Neonatal Sepsis in the Emergency Department

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Despite significant improvements in the care and management of acutely ill infants, septicemia remains one of the top 10 causes of neonatal death. Neonates can present either shortly after birth or later with subtle signs to suggest infection. Early diagnosis and prompt intervention are essential to prevent serious morbidity and mortality in neonates (<28 days of age) and infants (>28 days of age) with sepsis. Unlike older children, a young infant is often incapable of demonstrating clinical evidence of illness, and even a well-appearing infant may have a bacterial or viral disease. The immaturity of the newborn’s immune system may increase the susceptibility of these patients to infections. The following article is a review of the clinical presentation, differential diagnosis, and evaluation and management of a neonate presenting to the emergency department with suspected sepsis.

Sepsis is ranked as the sixth leading cause of death among neonates and the eighth leading cause of death for infants through the first year of life [1]. The incidence of neonatal sepsis is 1 to 5 per 1000 live births [2]. These vulnerable patients present to the emergency department (ED) or their primary care provider’s office with non-specific symptoms and are unable to articulate their concerns. Quite often, the only presenting symptom is fever, and not uncommonly, these infants are described as “well appearing.”

Neonatal sepsis is classified as either early or late based on the timing of presentation. In the literature, however, there is no definitive consensus as to what age limits apply, with early-onset sepsis ranging from 48 hours to 6 days after delivery [3]; late-onset sepsis generally occurs beyond the first week of life. The clinical relevance of this distinction is that early-onset disease is often due to organisms acquired during delivery. Late-onset disease is only occasionally a result of vertical transmission and is more frequently caused by organisms acquired after delivery (nosocomial or community sources) [3]. Characteristics of early and late neonatal sepsis are summarized in Table 1.

Risk Factors and Pathogenesis

Although no significant sex difference has been reported, it was noted as early as the 1960s that male infants had a higher incidence of neonatal sepsis than females, which may be related to X-linked immunoregulatory genes [2]. Early-onset sepsis occurs primarily via vertical transmission, and the most common risk factors are prolonged rupture of membranes (>18 hours before delivery), maternal fever (>100.5°C), chorioamnionitis, and preterm birth (<37 weeks estimated gestational age). The infant can either become colonized with bacteria during passage through an infected or colonized birth canal or via the
upward spread of infection after rupture of membranes. The pathogens that cause late-onset disease may be acquired vertically in the peripartum period or horizontally from fomites in the environment or from colonized caregivers after delivery [2].

Other risk factors for neonatal sepsis include a history of immune deficiency disorders such as severe combined immunodeficiency syndrome and some inborn errors of metabolism such as galactosemia, which may present in the first week of life with *Escherichia coli* (*E. coli*) sepsis or urosepsis. The presence of a ventriculoperitoneal (VP) shunt, central line, and need for recurrent bladder catheterization (as in infants with a neurogenic bladder as a result of myelomeningocele) also increase the risk for infection. Regardless of the risk factor, sepsis or bacteremia occurs when the skin or mucosal barrier become compromised and allow entry of organisms into the blood stream.

### Immunological Basis for Increased Susceptibility to Infection in Newborns

The immunologic system consists of 2 main defense mechanisms, innate and acquired immunity. Innate immunity consists of the natural barriers that do not require prior exposure to microbes or antigen and includes intact skin or mucous membranes, gastric acid, and digestive enzymes. The phagocytic cells beneath these layers constitute the next line of defense if microorganisms somehow breach the cutaneous and/or the mucosal barriers. Acquired immunity consists of the cell-mediated (T lymphocyte) and humoral (B lymphocyte and immunoglobulin) systems. Compared with older children and adults, all newborns have a developmentally immature immune system and increased susceptibility to invasive microbial infection [4].

