, which may be the first clues of a serious infection. Unexplained tachycardia or tachypnea and signs of poor skin perfusion also suggest the presence of sepsis or septic shock.

The Pediatric Assessment Triangle (PAT) is a useful, rapid tool to guide a clinician’s initial examination.\textsuperscript{16,17} First published in 2000 by the American Academy of Pediatrics as a tool for emergency medical services personnel, it is now included as a standard tool in the pediatric advanced life support (PALS) and advanced pediatric life support (APLS) courses.\textsuperscript{18,19} The PAT uses visual and auditory clues to quickly assess a child’s general appearance, work of breathing, and circulation (Fig. 1). A child’s overall appearance is useful as a screening tool of neurologic status. A child with septic shock may appear lethargic or inconsolable, have a weak or absent cry, make poor eye contact or be poorly interactive, or otherwise appear to have an abnormal level of consciousness. Increased work of breathing and tachypnea may be signs of a primary

Fig. 1. PAT. (Adapted from Dieckmann RA, Brownstein D, Gausche-Hill M. The pediatric assessment triangle: a novel approach for the rapid evaluation of children. Pediatr Emerg Care 2010;26(4):313; with permission.)
respiratory illness, a compensatory mechanism for a primary metabolic acidosis, or secondary to fever, anxiety, or pain.

Evaluating a child’s circulatory status and rapidly recognizing signs of inadequate tissue perfusion are often difficult at the child’s bedside. Unlike in adults, hypotension is usually a late and ominous finding in children. Tachycardia, bradycardia, and tachypnea, although not highly specific, should never be overlooked. Persistent tachycardia not otherwise caused by fever, anxiety, pain, dehydration, or anemia should always be regarded as a potential sign of early sepsis and shock.

A careful examination of a child’s skin may provide vital clues to a child’s circulatory status independent of BP measurements. Infants and children with severe sepsis and septic shock often are able to maintain a normal or even increased BP as a result of robust compensatory mechanisms including tachycardia and increased SVR. In these patients with cold shock, capillary refill time is prolonged, and pallor, cyanosis, or mottling may be evident. Children with warm shock, on the other hand, have warm, flushed skin and brisk or flash capillary refill time.

**LABORATORY TESTS AND BIOMARKERS**

Laboratory tests may be used both in the identification of sepsis as well as in guidance of sepsis management, but none is both highly sensitive and specific in children. The American College of Critical Care Medicine (ACCM) recommends diagnosing sepsis and septic shock in neonates and children using clinical examination rather than any specific biomarkers. However, because this diagnosis may be challenging, using laboratory tests as an adjunct is also recommended by some experts.

A complete blood count (CBC) with differential should be obtained in any child suspected of having a serious infection. Age-specific leukocytosis or leukopenia is a criterion for pediatric SIRS (see Box 1). The most extensive data regarding the usefulness of the white blood cell count in identifying occult serious bacterial infection are found in children younger than 3 years in the prevaccination eras; several studies identified an increased risk of occult pneumococcal bacteremia among unimmunized febrile children with white blood cells 15,000/μL or greater and absolute neutrophil count 10,000/μL or greater. Leukocytosis is less predictive for the presence of a serious bacterial infection in the fully immunized child. This finding has led some experts to question the routine use of CBC alone to guide the empirical administration of antibiotics.

Lactic acid, which is a by-product of anaerobic metabolism, can be used as a marker of tissue hypoperfusion. In adults with severe sepsis, an increased lactate level (>4 mmol/L) is a negative prognostic indicator and should trigger aggressive septic resuscitation according to the Surviving Sepsis Campaign guidelines. In addition, early lactate clearance, defined as a decrease in serum lactate level by 10% or more after initial fluid resuscitation, is associated with improved outcomes in severe sepsis and septic shock in adults.

Lactate levels have not traditionally been used in pediatric sepsis management and data are limited in this population. Nevertheless, an increased lactate level is predictive of serious bacterial infection in the pediatric emergency department as well as an increased risk of death in the pediatric intensive care setting. In addition, a recent small, prospective study suggests that an increased lactate level in the emergency department may predict which children have early sepsis and will progress to severe sepsis and septic shock. Further studies are likely needed before routine use of lactate levels is recommended in pediatric sepsis diagnosis and management.

