Although severe sepsis and septic shock is less common in the pediatric population, it has been estimated that approximately 100,000 infants and children present to emergency departments (EDs) annually with severe sepsis. In recent months, there has been increased focus on the management of sepsis in the pediatric population. In 2012, an update was published regarding the management of severe sepsis and septic shock, which included specific guidelines for the pediatric population. Although not intended specifically for emergency physicians, these guidelines were provided for anyone caring for term newborns or children with severe sepsis and septic shock.

**Practice Guideline Impact**

- Parameters in defining severe sepsis in children are age related.
- Initial resuscitation includes administering oxygen, obtaining intravenous and/or intraosseous access for fluid and medication administration.
- Antibiotics should be administered within 1 hour of identification of severe sepsis.
- Fluid administration is critical in treating septic shock. Consider inotropes if signs of volume overload develop and hypotension is still present.

Editor's Note: To read more about this publication and the background and methodologies for practice guideline development, go to: http://www.ebmedicine.net/introduction

Prior to beginning this activity, see “CME Information” on page 9.
Introduction To The Guideline: Pediatric Severe Sepsis And Septic Shock

This issue of *EM Practice Guidelines Update* reviews the pediatric section of “Surviving Sepsis® Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012” published by the Surviving Sepsis® Campaign.1


For this current update of the previous 2008 Surviving Sepsis® Guidelines, a consensus committee of 68 international experts representing 30 international organizations were appointed to different groups according to their areas of expertise. Each group was responsible for drafting the initial update for their assigned topic.

These recommendations are intended to provide the physician guidance in treating a term newborn or child with severe sepsis in both an intensive care unit (ICU) or non-ICU setting in an industrialized environment with full access to mechanical ventilation. The recommendations are intended to be best practice and are not meant to represent a standard of care.

In the United States, the hospital mortality rate for severe sepsis is 2% in healthy children and 8% in children with chronic illnesses.2 The definition of sepsis in children is similar to the definition of sepsis in adults, but it takes into account age-specific values.

Sepsis in children is defined as the presence of at least 2 of the following criteria, 1 of which must be abnormal temperature or abnormal leukocyte count:3

- Rectal temperature of > 38.5°C or < 36°C
- Tachycardia > 2 standard deviations above normal for age (in absence of external stimuli: pain, crying, drugs) OR in those aged < 1 year, bradycardia < 10th percentile (in the absence of drugs, congenital heart disease)
- Respiratory rate > 2 standard deviations above normal for age
- High or low leukocyte count for age or 10% bands

Severe sepsis is sepsis plus 1 of the following:3

- Cardiovascular dysfunction
- Acute respiratory distress syndrome
- Two or more other organ dysfunction/failure

**Description Of The Guideline Methodology**

Strength of evidence was determined using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Through this system, evidence is rated from high (A) to very low (D). Level A studies are well-done randomized control trials (RCTs); level B studies are downgraded RCTs (due to limitations, biases, inconsistencies, etc) or upgraded observational studies; level C studies are well-done observational studies with controlled RCTs; and a level D study is a downgraded controlled study or expert opinion-based evidence. Recommendations were also classified as strong (grade 1) or weak (grade 2). The higher the quality of evidence, the larger the difference between desirable and undesirable consequences, the more certainty or similarity in values, or the lower cost of an intervention to the alternative, the more likely a strong recommendation was given.
Recommendations For Initial Resuscitation

• We suggest starting with oxygen administered by face mask or, if needed and available, high-flow nasal cannula oxygen or nasopharyngeal continuous positive airway pressure (CPAP) for respiratory distress and hypoxemia. Peripheral intravenous access or intraosseous access can be used for fluid resuscitation and inotrope infusion when a central line is not available. If mechanical ventilation is required, then cardiovascular instability during intubation is less likely after appropriate cardiovascular resuscitation. (Grade 2C)

• We suggest that the initial therapeutic endpoints of resuscitation of septic shock be capillary refill of ≤ 2 seconds, normal blood pressure for age, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output > 1 mL/kg/h, and normal mental status. Thereafter, SCVO₂ saturation ≥ 70% and cardiac index between 3.3 and 6.0 L/min/m² should be targeted. (Grade 2C)

• We recommend following the American College of Critical Care Medicine-Pediatric Advanced Life Support (ACCM-PALS) guidelines for the management of septic shock. (Grade 1C)

• We recommend evaluating for and reversing pneumothorax, pericardial tamponade, or endocrine emergencies in patients with refractory shock. (Grade 1C)

Editorial Comment

Because lactate levels have not been shown to be correlated with septic shock in children (lactate levels can be normal in sepsis), the guideline recommends following cardiac index and SCVO₂; however, the specific modality used to do this is left to the practitioner. It is important to remember that an abnormal lactate level would be concerning, but a normal level does not rule out septic shock in children. Young infants have low functional residual capacity and may require early intubation.