After birth, immunoglobulin (Ig) A contributes significantly to the neonate's immune defense and is one example of the developmental evolution of the immune system and exemplifies how neonates and infants differ from older children and adults. Secretory IgA is a polymeric form of IgA that prevents bacterial adhesion to mucosal sites and therefore inhibits colonization. Some studies have demonstrated low levels of secretory IgA in saliva of human neonates in the first few days of life (adult levels in secretions are not generally achieved before 6 to 8 years of age) [5]. This low level of IgA is thought to allow for colonization and thus predispose newborns to invasive infections.

Another important component of humoral defense for the fetus and newborn is IgG. Maternal transfer of IgG begins around 22 weeks of gestation and continues throughout the third trimester. Type-specific antibody plays a major role in the clearance of not only viral organisms but also group B *Streptococcus* (GBS) and other pathogenic bacteria from the circulation as well [5]. The importance of type-specific antibody in immunity to GBS was demonstrated by Lancefield et al [8], and an association was proven for GBS types 1a, 1b, and 111 in the human neonate [6-9]. Type-specific antibodies appear to offer protection to some neonates born to mothers with colonized genital tracts who have higher antibody titers to GBS compared with the low level of protective antibody in the serum of pregnant women who are not colonized with GBS [5]. The remainder of the immunoglobulins (IgM, IgA, IgD, and IgE) do not cross the placenta and are of fetal or neonatal origin, and the presence of these immunoglobulins in the newborn circulation implies a fetal or newborn response to a particular pathogen and can be used as a tool to diagnose certain infections.

T-cell function is also developmentally immature in neonates. This is best exemplified by neonatal infections with *Listeria monocytogenes*. *Listeria* is an anaerobic facultative motile gram-positive intracellular bacillus that affects primarily neonates, immunocompromised adults, and the elderly. Although neonatal sepsis from *Listeria* is rare, if infected, neonates are at increased risk for developing overwhelming sepsis and meningitis without appropriate therapy. *Listeria* in neonates repels phagosome killing through its major virulence factor, listeriolysin O; cell-cell transmission of the organism occurs rapidly without exposure to the humoral antibodies or neutrophils. T lymphocytes provide the only natural recognition and immunity toward *L. monocytogenes*, and because cellular immunity is suppressed during pregnancy and is naturally deficient during early neonatal life, this predisposes the neonate to severe infections [10,11].
Other host responses to bacterial infections are delineated in Table 2.

### Etiology

The spectrum of organisms causing neonatal sepsis has changed over time. Since the late 1960s to early 1970s, *Streptococcus agalactiae* (GBS) has emerged as a major pathogen associated with neonatal sepsis and meningitis. Many infants with invasive GBS disease present with early-onset sepsis and are often identified and treated before discharge after birth. As a result of guidelines prepared by the Center for Disease Control and Prevention, the American Academy of Pediatrics, and the American College of Obstetrics and Gynecology [12], the attack rate of early-onset sepsis due to GBS in the United States has gradually declined since 1996 from 2 per 1000 live births to 0.36 per 1000 live births in 2005 [13]. However, many infants are discharged home before 48 hours and may present as outpatients with this serious disease. One study of febrile infants younger than 3 months presenting to their primary care physician’s office found that GBS was the second most frequently isolated organism in this age group [14]. A second large study found that among infants younger than 3 months presenting to an ED with a serious bacterial illness, 20% were positive for gram-positive organisms and 6% were positive for GBS [15]. Other gram-positive organisms causing disease in young infants include *Staphylococcus aureus*, *Enterococcus* species, *Streptococcus pneumoniae*, and less frequently, *L. monocytogenes* [14,15].

The most commonly isolated bacterial organisms in young febrile infants are gram-negative organisms [14-16]. *E. coli* is the most common gram-negative organism found in infants presenting with fever. Other gram-negative organisms include *Klebsiella* species, *Enterobacter* species, *Salmonella*, *Citrobacter* species, and *Neisseria* species.

