Abstract:
Sepsis is a significant cause of morbidity and mortality for neonates and infants. Neonates are at increased risk for sepsis due to their immature immune system. Bacterial, viral, and fungal organisms may cause sepsis in the young patient. Identifying septic neonates upon presentation to their primary care physician or the emergency department remains a challenge given the nonspecific manifestations of illness. Suspicion for sepsis should prompt evaluation to identify a source to tailor treatment appropriately. Timely diagnosis and management of neonatal sepsis, especially for those in septic shock, will lead to improved outcomes. The following article presents an overview of the most common organisms causing disease, clinical presentation, evaluation, and management for the neonate or infant presenting with suspected sepsis.

Keywords:
neonatal sepsis; bacterial infection; viral infection; fungal infection; emergency department

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Neonatal Sepsis

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Sepsis remains a major cause of morbidity and mortality during the first year of life. Sepsis is the sixth leading cause of death among neonates, and the eighth leading cause of death for infants during the first year of life.[1] Septic neonates and infants often present to the emergency department or to their primary care physician with nonspecific findings including lethargy, poor feeding, irritability, and temperature instability. Prompt diagnosis and treatment are important to improve the outcome for the presenting patient.

Neonatal sepsis is classified based on the infant's age at the onset of symptoms. Neonatal *early-onset sepsis* (EOS) is defined as bacteremia or bacterial meningitis occurring in the newborn at less than 7 days of age or at less than 72 hours in the hospitalized very low-birth-weight (VLBW) infant.[2–4] *Late-onset sepsis* (LOS), in the term neonate, generally occurs at 7 days of age or greater or after 72 hours in the VLBW infant.[4] EOS is generally due to vertical transmission, and LOS has mostly been attributed to nosocomial or horizontal acquisition.[5] Neonatal infections of viral or fungal etiology may also occur and must be differentiated from bacterial infections.[6,7]

EPIDEMIOLOGY AND PATHOGENESIS

All neonates are at increased risk for infection due to their immature immune defenses. Studies have shown an increased rate of neonatal infection associated with lower gestational age and lower birth weight.[8] In one study, the incidence of early-onset neonatal infection in infants born at term was 0.53 per 1000 live births.[9] In the preterm population, the incidence of EOS was 3.71 per 1000 live births and 10.96 per 1000 live births in VLBW infants.[2,10] There is also an increased incidence of LOS among VLBW neonates, especially those who require hospitalization, compared with term infants.[8]

Risk factors for EOS include preterm birth, maternal colonization with group B *Streptococcus* (GBS), prolonged rupture of membranes longer than 18 hours, or maternal signs or symptoms of intraamniotic infection.[11,12] GBS remains the leading cause of EOS in term neonates, although the overall national incidence has

decreased by 87% with the implementation of intrapartum antibiotic (IPA) for the prevention of early-onset GBS sepsis.[13] IPA does not change the risk of getting LOS. Since the initiation of IPA for GBS, *Escherichia coli* has emerged as the leading cause of EOS in preterm neonates.[2,14]

In addition to low birth weight and gestational age, other risk factors for sepsis include immunodeficiency, indwelling catheters, and some inborn errors of metabolism, such as galactosemia, which may present as *E coli* sepsis or urosepsis.[15] After GBS, the other prevalent gram-positive organisms causing neonatal sepsis include *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, *Enterococcus*, and *Listeria monocytogenes*. Other than *E coli*, the most common gram-negative organisms are *Klebsiella*, *Enterobacter*, *Citrobacter*, and *Pseudomonas*.[2,5,14]

Finally, viral and fungal organisms can also cause illness in neonates. Some key viral infections include herpes simplex virus (HSV), human immunodeficiency virus, enterovirus, respiratory syncytial virus, influenza, adenovirus, and rotavirus. Neonatal HSV generally presents in the first 6 weeks of life. Approximately 1500 cases of neonatal HSV infection occur every year in the United States.[16] Neonatal HSV can present as skin, eye, and mouth disease; central nervous system (CNS) disease; or disseminated disease. EOS and LOS can also be caused by fungal infections, most often *Candidia albicans* or *C parapsilosis*, found primarily in preterm VLBW infants.[17]

INITIAL MANAGEMENT AND DIAGNOSTIC TESTING

The septic infant or neonate may be "well-appearing" with few symptoms or may present in septic shock. Signs and symptoms of neonatal sepsis are more often nonspecific. Upon obtaining a complete history, any reported deviations in activity or feeding pattern should be taken seriously. An infant may have temperature instability, irritability, lethargy, respiratory distress, apnea, poor feeding, abdominal distension, jaundice, and/or tachycardia. Poor perfusion and hypotension are generally late findings but are sensitive indicators of sepsis.[10]

In an infant presenting in septic shock, initial management should focus on stabilizing the patient. This may include alleviating airway compromise, providing respiratory support, and obtaining intravenous access for restoration of circulation and perfusion.[18] According to the 2007 updated American College of Critical Care Medicine guidelines for management of pediatric and neonatal septic shock, fluid resuscitation with isotonic or colloid boluses should be given starting with 20 mL/kg up to a maximum of 60 mL/kg, with reassessment of liver size and rales indicating fluid overload. In a neonate in septic shock, correcting hypocalcemia and hypoglycemia is important. If fluid resuscitation does not restore perfusion, central access should be considered and inotropes started. Of note, until central access is available, inotropes may be started peripherally. Hydrocortisone should be administered to infants with suspected adrenal insufficiency, and until ductal-dependent congenital heart disease is ruled out, a prostaglandin infusion should be considered.

Laboratory testing should be performed on neonates with possible sepsis. Although available diagnostic testing is not always helpful in deciding who should receive antibiotics, it can assist in the decision regarding the appropriate time to discontinue treatment. According to the American Academy of Pediatrics guidelines on the management of early-onset neonatal sepsis,[19] a blood culture is required for all neonates with suspected sepsis. When a single pediatric blood culture bottle is used, a minimum of 1.0 mL of blood is needed. Cultures from tracheal aspirates should be obtained if intubated.[19] In addition, a complete blood count with differential and platelet count should also be obtained. If the patient presents in respiratory distress, a chest radiograph is recommended. A lumbar puncture should be performed if the infant has a positive blood culture, has suggestive laboratory data, is clinically symptomatic, or does not improve with initiation of antibiotics.[19]

When obtaining a lumbar puncture, cerebrospinal fluid (CSF) should be sent for culture, cell count, and protein and glucose concentration. Acceptable values for CSF differ between term and preterm neonates. Several studies have examined the various indices. The mean number of white blood cells in uninfected preterm and term infants was less than 10 cells/mm.[3,20,21] In infants with meningitis, the median number of white blood cells in those born less than 34 weeks was 110/mm^3, and in those greater than 34 weeks, it was 477/mm.[3,22,23] Protein concentrations in preterm infants are inversely proportional to gestational age.[19] In a term newborn, the protein concentration should be less than 100 mg/dL.[20,21] Normal CSF glucose concentrations are similar to those in children. It is important to remember that some infants with meningitis have normal CSF values.[20,21]

In infants 1 week of age or older, sterile urine culture and urinalysis are needed during the evaluation of LOS.[19] Infants with EOS generally do