Recommendations On Antibiotic Administration

• We recommend that empiric antimicrobials be administered within 1 hour of the identification of severe sepsis. Blood cultures should be obtained before administering antibiotics when possible, but this should not delay initiation of antibiotics. The empiric drug choice should be changed as epidemic and endemic ecologies dictate (eg, H1N1, methicillin-resistant Staphylococcus aureus, chloroquine-resistant malaria, penicillin-resistant pneumococci, recent ICU stay, neutropenia). (Grade 1D)

• We suggest the use of clindamycin and antitoxin therapies for toxic shock syndromes with refractory hypotension. (Grade 2D)

• Clostridium difficile colitis should be treated with enteral antibiotics, if tolerated. Oral vancomycin is preferred. (Grade 1A)

• We recommend early and aggressive infection source control. (Grade 1D)

Editorial Comment

Prompt administration of antibiotics reduces morbidity and mortality in children. The referenced literature for this recommendation includes 2 quality control studies focusing on improving time to antibiotics, a retrospective review examining daptomycin for MRSA infections and a retrospective cohort study examining risk factors for acquiring Enterococcus coli and Klebsiella species infections while in the ICU. Although the methodology is low, early antibiotics are strongly recommended, and they should be administered within 1 hour.

Children are more prone to toxic shock syndrome due to the lack of circulating antibodies to toxins. Therefore, clindamycin should be administered in children with erythroderma and suspected toxic shock. The use of antitoxin therapy (such as intravenous immunoglobulin [IVIG]) in the treatment of toxic shock syndrome is unclear, but may be considered in refractory cases. A multicenter retrospective cohort study published in 2009 examining its use in children with streptococcal toxic shock syndrome did not find improved outcome with its use, however.4
Recommendations On Fluid Resuscitation

- In the industrialized world, with access to inotropes and mechanical ventilation, we suggest that initial resuscitation of hypovolemic shock begin with infusion of isotonic crystalloids or albumin, with boluses of up to 20 mL/kg for crystalloids (or albumin equivalent) over 5 to 10 minutes. These should be titrated to reversing hypotension, increasing urine output, and attaining normal capillary refill, peripheral pulses, and level of consciousness without inducing hepatomegaly or rales. If hepatomegaly or rales develop, inotropic support should be implemented, not fluid resuscitation. In children with severe hemolytic anemia (severe malaria or sickle cell crises) who are not hypotensive, blood transfusion is considered superior to crystalloid or albumin bolusing. (Grade 2C)

Editorial Comment

It is important to remember that children often compensate well for early hemodynamic compromise, with increased heart rate and vasoconstriction preventing the initial drop in blood pressure typically seen in septic shock. Therefore, blood pressure alone should not be used to assess either the need for fluid resuscitation or the adequacy of resuscitation once started. Fluid resuscitation is recommended in children who are both normotensive and hypotensive. For initial resuscitation, 40 to 60 mL/kg (or more) may be needed. Multiple randomized control trials have demonstrated decreased mortality when adequate fluid resuscitation is administered to children in septic shock. In cases of purpuric or suspected meningococcal septic shock, aggressive hemodynamic resuscitation and support with fluid boluses, inotropes and/or mechanical ventilation are of particular importance as studies have shown a nearly 10-fold reduction in mortality with appropriate intervention in these children.

Recommendations For Inotropes/Vasopressors/Vasodilators

- We suggest beginning peripheral inotropic support until central venous access can be attained in children who are not responding to fluid resuscitation. (Grade 2C)
- We suggest that children with low cardiac output and elevated systemic vascular resistance states with normal blood pressure be given vasodilators in addition to inotropes. (Grade 2C)

Editorial Comment

Although the preferred method of delivery of an inotrope is through a central venous line, it has been shown in the literature that a delay in inotrope administration is associated with increased mortality risk. Therefore, administration should not be delayed and can be administered via a peripheral IV line until central access can be obtained. Available literature strongly supports the importance of early versus late inotropic administration when clinically indicated in septic children. These data underlie the recommendation for the use of inotropic agents via peripheral access as the difficulty associated with obtaining central access in children can lead to significant delays in care. The addition of vasodilator therapy is recommended for children with invasive monitoring in place and a persistent low cardiac output state with high systemic vascular resistance and normal blood pressure despite fluid resuscitation and inotropic support. Although the emergency clinician is unlikely to encounter this particular scenario, it is important to consider in cases where there is a delay in admission to the ICU or with a transfer to a higher-level facility.
Guidelines For The Management Of Pediatric Severe Sepsis And Septic Shock