Biomarkers have the potential to diagnose, monitor, and predict outcome in clinical systemic inflammation syndromes such as sepsis. No single biomarker currently...
available is both highly sensitive and specific to be trusted in isolation. C-reactive protein (CRP) is the most universally available.\textsuperscript{32} Although it has limited sensitivity in differentiating bacterial from viral infections, it does aid in identifying children with serious bacterial infections.\textsuperscript{24,33} Procalcitonin has more recently been studied in children. Its use as a diagnostic tool is similar to that of CRP.\textsuperscript{24} However, its lack of availability and higher cost limits its clinical usefulness. Although there may be some limited added value in combinations of tests to screen for serious infection, any diagnostic test must be interpreted in the context of the child’s clinical presentation.\textsuperscript{24}

Other routine laboratory tests are less likely to identify the presence of sepsis but may help guide management. A rapid bedside glucose level identifies life-threatening hypoglycemia, which commonly accompanies sepsis in young children and infants. A basic metabolic panel may help identify metabolic acidosis, renal insufficiency, and electrolyte abnormalities. Coagulation studies, fibrinogen, and D-dimer are indicated when there is a clinical suspicion for meningococcal infection or other concerns for disseminated intravascular coagulopathy. Increased total bilirubin and transaminase levels may support the diagnosis of organ dysfunction. Arterial or venous blood gas should be obtained if there is suspicion of acidosis or respiratory insufficiency. Appropriate cultures of all suspected sources of infection should be obtained but should not delay the administration of antibiotics.

**MANAGEMENT OF SEPSIS AND SEPTIC SHOCK**

The cornerstone of emergency department management of sepsis and septic shock is early recognition and rapid, aggressive resuscitation.\textsuperscript{2} The ACCM has developed an algorithm to help guide clinicians (Fig. 2).\textsuperscript{20} In a prospective study of 91 neonates and children who presented to a community hospital in shock, the children in whom shock was reversed within the first 2 hours had a 96% survival rate and a greater than 9-fold increase in the odds of survival compared with the children in whom shock was not quickly reversed.\textsuperscript{34} Moreover, for each hour in which shock was not reversed, there was a significant increase in mortality. Carcillo and colleagues\textsuperscript{15} similarly found that early use of PALS/APLS-recommended interventions was associated with reduced mortality and morbidity.

The goal of sepsis management in the emergency department is reversal of tissue hypoperfusion. Physiologic end points include normal BP, capillary refill time 2 seconds or less, normal range heart rate, normal pulses with no differentiation between central and peripheral pulses, urine output 1 mL/kg/h or greater, and restoration of normal mental status.\textsuperscript{20,35} Lactate levels and lactate clearance, which are shown in adults to be clinically relevant, are not part of the 2007 ACCM guidelines or 2012 Surviving Sepsis Campaign update but may be clinically useful.\textsuperscript{20,35}

**Sepsis Protocols**

Emergency department-based sepsis protocols are commonly used in adults to aid rapid recognition of sepsis and initiation of resuscitative interventions. These protocols rely on vital signs to initiate prioritized physician evaluation, a standard set of laboratory tests, rapid vascular access and fluid resuscitation, and early antibiotic administration.

There is a limited but growing subset of literature supporting a similar standard approach in pediatric patients. Larsen and colleagues\textsuperscript{21} implemented an emergency department sepsis protocol to rapidly identify children with early sepsis and initiate management quickly. Triage nurses relied on a simple reference tool that defined age-appropriate abnormal vital signs and physical findings for patients with possible septic shock. Positive triage screening triggered implementation of a septic shock
care guideline based on the 2007 ACCM Consensus recommendations. This triage-based screening tool successfully decreased length of stay in the emergency department and increased compliance with many elements of the recommended guidelines, most important of which were 3 key interventions known to decrease morbidity and mortality (ie, initial fluid resuscitation of ≥20 mL/kg in the first hour, an assessment of serum lactate, and antibiotics within 3 hours of emergency department admission).

Cruz and colleagues similarly studied a triage-based screening tool to recognize vital sign abnormalities and implement a septic shock protocol. Their results showed a significant reduction from the time of triage to the first fluid bolus and antibiotic administration. Overall, emergency department sepsis protocols may improve recognition of early sepsis and compliance with current sepsis guidelines.
As in all emergent resuscitation, the initial ABCs (airway, breathing, circulation) should be addressed according to PALS guidelines. Positioning the child’s head and neck in the sniffing position to optimize breathing is a basic yet potentially significant intervention. This positioning involves aligning the tragus of the ear with the patient’s sternum. In very young children, the sniffing position is usually achieved by placing a towel roll under the shoulders, whereas in older children elevating their head slightly may be necessary. Suctioning excess upper airway secretions, especially within the nasopharyngeal airways, may also be helpful in children younger than 6 months, because they are typically obligate nasal breathers.

