Future Directions in the Evaluation and Management of Neonatal Sepsis
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*Neoreviews* 2012;13:e103
DOI: 10.1542/neon.13-2-e103

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Future Directions in the Evaluation and Management of Neonatal Sepsis

Micah Bhatti, MD, PhD,* Alison Chu, MD,* Joseph R. Hageman, MD,† Michael Schreiber, MD,* Kenneth Alexander, MD, PhD*

Abstract
Although sepsis is one of the important etiologies of illness in hospitalized infants, it is often difficult to determine if an infant is truly infected and, moreover, how to treat these infections. To address the first issue, researchers have begun to examine techniques to shorten the amount of time it takes to culture and identify organisms. On the clinical side, the development of biomarkers may help physicians to better identify infants who are likely ill from infection versus those infants who are unstable from other processes. The ability to distinguish between these cohorts will help to curtail excessive use of empirical antibiotics. Even if infants are determined to truly have infection on the basis of a positive culture, it is becoming more challenging to appropriately treat causative organisms, as multidrug resistance becomes more prevalent. Furthermore, it becomes more important to evaluate strategies to prevent these infections before they occur.

Objectives After completing this article, readers should be able to:
1. Understand new developments in serum biomarker research.
2. Recognize the steps in identifying infectious organisms and how current research into new laboratory techniques may be able to expedite this process.
3. Understand the uses and limitations of less well-known antimicrobial agents in treating multidrug-resistant infections.
4. Understand the importance of hand hygiene and careful central catheter use in preventing neonatal infection.
5. Become familiar with recent research on the utility of nutrition, including early enteral feeding, human milk, and lactoferrin, in the prevention of infection.

Introduction
One of the most challenging aspects of neonatal sepsis is determining if an infant who is clinically unstable is truly infected. To improve our ability to accurately detect sepsis, research has been conducted assessing the use of various biomarkers. In addition, advancements in medical microbiology have led to faster detection of pathogens in blood samples. Another challenge to the management of critically ill infants is the emergence of multidrug-resistant (MDR) organisms that will require neonatologists to use unfamiliar antibiotics with well-known toxicities. In the wake of MDR organisms and limited antibiotics, hospitals have implemented rigorous prevention programs. We will review advances in the prevention and diagnosis of neonatal sepsis and the treatment of MDR infections.

Advances in Sepsis Detection
Clinical sepsis is defined as a whole-body inflammatory state (systemic inflammatory response syndrome) and the presence of a known or suspected infection. (1) This seemingly

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CLABS!</td>
<td>central line associated bloodstream infections</td>
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<tr>
<td>CRP</td>
<td>C reactive protein</td>
</tr>
<tr>
<td>EOS</td>
<td>early onset sepsis</td>
</tr>
<tr>
<td>GBS</td>
<td>group B streptococcal</td>
</tr>
<tr>
<td>HRC</td>
<td>heart rate characteristics</td>
</tr>
<tr>
<td>LOS</td>
<td>late onset sepsis</td>
</tr>
<tr>
<td>MDR</td>
<td>multidrug resistant</td>
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<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>PCT</td>
<td>procalcitonin</td>
</tr>
<tr>
<td>WC-MS</td>
<td>whole cell mass spectrophotometry</td>
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straightforward definition poses two major challenges. First, although many clinicians almost automatically ascribe neonatal systemic inflammatory response syndrome to infection, the causes of this syndrome are myriad and include many noninfectious processes. Second, the sensitivity of blood cultures for identifying pathogenic bacteria may be lower in neonates than in adults because of previous antibiotic treatment, small specimen volumes, and low-grade bacteremia. (2)(3) Complicating matters, it can take up to 48 hours to detect an organism on the basis of blood culture by using current methods (4) and then an additional 24 to 48 hours before the identity and antibiotic sensitivities are known. During this time, empirical antibiotics are administered.