In addition to bacterial etiologies, viruses are a significant cause of morbidity and mortality in neonates and young infants. There are numerous viruses known to cause infection in man, and most tend to occur in a seasonal fashion, and community outbreaks can increase one’s index of suspicion. In 2004, Byington et al [15] found that 35% of infants (n = 1385) who presented with fever to the ED were positive for one or more viruses; the most frequently isolated viruses were respiratory syncytial virus (RSV) and enterovirus (EV). An equally important consideration is whether febrile infants with viral illnesses could have a concomitant serious bacterial infection. During the 1970s to 1990s, several studies of infants and children up to 3 years old with RSV infection found a concomitant serious bacterial infection in 0% to 1.9% [15]. In a similar, but more recent, evaluation of infants 1 to 90 days old presenting to the ED with fever, the authors found that viral positive infants had a lower risk for serious bacterial infection in general and specifically a lower occurrence of bacteremia, urinary tract infection (UTI) (2.5% of the infants positive for RSV had a bacterial UTI), and soft tissue infection. Conversely, those who were virus negative were nearly 3.5 times more likely to have a serious bacterial infection (10.4% of the infants who were negative for viral infections had a bacterial UTI) [15]. The viruses isolated in this study were EV, RSV, influenza A or B, parainfluenza 1, 2, or 3, rotavirus, adenovirus, herpes simplex virus (HSV), and varicella virus.

### Table 2

**Host responses to bacterial infection in the neonate.**

<table>
<thead>
<tr>
<th>Component</th>
<th>Function</th>
<th>Status in Neonate</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complement</td>
<td>Opsonization, chemoattraction</td>
<td>Decreased complement components, especially in preterm infants C8, C9, and alternative pathway components are decreased more than others</td>
<td>↓ production of chemotactic factors, ↓ opsonization of bacteria</td>
</tr>
<tr>
<td>Antibody</td>
<td>Opsonization, complement</td>
<td>IgG concentration ↓ in preterm infants, term infants have higher concentration than adults; only IgG is transported across the placenta</td>
<td>Lack of antibody to specific pathogens results in ↑ risk of infection</td>
</tr>
<tr>
<td>Activation</td>
<td></td>
<td>IgA absent from secretions</td>
<td>↑ risk of mucosal colonization with potential pathogens ↓ inflammatory response, inability to localize infection</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>Chemotaxis</td>
<td>Impaired migration, impaired binding to chemotactic factors Impaired up-regulation of adhesive glycoproteins</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phagocytosis</td>
<td>Normal with sufficient quantities of opsonin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bacterial killing</td>
<td>Normal in healthy neonates, ↓ in stressed neonates</td>
<td></td>
</tr>
<tr>
<td>Monocyte</td>
<td>Chemotaxis</td>
<td>Decreased</td>
<td>↓ inflammatory response</td>
</tr>
<tr>
<td></td>
<td>Phagocytosis</td>
<td>Controversial</td>
<td>Uncertain</td>
</tr>
<tr>
<td></td>
<td>Bacterial killing</td>
<td>Controversial</td>
<td>Uncertain</td>
</tr>
</tbody>
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Modified and reprinted with permission from Polin and St Geme [5].
Enterovirus and herpes viral infections are important causes of neonatal morbidity and mortality. Enterovirus is a RNA virus from the Picornaviridae family. Five species of EV are known to infect humans (EV types A, B, C, D and poliovirus), which include 68 serotypes traditionally classified as polioviruses, echoviruses, coxsackieviruses, and numbered EVs [17]. Each year, an estimated 10 to 15 million symptomatic enteroviral infections occur in the United States. During 1970 to 2005, 44.2% of reported cases occurred in infants younger than 1 year, and the proportion of reports with fatal outcome had a bimodal distribution by age with peaks for ages less than 1 year and greater than 45 years [18]. According to the National Enterovirus Surveillance System report from 1970 to 2005, two thirds of reported cases of EV in infants younger than 1 year were caused by coxsackie B1.

