Infection in Late Preterm Infants

Daniel K. Benjamin Jr, MD, PhD, MPH\textsuperscript{a,\*}, Barbara J. Stoll, MD\textsuperscript{b,\*}

\textsuperscript{a}Department of Pediatrics, Duke Clinical Research Institute, Duke University, P.O. Box 17969, Durham, NC 27705, USA
\textsuperscript{b}Department of Pediatrics, Emory University, Atlanta, GA, USA
\textsuperscript{c}Children’s Healthcare of Atlanta, Atlanta, GA, USA

Late preterm neonates have unique susceptibilities to infection. The closed setting of the neonatal ICU (NICU) and the immunologic immaturity of premature infants set the stage for the development of nosocomial infections. Timing of presentation is one of the crucial factors in determining the cause, evaluation, and appropriate early treatment of neonatal infections. Timing of presentation can be divided broadly into three categories:

- Congenital infections: generally acquired before delivery
- Early onset: usually acquired during delivery and presenting within the first 72 hours of life
- Late onset: often acquired in the hospital and presenting after 72 hours of life

The overall neonatal mortality rate is low for late preterm infants. The tragedy of neonatal infections among these infants is that infection increases risk of neonatal complications, prolongs hospital stay, and increases mortality.

**Epidemiology**

**Congenital and perinatal infections**

These infections are acquired before delivery or during the intrapartum period. They result most commonly from \textit{Toxoplasma gondii}, rubella virus, cytomegalovirus, herpes virus, HIV, parvovirus B19 and \textit{Treponema
Risk of transmission varies depending on trimester of pregnancy during which maternal infection occurs. *Toxoplasma* transmission rates range from less than 5% during the first trimester to approximately 60% in the third trimester [1]. Severity of the infection also depends on the stage of pregnancy at which the maternal infection occurred. Congenital toxoplasmosis and rubella acquired during the first trimester often result in stillbirth or severe anomalies. Transmission of cytomegalovirus is dependent on whether the maternal infection is a primary infection or a recurrence. Nearly 40% of neonates born to mothers experiencing a primary cytomegalovirus infection during the pregnancy are affected, while only 1% of neonates are affected in pregnancies with recurrent cytomegalovirus infections [2]. Although both HIV and human herpes virus infections can occur in utero during pregnancy, these infections most often are acquired intrapartum; thus timing of rupture of membranes and modes of delivery influence risk. Similar to cytomegalovirus, maternal–infant transmission of herpes is more frequent if a mother has a primary infection with herpes at the time of delivery. Risk of HIV transmission is influenced by maternal viral load.

**Early-onset sepsis**

This almost always is caused by perinatally acquired infections. The neonate initially is colonized by exposure to various organisms present in the maternal genital tract, including nonpathogenic organisms such as *Lactobacillus*, *Peptostreptococcus*, and *Saccharomyces*. The neonate, however, also is exposed to potential pathogens such as group B *Streptococcus* (GBS), *Escherichia coli*, and *Candida*. Risk factors for development of sepsis such as preterm delivery, prolonged rupture of membranes (greater than 18 hours), maternal fever, and chorioamnionitis often are present in neonates developing early-onset sepsis [3]. Although GBS remains the most common cause of early-onset sepsis, the widespread use of intrapartum prophylaxis in women with known GBS colonization or with risk factors for disease has decreased the incidence of this organism as a cause of early-onset disease. Rates have declined by 70% [4]. In very low birth weight infants, some studies have suggested an increase in early-onset sepsis caused by gram-negative organisms that parallels the decline in early-onset GBS disease [5]. It is unclear whether there has been a shift in pathogen distribution among late preterm infants.

**Late-onset sepsis**

Late-onset sepsis may be caused by perinatally or postnatally acquired organisms, but it usually is a consequence of nosocomial transmission. Pathogens associated with late-onset infections in the late preterm infant include, *Staphylococcus aureus*, *Candida* species, or gram-negative rods [6,7]. GBS remains an important pathogen, because intrapartum prophylaxis has shown little effect on the rates of late-onset disease [3].
The organisms responsible for late-onset sepsis present a challenging management approach. Treatment is complicated because of the rapid emergence of antimicrobial resistance. Methicillin-resistant strains of *S. aureus* are common isolates. *Enterococcus faecalis* and *Enterococcus faecium* are important causes of invasive infection because of the potential for vancomycin resistance [8,9].