To improve the diagnosis of neonatal sepsis, new technologies are being introduced in clinical laboratories that will reduce the time required to identify a potential pathogen. In addition, various biomarkers and heart rate characteristics (HRC) monitoring are being assessed to determine whether it is possible to rapidly identify infected neonates.

**HRC Monitoring**

Research into cardiac electrical patterns has revealed that reduced variability and transient decelerations in heart rate may be early indicators of clinical instability and are hypothesized to be mediated by the cholinergic anti-inflammatory pathway. (5) The HRC index is a statistically derived interpretation of the beat-to-beat variation in a patient. (6) A low index indicates normal variation, but as normal variation is lost, the index rises, as does the risk of clinical deterioration. A recent randomized controlled trial of >3,000 very low birth weight infants revealed that the use of HRC monitoring significantly decreased the 30-day mortality rate after a septic-like event without a significant increase in antibiotic days. (5) The mechanism by which mortality is decreased in the monitored cohort remains unclear. In a separate study, neonates with culture-proven sepsis had a statistically higher HRC during the 24 hours leading up to the septic episode compared with healthy controls. (6) However, neonates with culture-negative, septic-like events had a statistically similar rise in HRC. Therefore, HRC is able to serve as an early warning of impending clinical instability, and additional research is needed to determine if it can differentiate between true sepsis versus a culture-negative, septic-like event.

**Serum Biomarkers**

Although a positive blood culture remains the standard for diagnosing neonatal sepsis, many investigators have assessed measuring the host response as an adjunct to culture-based diagnosis. The goal of serum biomarker research is to identify a means by which an infected child can be identified rapidly, before the onset of life-threatening symptoms. A good diagnostic host marker for sepsis with a high negative predictive value would reduce the inappropriate use of antibiotics, health care costs, and lengths of hospital stays. (7) An ideal biomarker should be elevated early in the course of infection and stay elevated for a sufficient period to provide opportunity for sampling. The biomarker should have well-defined values to differentiate infected from noninfected infants, with a very high sensitivity and negative predictive value. (8) It also is helpful if its values reflect the progression of disease and response to therapy. (8) Several serum biomarkers have been evaluated as potential indicators of neonatal sepsis.

C-reactive protein (CRP), the most commonly used biomarker, is synthesized within 6 hours of exposure to an infectious process and usually becomes abnormal within 24 hours. (7) Because CRP takes up to 24 hours after the onset of an infection to become abnormal, it has little utility in assisting in the early detection of sepsis. CRP is also limited in that other processes in addition to infection can result in elevation, including trauma and ischemia. (7) It does have a high specificity, between 93% and 100%; thus, a normal CRP in a septic-appearing neonate is unlikely to be ill because of an infectious process. Levels generally remain elevated until the infection is controlled; therefore, CRP can serve as a marker of successful treatment.

Procalcitonin (PCT) is a 116-amino acid peptide precursor to calcitonin that rises in response to most infections and some inflammatory processes. (9) The increase of PCT in sepsis seems to correlate with the severity and mortality of disease, and increases in PCT occur more rapidly than increases in CRP. (10) A meta-analysis of 22 studies found that PCT was more accurate in the diagnosis of late onset sepsis (LOS) than CRP. (9) A separate meta-analysis included 29 studies and found a pooled sensitivity and specificity of 81% and 79%, respectively. (11) In the neonate, PCT is increased during the first 2 days of life and is theorized to be secondary to peripartum proinflammatory changes, making it less diagnostic during this time period. (12) Levels can also be elevated in infants with noninfectious processes, such as respiratory distress syndrome, hemodynamic failure, and perinatal asphyxia, as well as postresuscitation. (10)