There are 2 types of HSV, types 1 and 2, which are known pathogens that can cause significant morbidity and mortality in the neonate. Herpes simplex virus is a DNA virus and humans are the only known reservoir [19]. The incidence of neonatal HSV infection ranges from 1:1400 to 1:30 000 deliveries, resulting in 1500 to 2200 cases of neonatal HSV infection each year in the United States [19]. Transmission of HSV results from close personal contact either at times of symptomatic disease, or more commonly, during periods of asymptomatic viral shedding [19]. The risk of vertical transmission of HSV relates to maternal serologic status; the risk is highest with primary HSV-2 infection and lowest with recurrent/reactivation of HSV-2 infection in the mother. The lower transmission rate in recurrent disease is attributed to the lower viral titer, transplacentally protective antibodies, and lower frequency of cervical viral shedding during recurrent infection [19].

Fungal infections are rare in healthy infants but may occur in infants with central line access, VP shunts, and infants requiring recurrent bladder catheterization. Fungemia in a healthy infant should raise concern for immunodeficiency beyond the developmental physiologic immunodeficiency of infancy.

Clinical Assessment

A detailed history and a complete physical examination are equally important in the assessment of an ill infant. Laboratory evaluations and diagnostic tests are also essential because it is important to remember that many ill infants present with nonspecific signs. An infant presenting with respiratory distress may demonstrate distress as a result of infection, congenital heart disease, or an inborn error of metabolism. Similarly, fever is a common reason for a caregiver to seek medical attention, but this too is a nonspecific finding in that dehydration, drug withdrawal, and extensive hematomas can also result in pyrexia [2]. Sick newborns and infants often present with temperature instability, and this may be as concerning, if not more so, than sustained fever. Therefore, a systematic approach as described in the article in this issue on the evaluation and management of the critically ill neonate is necessary for an appropriate assessment. In general, neonatal sepsis, both early and late, can present with temperature instability, feeding difficulties, diarrhea, respiratory instability such as tachypnea or apnea, lethargy, hypoglycemia, and persistent unexplained jaundice. In some cases, skin lesions may provide an important clue to the diagnosis, such as the presence of microabscesses in L. monocytogenes and grouped vesicular lesions in neonatal herpes. Late-onset bacterial sepsis differs from early-onset disease in that a significant number of infants with late-onset disease present with meningitis and UTIs.

Viral illnesses may also present with nonspecific symptoms in the neonate. Clinical presentation may range from a “well-appearing” infant with fever, cough, or rhinorrhea to a critically ill-appearing infant with coagulopathy, hypotension, and in severe cases, congestive heart failure and myocarditis. In addition, viral myocarditis may present with tachycardia (in the absence of fever), ST segment changes on electrocardiogram, and poor left ventricular function on echocardiogram.

The neonate presenting in septic shock must be recognized promptly because early intervention can significantly decrease morbidity and mortality [20]. Careful attention to the history and physical examination can provide important clues to the presence of shock. Vital sign abnormalities such as fever and tachycardia are common in infants with sepsis, but shock must be considered when these signs present with changes in mental status, an indicator of decreased cerebral perfusion. The neurologic finding of mental status change in a neonate may range from an irritable infant to one who is lethargic or unable to be aroused [21]. Bradycardia is unique to neonates and infants in septic shock as compared with older pediatric patients and adults and could be related to hypothermia (<36°C), which is frequently seen. Hypothermia may blunt tachycardia. The cardiovascular examination can indicate altered perfusion through abnormal capillary refill (sluggish, >2 seconds or flash) as well as altered pulses (weak or bounding). Other findings suggestive of shock include cool extremities and oliguria (urine output <1 mL/kg per hour).

The diagnosis of shock does not require that a neonate be hypotensive. It is a late finding in septic shock in neonates, and its presence confirms decompenasated shock [21,22]. A consensus panel on sepsis and organ dysfunction suggested vital sign parameters, which may help in identifying neonates with shock: heart rate less than 100 or greater than 180 beats per minute, respiratory rate greater than 50 breaths per minute for newborns in the first week of life and greater than 40 from 1 week until 1 month of age, and systolic blood pressure lower than 65 mm Hg within the first week of life and lower than 75 mm Hg from 1 week until 1 month old [22].
Laboratory Testing