Most studies of the epidemiology of late-onset sepsis have been conducted among hospitalized very low birth weight infants. There are limited recent multi-center data for the late preterm infant. But data from the very low birth weight population suggest that gram-negative bacilli are important causes of neonatal hospital-acquired infections. The dominant gram-negative pathogens differ among hospitals, and their importance in a given NICU varies over time. The most commonly isolated gram negative rod (GNR) organisms, in approximately equal distribution [10,11], are *E. coli, Klebsiella, Enterobacter, Serratia, and Pseudomonas*. Because many pathogens are resistant to commonly employed antimicrobial agents, the importance of recognizing the occurrence and antimicrobial susceptibility pattern of strains indigenous in a given nursery setting cannot be overemphasized. Routine use of third-generation cephalosporin agents as empirical therapy should be avoided, because their use promotes expression of chromosomal β-lactamases associated with resistance of *Enterobacter*. Additionally, their use has led to outbreaks of extended spectrum β-lactamase producing organisms [12]. *Candida* species are important causes of disseminated infection in the very low birth weight infant, and they may occur in the late preterm infant who has other risk factors, such as recent surgery or otherwise complicated inpatient clinical course. Extended use of broad-spectrum antibiotics, day of life (less than 30 days), and birth weight are the key factors enhancing the risk for invasive candidiasis [13–15]. *Candida albicans* and *Candida parapsilosis* are the most common species isolated from the infected neonate.

Community-acquired viruses, such as respiratory syncytial virus, influenza virus, parainfluenza virus, rotavirus, and varicella virus, can be transmitted nosocomially, especially in neonates not afforded the protection of maternally derived protective antibodies.

**Clinical presentation**

**Congenital and perinatal infections**

Although caused by various organisms, congenital and perinatal infections may present with similar clinical findings. Infections that are acquired before delivery (eg, cytomegalovirus, rubella, toxoplasmosis, and syphilis) often present with a combination of findings including intrauterine growth restriction, jaundice, rash, intracranial calcifications, microcephaly, chorio-retinitis, and thrombocytopenia. Hepatosplenomegaly, although a nonspecific finding, should encourage thorough evaluation for congenital infection in
the newborn. Many of the sequelae of congenitally acquired infections are present at birth; others (hearing loss, visual impairment/blindness, and developmental delay) may not manifest for months or years.

**Early-onset sepsis**

This is often nonfocal and fulminant in onset in contrast to late-onset disease, which may present focally as meningitis, urinary tract infections, septic arthritis, or pneumonia. Over 90% of neonates with early-onset sepsis present in the first 24 hours. Signs of perinatally and nosocomially acquired sepsis are often nonspecific and subtle, but sepsis is uncommon in the asymptomatic neonate [16,17]. Signs of neonatal sepsis include: temperature instability, lethargy, irritability, apnea, respiratory distress, hypotension, bradycardia, tachycardia, cyanosis, abdominal distension, hyperglycemia, jaundice, and feeding intolerance [18]. These signs overlap with a myriad of other disease processes presenting in the neonatal period, including: anemia, intestinal obstruction, congenital heart disease, respiratory distress syndrome, and metabolic disorders.

**Late onset infection**

Late-onset infection presents more frequently with signs of focal infection than early-onset disease; however, nonfocal and fulminant presentations remain common. Key risk factors for late-onset sepsis include increased risk with younger postconception age and prolonged NICU stay. Other risk factors include central vascular access, invasive procedures, and use of broad-spectrum antibiotics such as third-generation cephalosporins.