Supplemental oxygen should routinely be administered by face mask. In the presence of respiratory distress or hypoxemia, high-flow nasal cannula or nasopharyngeal continuous positive airway pressure (CPAP) may be appropriate. Children are more likely to require mechanical ventilation because they have decreased respiratory reserve and increased oxygen requirements. A definitive airway should be secured by endotracheal intubation if indicated. The decision to intubate is difficult but should be made based on clinical signs of increased work of breathing, inadequate respiratory effort, refractory hypoxemia, or a combination of these signs, rather than any specific laboratory test result. Although endotracheal tube intubation and mechanical ventilation should not be unnecessarily delayed, there is less risk of cardiovascular collapse during rapid sequence intubation (RSI) if the child has been adequately resuscitated before attempting intubation and initiating positive pressure mechanical ventilation.

Venous access should be established as quickly as possible. Peripheral intravenous catheters are preferred, but may be difficult to place in the dehydrated and septic child. If this procedure is unsuccessful, intraosseous access is recommended. Rarely, central venous access is necessary in the emergency department.

When invasive procedures or mechanical ventilation are necessary, procedural sedation or RSI is appropriate. Etomidate has been the induction agent of choice for many clinicians because of its lack of cardiovascular effects. However, although etomidate continues to be recommended by some experts, the current ACCM guidelines discourage the routine use of etomidate in children with septic shock because of concerns that it suppresses adrenal function and may increase mortality. Ketamine may be a more appropriate choice, because it helps maintain cardiovascular stability. Succinylcholine and rocuronium are both acceptable paralytic agents for RSI. However, the recommended dose of succinylcholine in young children (1.5–2 mg/kg) is larger than that usually given to adult patients (1–1.5 mg/kg).

The current recommendation from the ACCM for neonates and children in septic shock is the rapid intravenous administration of isotonic crystalloid or colloid solution in 20-mL/kg boluses over 5 minutes each (see Fig. 2). To accomplish this rapid fluid infusion through a small peripheral or intraosseous catheter, either a pressure bag or the push-pull system is superior to gravity drainage alone. After each bolus, the child’s hemodynamic status should be reevaluated for signs of normal perfusion and shock reversal. Children commonly require 40 to 60 mL/kg, and occasionally up to 200 mL/kg, intravenous fluid in the first hour of resuscitation. In general, children with septic shock who receive more fluid in the first hour have reduced morbidity and mortality than children who receive less.
Differentiating septic from cardiogenic shock is a common concern in the emergency department. Consideration should always be given to depressed cardiac contractility either as the primary cause of shock or as a result of septic shock. Aggressive fluid resuscitation in the first several hours in children with septic shock rarely causes ARDS. However, if a child develops rales or hepatomegaly during fluid resuscitation, the clinician should consider inotropic support and emergent echocardiography.

Vasoactive Agents

Vasoactive agents are recommended in children with fluid-refractory septic shock (ie, children who remain in shock despite 40–60 mL/kg or more intravenous fluid resuscitation) (see Fig. 2). Inotropic medications increase CO by increasing cardiac contractility or heart rate. Vasopressors increase SVR by increasing arterial circulation tone. Vasodilators decrease arterial resistance, resulting in a decreased afterload and increased CO. In many cases, a single drug may have combined effects that cause alterations in SVR and contractility or may have dose-dependent effects.

Central venous access is the optimal route of vasoactive drug administration, because it delivers the drug to the central circulation rapidly and eliminates the risk of peripheral extravasation. However, it is preferred that vasopressor administration not be delayed, and, therefore, it is recommended to start vasopressors via a peripheral intravenous or intraosseous catheter if central access is not rapidly available.

The choice of vasoactive agent for children with septic shock is a matter of debate, and the recommendations are consensus expert opinion rather than evidence based (see Fig. 2). Similar to volume resuscitation, the goal of vasoactive therapy in septic shock is the restoration of normal tissue perfusion. Because the cardiovascular response to severe sepsis is more variable in children than in adults, there is no single vasoactive agent that is appropriate for all children with septic shock. In addition, the age of the child, perfusion of the kidneys and liver, and presence of systemic inflammation may affect the pharmacokinetics and physiologic effects of vasoactive medications. Therefore, recommended agents and dosages are only approximations and should be titrated to clinical effects.

Dopamine traditionally has been used as a first-line medication for the support of circulation, and the ACCM guidelines continue to recommend its use in children with undifferentiated fluid-refractory septic shock. At midrange doses (5–10 μg/kg/min), it is believed that the vasopressor β-adrenergic effects of dopamine predominate, resulting in an increase in SVR. At higher doses, α-adrenergic receptor stimulation adds some inotropic effect as well. However, the dose-related effects of dopamine are unpredictable, and there is some evidence that suggests that adults who receive dopamine have increased morbidity compared with those who do not receive dopamine. In addition, young infants (<6 months old) may be insensitive to dopamine. As a result, many experts discourage the reflexive use of dopamine in septic shock.