As discussed earlier, identification of infants with serious infections on the basis of presenting signs is difficult. Therefore, accepted practice is to obtain a complete blood count, blood culture, urinalysis (UA), urine culture, and cerebrospinal fluid (CSF) from all neonates presenting with possible sepsis [23]; 1-2 mL is acceptable for a blood culture in neonates. The urine culture should be obtained via sterile urethral catheterization or suprapubic aspiration. A UA showing 10 or greater white blood cells (WBCs)/high-power field (HPF) and/or bacteria on Gram stain suggests a UTI. Normal values for CSF in neonates differ not only from those of older children but also between preterm and term babies. Accepted normal range values for preterm and term neonates respectively are 0-25, 0-22 cells/mm³ (WBC); 65-150, 20-170 mg/dL (protein); 24-63, 34-119 mg/dL (glucose) [24].

Whether to obtain additional diagnostic studies is case dependent. In the past, a workup for sepsis meant routinely obtaining a chest radiograph. It is no longer the norm for every patient in which infection is a concern but is suggested in those who present with respiratory symptoms and/or have fever. If the history, time of year, or examination findings raise concern for specific organisms, focused diagnostic testing should be ordered. For example, testing for RSV, influenza, or adenovirus requires sampling nasopharyngeal secretions for the antigen. For pertussis, culture of the nasopharynx would be the gold standard, but polymerase chain reaction may be available to some EDs. Latex agglutination to test for bacterial antigen may be helpful when a patient has already received antibiotic therapy; however, it should not replace obtaining a blood culture. Although this technology has been used on both urine and CSF, a retrospective study of older infants and children who had CSF agglutination tests showed that the test provided no added value to CSF Gram stain and culture in diagnosing or excluding meningitis in those treated before cultures were obtained [25].

When concerned about enteroviral or herpes meningoencephalitis, polymerase chain reaction should be ordered on the CSF specifically for those viruses. Additional sites to culture for herpes include the mouth, nasopharynx, conjunctiva, rectum, and any suspicious skin lesions. The blood buffy coat may also grow the virus. Enterovirus can be cultured from the throat, rectum, stool, and potentially from the blood and urine. Electrolytes, blood glucose, an arterial blood gas, and coagulation studies are worth obtaining because metabolic and hematologic derangements are observed in sepsis. Hypocalcemia and hypoglycemia, when detected, should be corrected. A blood gas will help establish the degree of metabolic acidosis as well as the presence of respiratory failure as a result of sepsis. Disseminated intravascular coagulation is another consequence of sepsis, and patients may have thrombocytopenia, prolonged prothrombin and activated partial thromboplastin times as well as low fibrinogen levels that may require transfusion.

Individual or combinations of laboratory tests would ideally identify infected neonates and distinguish between bacterial, viral, and other types of infections, with the goal of decreasing antibiotic exposure and unnecessary admissions to the hospital. Examples of these tests are the WBC count, absolute band count, UA, C-reactive protein (CRP), interleukins, and procalcitonin. These examples represent an abbreviated list of investigated markers. We include a brief discussion of some of these, keeping one important caveat in mind for the neonate: regardless of preliminary laboratory results, standard clinical practice includes initiation of antibiotics after obtaining cultures and then admission of infants 28 days or younger to the hospital if infection is a concern [23].

Leukocyte counts have been well studied in the workup for infection. Studies have used different ranges for risk assessment, commonly using 5000 to 15 000-20 000/mm³ as a range for placing infants in a low-risk category. However, even WBC counts in those low-risk ranges have been shown to have poor negative predictive value for serious bacterial infections in the neonate [26]. Counts above and below those levels may have relatively high predictive values for infection, but they are not specific to bacterial infection. The presence of immature cells has also been relied upon for identifying infected patients. Cutoff levels used to help rule out infection include an absolute band count of 1500/mm³ and an immature-to-total (I:T) neutrophil ratio of 0.2 or lower. Interlaboratory variability, with particular reference to the absolute band count, makes widespread application of single-center studies difficult [27]. Also, the determination of a neutrophil band form is a subjective assessment [28]. White blood cell and immature cell counts, therefore, cannot be relied upon alone for predicting the presence of infection.