Other immunologic markers are being studied for their utility in the detection of neonatal sepsis. Proinflammatory cytokines such as interleukin-6 and interleukin-8 were initially thought to be excellent markers for detecting infection, but the very short half-life of circulating
cytokines significantly increased the rate of false-negative results. (8)(12) Increased levels of circulating calprotectin, a major product of innate immune cells, were shown to have higher sensitivity and specificity (89% and 96%, respectively) for LOS sepsis than CRP, and, in one cohort of very low birth weight infants, levels were not influenced by postnatal age. (13) Advances in flow cytometry have allowed the investigation of cell surface antigens as potential markers. A study found CD64 expression to be significantly increased in infants with culture-proven sepsis compared with those with culture-negative sepsis or healthy controls, with a sensitivity of 88.6% and a negative predictive value of 94%. (14)

Despite thorough investigation into many other proteins and small molecules, no single biomarker has been perfect for detecting neonatal sepsis. Therefore, investigators have tried combining markers in an effort to boost their sensitivity and specificity. (8)(15) A study combining four different markers—soluble intercellular adhesion molecule 1, CRP, soluble E-selectin, and serum amyloid A—was able to generate a sensitivity of 90% and a negative predictive value of 91.3%. (16) Another study using a proteomic approach found that combining proapolipoprotein C-II and a des-arginine variant of serum amyloid A was effective in identifying sepsis, with a negative predictive value of 100% in their cohort. (17) Thus, the next phase in the early detection of neonatal sepsis will be the development of a panel of readily measurable markers that will assist in determining which infants are at increased risk for impending sepsis.

Although the study of biomarkers may assist in the early detection of sepsis, virtually all of the biomarkers studied to date are nonspecific indicators of infection and inflammation. They are incapable of providing information about the etiology of the infection, and therefore the microbiology laboratory remains necessary to identify the pathogen.

Molecular Microbiology
Isolation of a bacterial pathogen from blood requires growth of the organism in liquid media, subculture of the organism on solid media, and identification of the organism according to its characteristic appearance, growth properties, metabolism of various substrates, and expression of certain surface proteins. (5)(18) The entire process can take up to 4 days before the identity and sensitivities of a bacterium can be reported to the clinical care team. To reduce the time required to identify a pathogen, there is a shift toward identifying bacteria on the basis of genotypic analysis. The two most promising methods are whole-cell mass spectrophotometry (WC-MS) and amplification and sequencing of 16S ribosomal nucleic acid. (19)(20)

In WC-MS, bacterial cells undergo ionization that generates a unique protein spectral fingerprint. The protein spectral fingerprint allows bacterial identification by using a spectral database of known bacteria. (21) WC-MS can determine the identity of an organism in <10 minutes, reducing the time from sample collection to pathogen identification to 3 days. Current devices can resolve the species and genus of >90% of bacterial isolates, a rate that is superior to traditional biochemical approaches. (22) The recent development of automated whole-cell mass spectrophotometers will make this technology accessible to most clinical laboratories in the near future. (18) Ongoing research is being conducted to determine if WC-MS may be used to identify bacteria in samples taken directly from positive blood culture bottles, which would bypass the need for subculturing and reduce bacterial identification time to ≤2 days. (23)

Nucleic acid amplification and sequencing of 16S ribosomal nucleic acid is now considered the gold standard for identifying bacteria, although routine use has been limited by expense and time. (20) Several approaches are being used to bring 16S ribosomal nucleic acid detection into the clinical laboratory. The most advantageous is broad-range polymerase chain reaction (PCR), which utilizes amplification by using nonspecific 16S ribosomal DNA primers on DNA extracted directly from blood or spinal fluid without previous culturing. (2) Detection of a pathogen by using broad-range PCR takes <8 hours and requires <500 μL of sample. (19) The PCR product can be sequenced or probed to determine the identity of the pathogen. Therefore, in <24 hours, a physician would know whether a patient is bacteremic, and if so, with what pathogen. Implementation of 16S PCR in the detection of neonatal sepsis has been shown to decrease inappropriate use of antibiotics. (24) In recent studies, the sensitivity of broad-range PCR varied widely, from 41% to 100%. (19) More reliable methods for DNA extraction and the development of automated systems are necessary before this technique is ready for the clinical laboratory. (2)

