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Title

Pediatric Sepsis: ACH Guideline

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Pediatric Sepsis

Key Points:

- Sepsis is an overwhelming and life-threatening response to an infection that can cause dysfunction of multiple organ systems.
- In pediatrics, diagnosing sepsis is especially challenging as children can compensate for severe illness for prolonged periods.
- Septic children can look well and still be septic; they often show subtle signs of stress as compared with adults.
- When evaluating the ill child, it is essential for the physician to consider pediatric sepsis in the differential diagnosis.
- Due to the differences in children, it is essential to appreciate the characteristics of sepsis and treat sepsis early in pediatric patients.

1. **Definitions:**
    a. Systemic Inflammatory Response Syndrome (SIRS): The complex pathophysiological response to an insult leading to an increased inflammatory state.
        i. Positive SIRS criteria requires abnormalities in two or more of the following, one of which must be abnormal temperature or white blood cell count:
            1. Temperature > 38.5°C or < 36°C
            2. White blood cell count > 12,000 cells/mm^3 or < 4,000 cells/mm^3
            3. Respiratory rate more than two SD above normal
            4. Heart rate more than two SD above normal
    b. Sepsis: The presence of SIRS and a known or possible infection.
    c. Severe Sepsis: Sepsis with signs and symptoms of organ hypoperfusion or dysfunction including cardiovascular dysfunction, respiratory distress, or multiorgan dysfunction in 2 or more organ systems.
    d. Septic Shock: Sepsis with cardiovascular dysfunction that persists despite fluid resuscitation (40ml/kg isotonic fluid).
        i. Hypotension is not needed to meet the criteria of septic shock
        ii. Hypotension is indicative of late, decompensated shock.
    e. Refractory Septic Shock: Septic shock that persists despite fluid resuscitation (60ml/kg isotonic fluid) or administration of Inotropes.

2. **Epidemiology**
    a. Sepsis is a leading cause of morbidity and mortality.
    b. As of 2015, the global prevalence of pediatric severe sepsis was 8.2%.
    c. Sepsis can occur in all ages but is more common in toddlers,
        i. Median age: three years.
    d. Most common sites of infection leading to sepsis:
        i. Respiratory tract
        ii. Bloodstream.

e. The mortality rate for pediatric septic shock admitted to the pediatric intensive care unit (PICU) is 5.6% to 17-24%.

1) **Etiology**
   a. Sepsis, in all of its forms, necessitates a known or suspected infectious source.
   b. The source of sepsis can be
      i. Bacterial
         1. Rates of sepsis from *Streptococcus pneumoniae* and *Neisseria meningitidis* are decreasing due to vaccinations.
         2. *Staphylococcus aureus*:
            a. MSSA: Community-onset infection rates have increased (3.9% per year, $p<0.0001$) from 2012 to 2017.
            b. MRSA: Community and hospital onset infection rates have decreased (6.9% and 17.1% per year respectively) from 2005 to 2016.
      ii. Fungal (Candida)
      iii. Viral (HSV, Enterovirus)
   c. Risk factors that increase the likelihood of developing sepsis and septic shock:
      i. Age < 1 month: Group B Strep and Escherichia coli are most common.
      ii. Asplenia: Higher risk of infection with encapsulated microorganisms
      iii. Serious injury (e.g. major trauma, burns, or wounds)
      iv. Chronic medical condition: At risk for multi-drug resistant bacteria
      v. Sickle cell disease
      vi. Immunosuppression
      vii. Transplant recipient
      viii. Indwelling medical device: Allow entry of organisms
      ix. Urinary tract abnormalities
      x. Recent steroid use

3. Pathophysiology
   a. Sepsis involves a complex interaction between the host's immune system and a pathogen.
      i. Infection leads to a normal physiological response:
         Release of chemokines, cytokines, and interleukins from neutrophils and macrophages causing:
         a. Vasodilation,
         b. Increased endothelial permeability
         c. Activation of coagulation pathways.
      ii. This normal response can escalate and become unregulated resulting in end-organ damage.
   b. Toxic Shock Syndrome: stems from a superantigen toxin that leads to a cytokine storm and can lead to multisystem disease.

4. Clinical presentation
   a. The presentation of sepsis varies with the age of the patient.
      i. Tachycardia may be the only sign.

ii. In neonates: Any change from the patient's baseline behavior should raise suspicion for sepsis.
iii. Children with intact cardiovascular systems can maintain a normal blood pressure for a relatively long period of time despite having sepsis or severe sepsis.
iv. If compensated shock remains unrecognized and untreated, the child will deteriorate quickly.

b. It is essential to ask about the patient's vaccination status, current medical conditions, and any recent illnesses or procedures that may increase the likelihood of sepsis.
c. Any risk factor that can increase the likelihood of infection or decrease the body's ability to fight an infection should raise suspicion for sepsis, if present.