Norepinephrine is the preferred vasoactive agent in adults with septic shock, because adults more predictably have increased CO and decreased SVR. There is some controversy regarding its use in children. In children who clinically have fluid-refractory warm shock, the ACCM guidelines recommend the use of norepinephrine (0.03–0.05 μg/kg/min) as the first-line vasopressor rather than dopamine.

In patients with cold shock, inotropic and possibly vasodilatory support is beneficial, because these children have increased SVR and decreased CO. The most commonly used inotropic agents in the emergency department are dopamine and epinephrine. The ACCM guidelines recommend dopamine as the first-line inotrope in cold septic shock. This recommendation is based on wide availability, practitioner familiarity...
with the drug, and because, unlike in adult populations, dopamine has not been linked to increased mortality in children. For patients who are hypotensive with cold shock, epinephrine (0.05–0.3 µg/kg/min) is the preferred vasoactive agent. However, at doses exceeding 0.1 µg/kg/min, epinephrine may have more pronounced \( \alpha \)-adrenergic effects, causing increased systemic vasoconstriction. There are no studies that have directly compared dopamine and epinephrine in the treatment of septic shock in children.

Dopamine is a reasonable first-line drug for undifferentiated septic shock in children. However, norepinephrine for hypotensive warm shock and epinephrine for hypotensive cold shock may be better options. Most children who fail to respond to dopamine respond to norepinephrine or epinephrine.

Overall, the use of vasoactive agents in children with septic shock is a dynamic process in which vasopressors, inotropes, and even vasodilators are titrated to clinical signs of perfusion and shock reversal in each individual patient rather than being administered at a standard infusion rate. This procedure is best achieved by actively attending at the child’s bedside. Once the child is in the intensive care unit, other inotropic agents (dobutamine), vasopressors (vasopressin, angiotensin), vasodilators that reduce pulmonary and SVR (sodium nitroprusside), and phosphodiesterase inhibitors that act as inotropes and vasodilators (milrinone) may be indicated.

**Antibiotics**

Empirical, broad-spectrum antibiotics should be administered as soon as possible in the emergency department whenever sepsis is suspected. The appropriate antibiotic choice is based on suspected infection site, suspected organism, whether the infection was likely acquired in the community or health care setting, host factors such as immunosuppression, and local resistance patterns.

Few studies have analyzed the causes of sepsis and septic shock in all patients presenting to the emergency department, and, therefore, it is difficult to make broad recommendations. In general, all children with septic shock, if not otherwise contraindicated, should receive a third-generation or fourth-generation cephalosporin plus coverage for methicillin-resistant *Staphylococcus aureus*, usually vancomycin. Children who are immunocompromised or are otherwise at risk for infection with *Pseudomonas* species should receive appropriate additional coverage. When gastrointestinal or genitourinary sources are suspected, adding coverage for enteric organisms with an aminoglycoside, piperacillin/tazobactam, clindamycin, or metronidazole is appropriate. Empirical coverage for *Listeria* with ampicillin and for herpes simplex virus with acyclovir should be considered in neonates. It is prudent and recommended to consult a pediatric infectious disease specialist when considering empirical antibiotics in a child with septic shock.

Ideally, appropriate culture should be obtained before antibiotics. However, antibiotics should never be delayed because cultures have not been obtained. The goal is to administer antibiotics within 1 hour of onset of septic shock, because this has been shown to reduce mortality in adults.44

**Other: Steroids, Glucose, Site Control, Extracorporeal Membrane Oxygenation**

If a child is at risk for absolute adrenal insufficiency or adrenal axis failure, such as congenital adrenal hyperplasia, recent systemic steroid therapy, or preexisting hypothalamic/pituitary abnormalities, or there is a clinical concern for purpura fulminans, hydrocortisone should be administered.20 There is no ideal laboratory method for detecting absolute or relative adrenal insufficiency, but a blood sample for baseline serum cortisol measurement should be obtained before giving hydrocortisone.
Hydrocortisone may be given either as an intermittent bolus dose or as a continuous infusion. The dose ranges for 1 to 2 mg/kg/d for stress coverage to 50 mg/kg/d for reversal of shock. (See further discussion later regarding steroid use in fluid-refractory and catecholamine-resistant septic shock.)

Because hypoglycemia is common among children with sepsis, consideration should always be given to infusing a dextrose-containing fluid at maintenance rate in addition to resuscitative fluid boluses of non–dextrose-containing crystalloid.