Treating MDR Infections
Many clinicians are now finding that their infant patients are infected with antibiotic-resistant nosocomial pathogens such as vancomycin-resistant Enterooccus, carbapenemase-producing Enterobacteriaceae, Pseudomonas aeruginosa, and Acinetobacter baumannii. (25) Described here are several antibiotic agents, not routinely used in the NICU, that are capable of treating infections caused by resistant organisms. As with older antibiotics, the emergence of
microbial resistance to these newer antibiotics is inevitable and has, in many cases, already occurred. Thus, continued judicious use of antibiotics is necessary to maintain the usefulness of these new antimicrobials.

**Gram-Positive Infections**

Gram-positive organisms are the most commonly isolated organism in the laboratory evaluation of LOS. Unfortunately, antimicrobial resistance among Gram-positive organisms is now common. Recent studies have reported the use of linezolid and daptomycin in children and neonates for treatment of infections caused by Gram-positive organisms resistant to β-lactams and vancomycin.

Linezolid is an oxazolidinone antimicrobial that was licensed by the US Food and Drug Administration for use in pediatrics in 2002. The drug’s antimicrobial effect is mediated through disruption of bacterial protein synthesis induced by linezolid binding to ribosomal RNA. (26) Although linezolid is bacteriostatic against all *Staphylococcal* and *Enterococcal* species, it has been successfully used to treat neonatal methicillin-resistant *Staphylococcal* and vancomycin-resistant *Enterococcal* infections. (26) A subset analysis of 63 neonatal patients included in a pediatric Phase III study compared the use of linezolid with vancomycin in the treatment of resistant Gram-positive infections and revealed equal cure rates and lower adverse events in the linezolid group. (27) Linezolid has good penetration into the skin and lungs and is approved for the treatment of pediatric skin and soft-tissue infections and nosocomial pneumonias. Linezolid is not recommended as a first-line drug in the treatment of endocarditis or catheter-related infections because it is bacteriostatic and has been associated with high adverse events in adult patients with catheter-related infections. However, linezolid has been used successfully to treat pediatric bloodstream infections and endocarditis caused by vancomycin-resistant organisms. (28) Adverse effects of linezolid treatment are seen more commonly in therapy courses lasting >2 weeks and include reversible myelosuppression and lactic acidosis. During treatment with linezolid, patients should have their serum lactate and blood cell counts checked periodically. Currently, resistance to linezolid is rare; however, outbreaks of linezolid-resistant organisms have been reported. (29)

Daptomycin is a cyclic lipopeptide antimicrobial derived from *Streptomyces roseosporus* and is bactericidal against resistant Gram-positive organisms. The mechanism of action is poorly understood, but daptomycin is theorized to form pores in the cell membranes of Gram-positive organisms. (30) Although daptomycin has had great success in treating adult bloodstream infections and endocarditis, it is not currently approved by the US Food and Drug Administration for use in pediatric patients. (31) A small number of reports describe the successful off-label use of daptomycin for the treatment of resistant infections that occurred in neonates while receiving vancomycin therapy. (31)(32) Daptomycin is inactivated by pulmonary surfactant, rendering it ineffective in treating pulmonary infections. Until appropriate pharmacokinetic studies are performed in the pediatric population, daptomycin should be used only as a second-line drug for treatment of neonatal vancomycin-resistant infections, including bloodstream infections and endocarditis.

**Gram-Negative Infections**

In neonates with LOS in the United States and other developed countries, Gram-negative organisms are isolated less frequently than Gram-positive organisms. However, in some developing nations, Gram-negative organisms are more common in both early onset sepsis (EOS) and LOS. (33) Unfortunately, the global epidemic of antibiotic resistance has created a major problem in treating Gram-negative sepsis everywhere. (34) Therefore, the evaluation of antimicrobial agents effective against Gram-negative organisms not previously used in the pediatric population has become critically important. Here we review the use of ciprofloxacin and colistin in neonates.