C-reactive protein is a nonspecific marker of inflammation produced by the liver. An acute phase reactant produced by hepatocytes, this protein is often used as an aid in diagnosing infection as well as in deciding the duration of therapy [29]. For the immediate perinatal period, it is an attractive aid because intrapartum antibiotic administration may cloud blood culture results. In the ED, an isolated CRP may be of little value because the statistical correlations used to link CRP with infection, whether they be sensitivity, negative predictive value or others, show increased reliability with serial values [30]. For instance, in 134 infants with culture-proven late-onset sepsis, the sensitivity rose from 61.5% to 84.4% by obtaining a second CRP, and the negative predictive value rose from 82% to 94.6%. Specificity and positive predictive values at best were 74.6% and 47.4%, respectively [30]. This improved accuracy may be partly due to the fact that the increase in CRP lags after onset of infection because transcription of this protein is under direction of other cytokines. Theoretically, a low CRP in the ED may result from
obtaining the test too close to onset of infection. To make this test of greater value, it might be prudent to discuss the practices of the inpatient services that care for neonates within the same facility as the ED. If the inpatient services routinely use serial CRPs, it may be worth obtaining the initial value in the ED.

Cytokines such as proinflammatory interleukins 6 and 8 and antinflammatory interleukin 10 show promise as useful diagnostic aids for infection [28,31]. Interleukin levels rise early in the inflammatory response to an infection as opposed to CRP, providing an earlier signal of infection [32]. However, these tests also do not have acceptable sensitivity or specificity, and they may be elevated in situations other than infection. Another consideration is that the half-lives of these cytokines are short. Interleukins may drop to low levels after acute increases even when infection persists [28,34]. It is conceivable that levels may have already decreased depending on the time between onset of infection and presentation to the ED.

The peptide procalcitonin is another marker applied to the diagnosis of sepsis. Its relation to infection is unclear and, as with other markers, can be elevated in situations outside sepsis [33]. In fact, elevations occur in healthy neonates in the immediate postnatal period. The sensitivity of this test has been reported to be as low as 50% and as high as 99%; variation in study results stems from the heterogeneous methods used in different studies, including subjects of wide age ranges, varied definitions of sepsis, as well as different threshold levels used for procalcitonin [33]. This test may best be used in conjunction with other laboratory information.

More markers including cell surface antigens (CD64, CD69, HLA-DR), granulocyte colony-stimulating factor, and adhesion molecules are being evaluated as aids in diagnosing infection in neonates [28,31,34]. The rise of antibiotic resistance alone brings value to discovering accurate indicators that would confirm or refute the presence of infection. To date, most studies looking at indicators of infection in neonates occur in the inpatient setting. For application in the ED, future investigations should pursue the applicability of these tests to potentially septic neonates presenting to the ED as well as the ability to distinguish between bacterial and other infectious etiologies. Currently, no test seems reliable entirely on its own in the ED evaluation of a neonate for sepsis. These diagnostic markers are more often useful in conjunction with one another and in series.