5. Diagnosis

a. Sepsis is a clinical diagnosis.
b. A child may present with signs ranging from a slightly elevated or increasing heart rate to more overt signs such as respiratory failure or altered mental status.
c. A diagnosis of sepsis should be considered in children with persistently abnormal vital signs, and it is important to follow trends over time for early detection.
d. Common physical exam findings for severe sepsis and shock include:
    i. Tachycardia
    ii. Cold/pale extremities
    iii. Delayed capillary refill time (CRT) > 3 seconds or flash CRT
    iv. Bounding or weak pulses
    v. Mottled skin
    vi. Decreased urine output
    vii. Dry mucous membranes
    viii. Tachypnea
    ix. Apnea
    x. Grunting
    xi. Nasal flaring
    xii. Hypoxia
    xiii. Lethargy
    xiv. Agitation
    xv. Hypotension as a late symptom
e. Blood cultures should be obtained before initiating antibiotic therapy, but should not delay the administration of antibiotics in a critically ill child.
    i. Culture any possible source of infection (urine, CSF, abscess, wound, stool, etc.).
    ii. Consider HSV testing in neonates
f. Labs and studies can assist in diagnosing abnormalities and organ dysfunction in sepsis, but are not necessary for the diagnosis of sepsis:
    i. Complete Blood Count:
        1. Leukocytosis or leukopenia
        2. Thrombocytosis or thrombocytopenia.
    ii. Basic metabolic panel:

1. Hypoglycemia and hypocalcemia, should be corrected.
2. A twofold increase in creatinine can reflect kidney injury.
3. A low bicarb may reflect metabolic acidosis.

iii. Urinalysis: To assist in the diagnosis of a urinary tract infection.

iv. Liver function tests: Total bilirubin ≥ 4 mg/dL or alanine aminotransferase (ALT) > 2 times the upper limit of normal indicates liver dysfunction.

v. A blood gas can assist in the evaluation of oxygenation, ventilation, and acid-base disturbances.

vi. Lactate: Elevation can indicate an insufficient delivery of oxygen to tissue.

vii. Procalcitonin: Can be increased when there is a bacterial infection.

viii. Coagulation studies: If there are concerns for disseminated intravascular coagulation (DIC).

1. Decrease in fibrinogen
2. Elevation in prothrombin time, partial thromboplastin time, INR, and/or D-dimer.

6. Treatment

a. Early recognition of sepsis and septic shock is crucial to improving outcomes.

i. A one-hour delay in the initiation of appropriate resuscitation measures has been associated with increased mortality (OR, 2.29; 95% CI, 1.19-4.44).

ii. Once severe sepsis or septic shock is identified, there should be a rapid assessment of the child, followed by the initiation of time-sensitive, goal-directed management and support.

b. In the first 5 minutes,

i. Initiate intravenous (IV) access with two large-bore IV catheters.

1. If IV access is unable to be acquired, then intraosseous (IO) access should be obtained.

ii. Supplemental oxygen should be provided.

1. If the child is in respiratory distress, consider high-flow nasal cannula or noninvasive positive-pressure ventilation.

c. In the first 15 minutes:

i. Obtain laboratory tests.

ii. Prepare IV antibiotics.

iii. Initiate fluid resuscitation.

1. An initial volume of 20 mL/kg of an isotonic solution should be administered.
    a. Crystalloid fluids, such as normal saline and Ringer's lactate, are equally effective as colloids.
    b. These fluids should be rapidly pushed via 60 mL syringes or with a rapid infuser.
    c. IV infusion pumps may be too slow.
2. Reassess the patient’s response to IV fluids to monitor for fluid overload.
    a. Signs of fluid overload include:
        i. crackles in the lungs

ii. hepatomegaly
iii. Increased heart rate in response to fluids.

b. Children at increased risk for fluid overload should receive less aggressive fluid therapy and require more attentive evaluation after boluses:
i. Increased risk factors include:
1. Neonates
2. Underlying renal disease
3. Cardiac disease.

d. In the first 60 minutes
i. The total goal for fluid resuscitation is 60 mL/kg within the first 60 minutes.
ii. When the shock state persists after 60 mL/kg of fluid resuscitation, the clinical diagnosis is fluid-refractory shock (i.e., septic shock).
1. Inotropes and/or vasopressor infusions should be initiated with:
a. Fluid-refractory shock
b. Fluid overload during the fluid resuscitation.
2. Vasoactive agents are chosen based on whether the child is in cold shock or warm shock.
a. Cold shock: Low cardiac output and high systemic vascular resistance from peripheral vasoconstriction.
i. Epinephrine infusion should be initiated.
ii. Symptoms:
1. Mottled with cold extremities
2. Delayed capillary refill
3. Weak pulses.
b. Warm shock: High cardiac output and low systemic vascular resistance from peripheral vasodilation.
i. Norepinephrine infusion should be initiated
ii. Symptoms:
1. Warm extremities
2. Bounding peripheral pulses
3. Flash capillary refill
4. Wide pulse pressure.
c. The initiation of any of these inotropes should not be delayed due to a lack of central venous access. These medications can be infused through a peripheral IV or IO until central venous access is acquired.
iii. Septic shock is a dynamic process; patients can shift from one type of shock to another, requiring changes to their selected vasoactive medications over time.