Ciprofloxacin is a fluoroquinolone that inhibits bacterial DNA topoisomerases. (35) Ciprofloxacin is bactericidal against most Gram-negative organisms, including *P aeruginosa*. The use of fluoroquinolones in pediatrics has been limited by reports of increased musculoskeletal adverse events in young animals. (36) A recently published systematic review suggests that there is increased risk of arthropathy in ciprofloxin-treated pediatric patients, but that this risk is relatively low and that the arthropathy is reversible. (36) Despite concerns over possible adverse effects, ciprofloxacin has been approved by the US Food and Drug Administration for the treatment of complicated urinary tract infections in children. It has been used off-label in many countries with good outcomes in the treatment of various Gram-negative infections. (35) A systematic review of five cohort studies evaluated the use of ciprofloxacin for the treatment of neonatal sepsis caused by antibiotic-resistant Gram-negative organisms. (37) Two of the five cohorts assessed clinical response, with one showing a significantly higher survival rate in the ciprofloxacin-treated group versus treatment with ampicillin, gentamicin, and/or cefotaxime. The other cohort reported equal survival rates between the ciprofloxacin-treated group and the control group. None of the five cohorts reported any major adverse events associated with
the use of ciprofloxacin. Two significant limitations to the use of ciprofloxacin in neonates are the paucity of pharmacokinetic data in the neonatal population and the very high doses of ciprofloxacin needed to successfully treat infections caused by Acinetobacter and Pseudomonas organisms. (37) Resistance to fluoroquinolones has been well documented and may be increasing in certain parts of the world. (34) In an effort to minimize resistance, the use of ciprofloxacin should be restricted to infections caused by resistant organisms.

Colistin is a polymyxin initially discovered in 1947, and it functions as a detergent, dissolving the cellular membranes of Gram-negative organisms. (38) Systemic polymyxins fell into disuse in the early 1980s in favor of less toxic aminoglycosides and broad-spectrum β-lactams. However, with the continued emergence of MDR organisms, polymyxins have again found use as the only antibiotic left to treat some Gram-negative infections. In a retrospective study of neonates with MDR Gram-negative infections susceptible to only colistin, 12 neonates were bacteremic; two had concomitant meningitis. (39) Of the colistin-treated cohort, two-thirds of the patients survived, including one with meningitis. Two infants developed renal impairment, the main toxicity associated with colistin use, but both infants had multiorgan dysfunction before starting colistin therapy. In view of the situations requiring its use, which are often desperate, the rate of colistin-related nephrotoxicity is tolerable; however, regular monitoring of patients’ renal function during colistin therapy is recommended. (38) Colistin dosing guidelines have not been well established in the neonatal population. Finally, although rare, resistance to colistin has emerged, leaving patients mortally infected by organisms resistant to all commercially available antibiotics. (40)

It should be emphasized that none of the antibiotics discussed here are superior for treatment of infections sensitive to older, more commonly used antibiotics. The use of these newer antibiotics should remain restricted to the definitive therapy of infections caused by resistant organisms. None of these drugs should be used for empirical therapy. The recommended doses of antibiotics mentioned here and in the two previous articles are listed in Table 1.

**Prevention of LOS**

Although research involving the prevention of EOS has largely been limited to the use of intrapartum prophylaxis, there is a myriad of proposed interventions for the prevention of LOS. Of these many proposed preventive interventions, the only established effective means for decreasing the rate of LOS are hand hygiene and the safe use and early removal of intravascular catheters. Other potentially promising interventions for prevention of LOS are being studied, including the concept of bundles, early enteral feeding, nutritional supplements, and maternal vaccination.

**Reducing Central-Line—Associated Bloodstream Infections**

Although there is an abundance of research evaluating complex and expensive methods for prevention of neonatal sepsis, there are several simple, low-cost strategies that are highly effective. First and foremost is good hand hygiene. (41) Despite being a well-studied and established means for preventing and controlling transmission of infectious organisms, hand hygiene is poorly instituted, and the rates of hand hygiene protocol adherence by care providers are often well below 50%. Nonetheless, improved compliance with hand hygiene protocols can be achieved through a multimodal approach.