**Limitations of Clinical and Laboratory Assessment in Identifying Infants With Sepsis**

Several studies have concluded that even detailed clinical and laboratory assessment may not identify all infants with serious illness. In 1993, Baker et al [35] studied 747 infants who were 29 to 56 days of age presenting with fever (defined in this study as a rectal temperature of 38.2°C or higher) and found that two thirds of those with bacterial disease appeared “well” to the examining attending physician. Bonadio et al [36] sought to determine the reliability of observation variables in distinguishing infectious outcomes of febrile infants aged 0 to 8 weeks. In this prospective study, 7 observational variables (level of activity, level of alertness, respiratory status/effort, peripheral perfusion, muscle tone, affect, and feeding pattern) were assigned a score; the higher the score, the greater the degree of compromise. All infants (n = 233) received physical examinations and sepsis evaluations (lumbural puncture, complete blood count, blood culture, and UA/urine culture). There were 29 infants with serious bacterial infection (10 with bacterial meningitis, 12 with bacteremia, 7 with UTIs), and 45 cases had aseptic meningitis. Two of the infants with serious bacterial infections had normal observation scores and appeared well; however, both had abnormal laboratory findings suggestive of infection. The variables that best identified the presence of serious bacterial illness were as follows: affect or change in mental status, respiratory status/effort, and peripheral perfusion [36]. In a more recent study, 11 of 15 infants younger than 3 months (2 were <1 month old) presenting to the ED with fever were “well appearing” but were found to be blood culture positive (one with *Citrobacter freundii* meningitis had a temperature of 38.5°C and a negative blood culture) [37]. Thus, caution is advised when assessing a febrile neonate who is well appearing to the clinician.

Three main studies emerged between 1985 and 1994 which sought to avoid unnecessary hospitalization by defining low-risk criteria to assist in determining whether infants younger than 3 months presenting to the ED would require definitive hospital admission and antibiotic treatment, or if these infants could be discharged home from the ED with close outpatient follow-up [35,38,39]. The Philadelphia group studied 29 to 60-day-old infants with fever higher than 38.2°C who were well appearing and had low-risk criteria defined as having WBC less than 15 000/mm³, band-neutrophil ratio less than 0.2, UA less than 10 WBC/HPF with negative Gram stain, CSF cell count less than 8 WBC/mm³ with negative Gram stain, and a negative chest radiograph [35]. The Rochester study included well-appearing infants younger than 60 days with fever higher than 38.0°C who were term with unremarkable perinatal history and uncomplicated discharge to home after delivery. Additional low risk criteria included WBC 5000-15 000/mm³, absolute band count <1500/mm³ and UA <10 WBC/HPF [39]. The Boston study included infants aged 28 to 89 days who were non-toxic-appearing previously healthy term infants with uncomplicated newborn nursery stays and had laboratory criteria including WBC less than 20 000/mm³, UA less than 10 WBC/HPF, negative chest radiograph, and CSF WBC of less than 10/mm³ [38]. All infants from these 3 studies had close follow-up as a requirement; the Boston group gave empiric
antibiotics in addition to requiring follow-up. All 3 studies concluded that infants meeting the low-risk criteria as defined in their respective studies could be discharged home from the ED with close follow-up. The 3 studies mentioned above evaluated infants older than 29 days; younger infants, however, are in a different risk category. Applying the low-risk criteria from the above studies, Kadish et al [16] sought to identify febrile infants 1 to 28 days with low risk for serious bacterial illness. They concluded that based on these criteria, 3% of infants with serious bacterial illness would have been assessed to be at low risk at the time of presentation and would have been sent home without treatment. They concluded that these guidelines could not safely be recommended for febrile neonates. Similarly, Baker and Bell [40] applied the Philadelphia protocol to febrile infants from birth to 1 month old and concluded that these criteria lacked the sensitivity and negative predictive value to identify neonates at low risk for serious bacterial illness.

### Treatment

Because of the difficulties in accurately identifying neonates with sepsis after a careful evaluation, it is recommended that all neonates presenting to the ED with possible sepsis should receive antimicrobial therapy. Although there are no data to support a particular antibiotic regimen [41], consideration of the potential organisms helps tailor the drugs chosen. For the coverage of gram-positive organisms, ampicillin is suggested. It is particularly justified given concerns for *Listeria* [42]. Ampicillin has also been a therapy used for *E. coli* infection; however, there is considerable resistance now, and careful attention must be paid to patterns of sensitivities within individual institutions or communities [43]. Because gram-negative organisms are potential pathogens, therapy should include either an aminoglycoside or a third-generation cephalosporin.