Recommendation For Extracorporeal Membrane Oxygenation
• We suggest extracorporeal membrane oxygenation (ECMO) in refractory septic shock or with respiratory associated failure with sepsis. (Grade 2C)

Editorial Comment
Reviews of the Extracorporeal Life Support Organization Registry have shown survival rates of 73% for neonates and 39% for children after the use of ECMO for the treatment of sepsis. The survival rate was higher for those undergoing venoarterial ECMO. A separate review of the database reported a 41% survival rate to discharge for those children undergoing ECMO for sepsis. A retrospective study, looking at 1 institution’s experience with venoarterial ECMO in refractory septic shock reported a 74% (17 patients) survival rate to discharge. Because many centers are currently not capable of performing ECMO on children, it is important to remember that early transfer to an appropriate institution may be necessary for the survival of these patients.

Recommendations For Blood Products And Plasma Therapies
• We suggest similar hemoglobin targets in children as in adults. During resuscitation of low superior vena cava oxygen saturation shock (< 70%), hemoglobin levels of 10 g/dL are targeted. After stabilization and recovery from shock and hypoxemia, a lower target > 7.0 g/dL can be considered reasonable. (Grade 1B)
• We suggest similar platelet transfusion targets in children as in adults. (Grade 2C)
• We suggest the use of plasma therapies in children to correct sepsis-induced thrombotic purpura disorders, including progressive disseminated intravascular coagulation, secondary thrombotic microangiopathy, and thrombotic thrombocytopenic purpura. (Grade 2C)

Editorial Comment
The evidence regarding the optimal hemoglobin level in children with severe sepsis is limited. One trial compared hemoglobin levels of 7 g/dL versus 9.5 g/dL without showing any difference in outcome. The current recommendations suggest using the same target number as for adults.

Recommendation For Corticosteroids
• We suggest timely hydrocortisone therapy in fluid-refractory, catecholamine-resistant shock and suspected or proven absolute (classical) adrenal insufficiency. (Grade 1A)

Editorial Comment
It has been shown in a prospective cohort study that absolute and relative adrenal insufficiency is common in children with fluid-refractory, catecholamine-resistant shock. Another study investigating whether serum cortisol and adrenocorticotropic hormone (ACTH) levels correlate with severity of illness in severe meningococcal disease showed that low cortisol and high ACTH concentrations were associated with poor outcomes. Approximately 25% of children with septic shock have adrenal insufficiency. Those at risk for adrenal insufficiency include patients with: severe septic shock, purpura, previous steroid use in chronic illness, and pituitary or adrenal abnormalities. Treatment consists of IV hydrocortisone infusion at stress dose levels (50 mg/m²/24 h). Death from adrenal insufficiency and septic shock often occurs within 8 hours of presentation; however, a multicenter retrospective cohort study that included 477 children with severe sepsis did not find a definitive improvement in outcomes for those receiving corticosteroid therapy compared to those who did not.

Recommendation For Mechanical Ventilation
• We suggest providing lung-protective strategies during mechanical ventilation. (Grade 2C)

Editorial Comment
The evidence cited in this recommendation includes a case series for airway pressure release ventilation and a prospective clinical study for the use of HFOV. A recent study from Brazil reported increased survival using high-frequency oscillatory ventilation in children with ARDS. Although it is unlikely that the emergency clinician will find themselves using this type of ventilation in the ED setting, it is important to recognize its potential utility in children with sepsis suffering from ARDS.
Recommendations For Sedation/Analgesia/Drug Toxicities

- We recommend use of sedation with a sedation goal in critically ill mechanically ventilated patients with sepsis. **(Grade 1D)**
- We recommend monitoring drug toxicity laboratory results because drug metabolism is reduced during severe sepsis, putting children at greater risk of adverse drug-related events. **(Grade 1C)**

Editorial Comment
Propofol should be avoided in children aged < 3 years due to association with fatal metabolic acidosis. Etomidate use is discouraged as well, as it can lead to hemodynamic instability from inhibition of the adrenal axis and sympathetic nervous system.