A bundle is a group of specific, evidence-based practices that, when performed together, result in improved patient outcomes. (42) The bundle concept has been applied successfully to reduce central line–associated bloodstream infections (CLABSI). A study in the NICU setting revealed that the use of an insertion and maintenance bundle, including improved hand hygiene, use of good sterile technique during placement (sterile gown, sterile gloves, surgical mask and hat, and thorough skin disinfection), aseptic technique when accessing the catheter, and daily inspection of central catheters reduced CLABSI by 67%.

The use of antimicrobial prophylaxis remains a highly controversial method for preventing CLABSI. A Cochrane review assessing the use of a prophylactic systemic antibiotic found that almost 10 infants need to be given preventive antibiotics to avoid one case of infection. (43) Given the toxicities associated with broad-spectrum antibiotics and the potential for resistant organisms, antimicrobial prophylaxis is not recommended. Similarly, although there are some data supporting the use of vancomycin catheter locks for prevention of CLABSI, (44) the risk of selection of vancomycin-resistant organisms is substantial. Further studies need to be conducted before vancomycin line locks can be used outside of a controlled clinical trial. (45)

**Nutrition and Nutritional Supplements**

Altered bacterial colonization of the gut in premature infants as a consequence of delayed enteral feeding, antibiotic exposure, and immature gut barrier function may impair the development of innate and adaptive immunity.
Based on this hypothesis, research has been conducted to determine if early enteral feedings with human milk may be protective against sepsis in the neonate. Although early enteral feeding may have benefit, there is concern that early enteral feeding also increases the risk of necrotizing enterocolitis. In a few retrospective studies, there was an inverse relationship between risk of nosocomial infection and the initiation of feeding, without increased risk for necrotizing enterocolitis. (46)(47) Human milk, which contains lactose, nucleotides, oligosaccharides, and lactoferrin, has been shown to be protective against a variety of infections in the newborn. (48) Lactoferrin, a glycoprotein found in human milk, has antimicrobial, anti-inflammatory, and immunomodulatory properties. A statistically significant decrease in the rates of sepsis was seen in infants randomized to receive lactoferrin supplementation (4.6%) versus those receiving placebo (17.3%, p < 0.001). (49)

Because poor bacterial gut colonization secondary to prematurity and antibiotic exposure may increase the risk of infection, therapeutic colonization of the neonatal gut with probiotic organisms may help to prevent LOS. However, studies using different combinations of Lactobacillus species, Bifidobacterium species, and Streptococcus thermophilus have been inconclusive. (50)