Physical measures undertaken to eliminate a focus of infection, referred to as source control, are an important consideration in any patient with septic shock. Specific sources of infection that may require surgical site control include abscesses, empyemas, necrotizing fasciitis, peritonitis, and cholangitis. Other potentially complicated infections that may benefit from removal of a potentially infected device include artificial valve-associated endocarditis, catheter-related bacteremia, and orthopedic hardware-related septic arthritis and osteomyelitis. Infections associated with extensive necrotic tissue may also benefit from surgical debridement.

Although extracorporeal membrane oxygenation (ECMO) is not an emergency department therapy, it is worth mentioning as a viable option for refractory shock. Neonates and children have high survival rates (80% and 50%, respectively) when placed on ECMO for septic shock. This rate is similar to survival rates for refractory respiratory failure. However, thrombotic complications may be more common when ECMO is used for septic shock.

**Fluid-Refractory and Catecholamine-Resistant Shock**

Pediatric septic shock is usually associated with severe hypovolemia, and children usually respond well to aggressive volume resuscitation and vasoactive therapy. Fluid-refractory, catecholamine-resistant septic shock is defined as persistent cardiovascular dysfunction despite the administration of at least 60 mL/kg of intravenous fluid resuscitation in the first hour and maximum dopamine or norepinephrine or epinephrine therapy. In these patients, it is important to search for alternative causes of persistent shock, including pericardial tamponade, tension pneumothorax, and intra-abdominal compartment syndrome (intra-abdominal pressure >12 mm Hg). The use of hydrocortisone or other steroid therapy in children with fluid-refractory and catecholamine-resistant septic shock remains controversial. Relative or absolute adrenal insufficiency is more common in children. In addition, there is evidence that children who die from septic shock are more likely to have lower cortisol levels than survivors. However, another retrospective study found that the mortality among children with septic shock who received steroids was 30% compared with 18% among those who did not receive steroids. Because this study lacked illness severity data, it is impossible to know if steroids were preferentially given to the more ill children. A subsequent study that did account for disease severity found no mortality benefit from steroid therapy. As a result of the limited and potentially flawed data available, the ACCM continues to maintain clinical equipoise of the topic of adjunctive steroid therapy for pediatric septic shock in the absence of a clinical suspicion for absolute adrenal insufficiency, such as children with purpura fulminans and Waterhouse-Friderichsen syndrome, those who have received steroid therapies for chronic illnesses, and children with known pituitary or adrenal abnormalities.

In patients with suspected absolute adrenal insufficiency and catecholamine-resistant shock, the ideal dose of hydrocortisone also remains unknown. The recommendation from the Surviving Sepsis Campaign is an initial stress dose (50 mg/m²/24 h), with the caveat that some children may require higher infusion rates.
(<=50 mg/kg/24 h) to reverse shock in the short-term. The ACCM suggests titrating the dose to resolution of shock using between 2 mg/kg/d and 50 mg/kg/d as a continuous infusion. The treatment should be weaned off as quickly as tolerated to minimize potential side effects.

PROGNOSIS

Since the 1960s, the mortality from sepsis in children in the United States has decreased from 97% to less than 10%, which is dramatically lower than the 30% estimated mortality in adults. Mortality is highest among children with chronic medical diseases. However, the overall incidence seems to be increasing. This increase is most likely because of the increased incidence of very-low-weight neonates.

SUMMARY

Despite major advancements in the prevention, recognition, and management of sepsis and septic shock in children, infectious diseases remain a significant burden on childhood health worldwide. Although use of broad-spectrum antibiotic and early goal-directed therapy have together decreased mortality from sepsis in the developed world from more than 90% to approximately 10%, early recognition and aggressive initial management in the emergency department remain obstacles despite their proven benefit.

Early recognition of sepsis and septic shock in children relies on obtaining an attentive clinical history, accurate vital signs, and a physical examination focused on mental status, work of breathing, and circulatory status. Laboratory tests, including a white blood cell count and lactate level, may support the diagnosis but are not reliable in isolation.

The goal of septic shock management is reversal of tissue hypoperfusion. Resuscitation priorities include airway management, respiratory support, aggressive fluid administration, and vasopressor support, as well as early, broad-spectrum, empirical antibiotic therapy. The therapeutic end point is shock reversal, as shown by improved hemodynamic signs on examination rather than laboratory end points.

Overall, children are able to tolerate the physiologic effects of severe sepsis better than adults. Mortality is significantly better among children when managed appropriately; but the stakes remain high. Every physician who cares for children must strive to have a high level of suspicion and keen clinical acumen for recognizing the rare but potentially seriously ill child.

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