e. Antibiotics:
i. The Surviving Sepsis Guidelines emphasize the importance of antibiotic administration within one hour of sepsis recognition.

ii. Mortality increases with every one-hour delay in the administration of antibiotics; this reaches statistical significance once a three-hour delay in the initial dose occurs.
iii. If obtaining IV access is difficult, many antibiotics can be given intramuscularly.
1. Start with broad-spectrum antibiotics.
a. Empiric treatment with ceftriaxone and vancomycin provides considerable gram-negative and gram-positive coverage.
i. These antibiotics are widely available and easy to administer.
2. The child's age and history should be considered when determining antibiotic choices:
a. Children less than 1 month:
i. Ampicillin and a third-generation cephalosporin or an aminoglycoside should be used to cover:
1. Listeria monocytogenes, group B Streptococcus, and Gram-negatives
ii. Acyclovir should be used if there is concern for HSV
b. Site of the infection:
i. Skin infection: Consider adding MRSA coverage
ii. Feet: Consider adding *Pseudomonas aeruginosa* coverage.
iii. Pneumonia with empyema: Add MRSA coverage.
iv. Gastrointestinal: Add anaerobic coverage.
c. Review previous positive cultures to evaluate for resistant organisms.
d. Immunosuppression predisposes the patient to gram-negative bacteremia and fungemia
e. If toxic shock syndrome is suspected: Add clindamycin.
f. The overall treatment goals:
i. Support oxygenation and ventilation with a goal SpO_2^* > 94%.
ii. Administer broad spectrum antibiotics in the first hour
iii. Restore peripheral and end-organ perfusion.
iv. Achieve a normal heart rate for age.
v. Attain a normal blood pressure for age.
vi. Establish adequate oxygenation, ventilation, and circulation within the first hour of shock recognition.
g. The child should be reassessed after each intervention while targeting specific therapeutic goals.

7. Disposition

a. All children with proven or suspected severe sepsis or septic shock should be hospitalized.

b. If hemodynamically stable, a child may be admitted to the inpatient floor with frequent monitoring, a plan to rapidly identify clinical changes, and an escalation plan if there are clinical changes consistent with worsening sepsis.
c. ICU team/rapid response team should be notified if clinical changes and need to admit or transfer to the PICU.
d. All children with septic shock should be admitted to a PICU.
e. Consider infectious disease consultation to assist with evaluation and antibiotic management.

References

1. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):2-8. doi: 10.1097/01.pcc.0000149131.72248.e6.

2. Biban P, Gaffuri M, Spaggiari S, Zaglia F, Serra A, Santuz P. Early recognition and management of shock in children. *Pediatr Rep*. 2012;4(1):e13. doi: 10.4081/pr.2012.e13.

3. Weiss SL, Fitzgerald JC, Pappachan J, et al. Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. *Am J Respir Crit Care Med*. 2015;191(10):1147-1157. doi: 10.1164/rccm.201412-2323oc.

4. Hartman ME, Linde-Zwirble WT, Angus DC, Watson RS. Trends in the epidemiology of pediatric severe sepsis. *Pediatr Crit Care Med*. 2013;14(7):686-693. doi:10.1097/pcc.0b013e3182917fad.

5. Schlapbach LJ, Straney L, Alexander J, et al; ANZICS Paediatric Study Group. Mortality related to invasive infections, sepsis, and septic shock in critically ill children in Australia and New Zealand, 2002-13: a multicentre retrospective cohort study. *Lancet Infect Dis*. 2015;15(1):46-54. doi: 10.1016/s1473-3099(14)71003-5.

6. Tavare A, O'Flynn N. Recognition, diagnosis, and early management of sepsis: NICE guideline. *Br J Gen Pract*. 2017;67(657):185-186. doi: 10.3399/bjgp17x690401.

7. Davis AL, Carcillo JA, Aneja RK, et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. *Crit Care Med*. 2017;45(6):1061-1093. doi: 10.1097/ccm0000000000002425.

8. Han YY, Carcillo JA, Dragotta MA, et al. Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. *Pediatrics*. 2003;112(4):793-799. doi: 10.1542/peds.112.4.793.

9. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med*. 2017;43(3):304-377. doi: 10.1007/s00134-0174683-6.

10. Weiss SL, Fitzgerald JC, Balamuth F, et al. Delayed antimicrobial therapy increases mortality and organ dysfunction duration in pediatric sepsis. *Crit Care Med*. 2014;42(11):2409-2417. doi: 10.1097/ccm.0000000000000509.

11. Kourtis AP, Hatfield K, Baggs J, et al. Vital Signs: Epidemiology and Recent Trends in Methicillin-Resistant and in Methicillin-Susceptible Staphylococcus aureus Bloodstream Infections - United States. *MMWR Morb Mortal Wkly Rep*. 2019;68(9):214-219. Published 2019 Mar 8. doi:10.15585/mmwr.mm6809e1