Table 1. Dosing of Antimicrobial Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing</th>
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<tbody>
<tr>
<td>Amphotericin B (conventional)</td>
<td>1 mg/kg per dose q24h</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>50 mg/kg per dose</td>
</tr>
<tr>
<td></td>
<td>&lt;7 d</td>
</tr>
<tr>
<td></td>
<td>≤2 kg: q2h</td>
</tr>
<tr>
<td></td>
<td>2 kg: q8h</td>
</tr>
<tr>
<td>GBS meningitis</td>
<td>300 mg/kg per d divided q8h</td>
</tr>
<tr>
<td></td>
<td>&gt;7 d</td>
</tr>
<tr>
<td></td>
<td>&lt;1.2 kg: q12h</td>
</tr>
<tr>
<td></td>
<td>1.2–2 kg: q8h</td>
</tr>
<tr>
<td></td>
<td>&gt;2 kg: q6h</td>
</tr>
<tr>
<td>GBS meningitis</td>
<td>300 mg/kg per d divided q6h</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>25 mg/m² per dose q24h</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>50 mg/kg per dose</td>
</tr>
<tr>
<td></td>
<td>&lt;7 d, ≤2 kg: q12h</td>
</tr>
<tr>
<td></td>
<td>7 d, ≥2 kg: q8h</td>
</tr>
<tr>
<td></td>
<td>&gt;7 d</td>
</tr>
<tr>
<td></td>
<td>&lt;1.2 kg: q12h</td>
</tr>
<tr>
<td></td>
<td>1.2–2 kg: q8h</td>
</tr>
<tr>
<td></td>
<td>&gt;2 kg: q6h</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>10 mg/kg per dose q12h</td>
</tr>
<tr>
<td>Colistimethate</td>
<td>2.55 mg/kg per d (expressed as colistin base) divided q6h–q12h</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Limited data regarding neonatal dosing</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>12 mg/kg per dose q24h</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2.5–3.5 mg/kg per dose q8h–q24h based on postnatal age, weight, and serum concentrations (varies according to institution)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>10 mg/kg per dose</td>
</tr>
<tr>
<td></td>
<td>GA ≤34 wk</td>
</tr>
<tr>
<td></td>
<td>PNA &lt;7 d: q12h</td>
</tr>
<tr>
<td></td>
<td>PNA ≥7 d: q8h</td>
</tr>
<tr>
<td>Meropenem</td>
<td>GA ≤30 wk: 20 mg/kg per dose q12h</td>
</tr>
<tr>
<td></td>
<td>GA &gt;30 wk</td>
</tr>
<tr>
<td></td>
<td>PNA &lt;7 d: 20 mg/kg per dose q12h</td>
</tr>
<tr>
<td></td>
<td>PNA &gt;7 d: 20–40 mg/kg per dose q8h</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>10–15 mg/kg per dose q8h–q24h based on postnatal age, weight, and serum concentrations (varies by institution)</td>
</tr>
</tbody>
</table>

Dosing regimens from Lexicomp online (http://online.lexi.com/). Only agents mentioned in the articles of this series are included. GA, gestational age; PNA, postnatal age.

*Higher doses may be necessary to treat organisms such as Pseudomonas and Acinetobacter. (37)

*Use of 10 to 15 mg/kg q24h has been reported. (31)
Maternal Group B Streptococcal Vaccination

Another potential mechanism for prevention of EOS and LOS is the use of vaccines. Initial investigations into the development of group B streptococcal (GBS) vaccines have been promising. The vaccines target conserved surface antigenic proteins, such as the Sip protein located on the cell surface or immunogenic proteins from GBS pil. If a protective immune response is achieved, it would inhibit GBS adhesion to host tissue and prevent transepithelial migration. Although not yet commercially available, several vaccines are close to being released and will hopefully prove to be efficacious in decreasing the rates of EOS and LOS caused by GBS. (51)

Conclusions

The diagnosis of neonatal sepsis continues to be a major clinical challenge. In an effort to improve outcomes of infected infants, research is being conducted to improve our ability to detect sepsis sooner and identify organisms more quickly. The use of biomarkers and the HRC index will hopefully provide additional tools for neonatologists to recognize and treat potentially infected infants. New technology being introduced into the microbiology laboratory will be able to confirm the presence of a pathogen by using faster and more reliable methods. Another important challenge in neonatal sepsis is the increasing rates of antimicrobial resistance, requiring the use of unfamiliar antimicrobial agents to treat MDR organisms. Initial studies of newer antibiotics are promising, but larger studies are needed to better evaluate these agents and provide better neonatal pharmacokinetic data. Lastly, because novel treatment agents will only take us so far, more research is needed to determine how to prevent these infections.

ACKNOWLEDGMENTS

The authors thank Elisabeth Mouw, PharmD, for her assistance with dosing recommendations for antimicrobial agents presented in Table 1.

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the clinical manifestations, laboratory features, and differential diagnosis of neonatal sepsis.
- Know the effective techniques for control of nosocomial infection in the nursery, neonatal intensive care unit, and obstetrical unit.
- Know the pathogenesis and prevention of transmission of infections with multidrug resistant bacteria.

References


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