Based on the reports of neonatal deaths related to the interaction between ceftriaxone and calcium-containing products, the Federal Drug Administration and Roche (Nutley, NJ), manufacturer of Rocephin (ceftriaxone sodium), recently released new guidelines for administration of this frequently used cephalosporin. These guidelines recommend that ceftriaxone should not be reconstituted or mixed with a calcium-containing product, such as Ringer’s or Hartmann’s solution or parenteral nutrition containing calcium, and ceftriaxone and intravenous calcium-containing products including parenteral nutrition should not be administered to any patient, particularly neonates, by the same or different infusion lines or sites within 48 hours of each other. Although there are no reported cases of ceftriaxone-calcium precipitates in patients other than neonates, there is a potential for the interaction between ceftriaxone and calcium-containing products in patients of any age. There are no data on interactions between intravenous ceftriaxone and oral calcium-containing products or between intramuscular ceftriaxone and intravenous or oral calcium-containing products. More details on this advisory can be obtained at either the Federal Drug Administration (http://www.fda.gov/cder/drug/InfoSheets/HCP/ceftriaxone.htm) or Roche (http://rocheusa.com/products/rocephin/rocephin-hcp-letter.pdf) Web sites [44].

Antibiotic resistance is surely changing the epidemiology of invasive pathogens. Still, even with the emergence of organisms such as methicillin-resistant *S. aureus* and ampicillin-resistant *Enterococcus*, wide use of medications such as vancomycin for neonates in the ED at this time is not warranted. Children suited to receive vancomycin when being evaluated for infection are those with indwelling devices such as central venous catheters and VP shunts.

Physicians must maintain a high index of suspicion for herpes infection and promptly initiate antiviral therapy with acyclovir if the clinical scenario is suggestive. Acyclovir should be administered at 60 mg/kg per day intravenously (IV), divided into 3 doses. This regimen has improved morbidity and mortality from disseminated disease and mortality from encephalitis but, unfortunately, has not impacted morbidity among survivors of HSV encephalitis [45].

In addition to antimicrobial administration, treatment must support compromised organ systems. Septic neonates will need vascular access. This will allow for correction of fluid deficits, electrolyte and acid-base disturbances as well as hematologic abnormalities amenable to transfusion therapy.

### Management of Septic Shock

The American College of Critical Care Medicine published guidelines for intervention in neonates, infants, and children who present in septic shock [21]. The goal is the restoration of circulation and perfusion and adherence to these guidelines has been shown to improve survival [46]. Two algorithms were recommended, one for neonates and one for infants. There are common interventions and time goals for both algorithms, and practitioners should be familiar with them (Figure 1). The goal is to restore circulation within 60 minutes. Within the first 5 minutes of presentation, shock should be recognized and a stable airway maintained and access obtained. By 15 minutes from presentation, fluid resuscitation with isotonic or colloid boluses to a maximum volume of 60 mL/kg should be accomplished. In addition, hypoglycemia and hypocalcemia should be corrected. The appropriate intervention for hypoglycemia is 10% dextrose solution at 2 mL/kg IV push and hypocalcemia may be treated with slow IV administration of calcium gluconate at a dose of 100 mg/kg. Should fluid resuscitation restore perfusion, the next appropriate step is observation in an ICU setting. If shock persists, central venous and arterial access should be obtained and vasoactive agents should be started, with dopamine as a first-line agent. If after the first hour circulation is not restored with further pressor support,
concern for adrenal insufficiency should be raised and the need for hydrocortisone therapy should be considered. As mentioned earlier, practitioners must also consider other diseases that may present with shock in the neonatal period, such as ductal-dependent congenital heart disease, and support the patient as needed [47].

Summary
An estimated 7% of neonates presenting to the ED are diagnosed with sepsis [48]. Neonatal physiology makes this patient population more susceptible to sepsis compared with older pediatric patients. After considering other diseases that may present with a picture similar to that of sepsis, emergency physicians should try to differentiate between potential pathogens to focus laboratory investigations and tailor therapy. The combination of individual laboratory tests may further increase sensitivity and specificity, but an optimal panel of tests is yet to be identified. Crucial steps in the ED care of the septic neonate are identification of patients in septic shock and then rapid restoration of their circulation to improve outcomes.

References