Recommendation For Glycemic Control

- We suggest controlling hyperglycemia using a similar target as in adults (≤ 180 mg/dL). Glucose infusion should accompany insulin therapy in newborns and children. **(Grade 2C)**

Editorial Comment
A prospective cohort study on children with septic shock showed that serum glucose levels > 178 mg/dL are associated with increased mortality risk.12 A prospective randomized controlled study was performed in 2009 investigating the effect of keeping serum glucose levels at age-adjusted fasting levels in critically ill children.13 Short-term outcome was found to be better in those receiving insulin therapy; however, long-term survival and morbidity was not investigated. It is common for critically ill children to develop hyperglycemia, and efforts should be made to keep serum glucose levels < 180 mg/dL. Infants are at risk for developing hypoglycemia when they depend on intravenous fluids. This means that a glucose intake of 4 to 6 mg/kg/min or maintenance fluid intake with dextrose 10% normal saline is advised (6-8 mg/kg/min in newborns).

Recommendation For Diuretics And Renal Replacement Therapy

- We suggest use of diuretics to reverse fluid overload when shock has resolved and, if unsuccessful, continued venous hemofiltration or intermittent dialysis > 10% total body weight fluid overload. **(Grade 2C)**

Editorial Comments
When evaluating a child in severe sepsis/septic shock, it is important to remember that there are differences in how they look or respond when compared to their adult counterparts. These guidelines were written to provide guidance to those caring for infants and children with severe sepsis and septic shock. When reading through these guidelines, the emergency clinician should remember that although many of the therapies recommended will likely occur outside of the ED (ie, in the ICU setting), it is important to be familiar with them in case the need to provide prolonged care in the ED arises.

It should be noted that in a child with suspected severe sepsis/septic shock, blood pressures can often be normal, as children can compensate for hypotension with elevated heart rates and vasoconstriction more effectively than adults. Low blood pressure is usually a late finding and cardiovascular collapse may be imminent in the hypotensive child. Therefore, it is imperative to begin fluid resuscitation in normotensive children with suspected sepsis. Delay in fluid administration may be quite harmful to the patient and result in continued deterioration of the patient's clinical status. Obtaining intravenous access may be extremely difficult in the child with sepsis as they are often severely vasoconstricted from septic shock and/or dehydrated as a result of fever or not tolerating fluids. Intraosseous access is a perfectly acceptable method of giving antibiotics, medications, and fluids until a more secure line can be established.

Once severe sepsis is identified, early administration of antibiotics is essential. Although the preferred method is to collect cultures prior to giving antibiotics, that is not the main priority in patients with sepsis. Treating sepsis with antimicrobials as soon as possible is the goal. It is important to remember that the choice of empiric antibiotics can and should be altered based on endemic and epidemic ecologies.
Guidelines For The Management Of Pediatric Severe Sepsis And Septic Shock

References


CME Questions

To take the CME test, visit: www.ebmedicine.net/CME or scan the QR code below with a smartphone:

1. Etomidate is the first-line sedative in meningococcal sepsis.
   a. True
   b. False

2. If hepatomegaly or rales develop during resuscitation in a child with septic shock, you should
   a. Continue fluid resuscitation until blood pressure normalizes
   b. Reverse volume overload with diuretics and continue fluid resuscitation
   c. Begin inotropic support and continue fluid resuscitation
   d. Stop fluid resuscitation, give diuretics, and begin inotropic support

3. Once severe sepsis is identified, antibiotics should be given:
   a. Once all cultures have been obtained
   b. Within 1 hour
   c. Once the source is identified
   d. Upon consultation with an infectious disease specialist

3. Which child is in severe sepsis?
   a. A 4-year-old boy with temperature of 38°C, normal white cell count, heart rate of 168 beats/min, and wheezing
   b. A 4-year-old boy with temperature of 39°C, normal white cell count, heart rate of 168 beats/min, and wheezing
   c. A 4-year-old boy with temperature of 39°C, normal white cell count, heart rate of 168 beats/min, and hypoxia despite being on 100% nonrebreather mask
   d. A 4-year-old boy with temperature of 37°C, normal white cell count, heart rate of 168 beats/min, and no urine output in 18 hours
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Goals: Upon completion of this article, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence, (2) cost-effectively diagnose and treat the most critical ED presentations, and (3) describe the most common medicolegal pitfalls for each topic covered.

Objectives: Upon completion of this article, you should be able to: (1) describe the differences in management of severe sepsis and septic shock between children and adults; (2) summarize the guideline’s recommendations on fluid administration in septic shock; and (3) apply antibiotic administration guidelines to children with severe sepsis.

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