**Laboratory evaluation**

**Congenital infections**

High pretest probability for congenital infections may be achieved through clinical presentation and a review of the maternal history; history and physical examination often provide guidance as to which laboratory tests should be obtained. Diagnostic methods for congenital infections have advanced substantially in the polymerase chain reaction (PCR) era [19–23]. HIV should be diagnosed by means of DNA PCR. Herpes virus can be diagnosed by DNA PCR of cerebrospinal fluid (CSF) or culture of skin lesions, mouth, nasopharynx, and eyes. Varicella can be diagnosed by IgM antibody or DNA PCR. Likewise, parvovirus B19 can be diagnosed by IgM antibody or DNA PCR. Cytomegalovirus can be diagnosed by shell vial assay, culture of virus from urine, or DNA PCR, and *Toxoplasma* can be diagnosed by IgM or IgA antibody, blood or urine culture, or DNA PCR. Treponema diagnosis and early empirical or presumptive therapy for neonatal syphilis are based on guidelines that have been outlined by the American Academy of Pediatrics [24].
Early- and late-onset infections

Screening tests, including white blood cell counts and acute phase reactants, such as a C-reactive protein (CRP), have poor positive predictive values in septic neonates: 40% in symptomatic neonates and as low as 1% to 2% in asymptomatic neonates at risk for GBS [16,25]. The development of effective screening tests continues to be an unmet medical need in neonatal infections.

For bacterial and fungal infections, culture of normally sterile body fluids remains the standard for diagnosis; however the performance of the blood culture is extremely variable. There is no consensus as to the recommended number of blood cultures or volume of blood to culture. Obtaining blood cultures from multiple sites, however, increases the ability to distinguish between cultures contaminated with skin flora and those representing true infection [27]. Although a blood culture inoculum of 0.5 mL is used commonly in preterm infants and is thought to have good sensitivity in neonates for bacteria, some studies have shown that 0.5 mL of blood may not detect low-level bacteremia [28,29]. The performance of the blood culture likely is compromised further by maternal intrapartum antibiotic administration or empirical antibiotics administered to the neonate. Positive blood cultures for pathogenic bacteria are evident by 48 hours of incubation in most cases [26]; however, blood cultures are often negative for Candida.

The incidence of bacterial meningitis is higher in the first month of life than at any other time and complicates up to one third of the cases of bacterial sepsis in this population [30]. Diagnosis of meningitis and identification of the offending organisms requires examination of CSF. Unless neurologic signs are present at the time of the sepsis evaluation, clinicians often defer the lumbar puncture until the blood cultures are positive for a pathogenic organism or the neonate is more stable [31]. Studies of otherwise asymptomatic neonates with respiratory distress syndrome found evidence of meningitis in less than 1% of cases on admission to the NICU [31]. Blood cultures, however, were noted to be negative in 28% (12/43) of neonates with culture-proven bacterial meningitis diagnosed in the first 72 hours of life in a series of nearly 170,000 neonates [32]. Investigators of the National Institute of Child Health and Human Development (NICHD)-sponsored Neonatal Research Network found that blood cultures were negative in 34% (45/134) of very low birth weight neonates with culture-proven meningitis [33]. Frequent blood culture-CSF culture discordance also was reported by investigators from the Pediatric Group and Duke University [7]. The culture discordance observed in the Pediatric data set was supported by CSF parameters (white cell, red cell, protein, and glucose) and included late preterm neonates.

The similar findings from different nurseries, reported by different investigators across time, lend strength to the advice that clinicians should
include the lumbar puncture as part of the neonatal sepsis evaluation provided that the infant is sufficiently stable to tolerate the procedure.

Urine cultures should be obtained as part of the sepsis evaluation in neonates after day of life 3, but they are of low yield before this point [34]. Urine cultures should be obtained by suprapubic tap or catheterization. Bag specimens are difficult to evaluate because of contamination and may lead to unnecessary antibiotic administration and radiological studies.

Antimicrobial therapy

Therapy may be considered broadly as definitive, presumptive, empirical, and prophylaxis. Definitive treatment is the administration of antimicrobial agents for documented disease (eg, administration of ampicillin and gentamicin for 10 days because GBS has been isolated from the blood). Presumptive therapy is administered when the clinician strongly suspects disease, but the documentation is incomplete. For example, an infant has a positive blood culture for GBS; due to clinical instability, a lumbar puncture is deferred initially. After the blood culture results are known, the lumbar puncture is obtained and reveals 330 white blood cells, 0 red cells, protein 120, and glucose 20, but the CSF culture is negative. Even though the CSF culture is negative, the infant is presumed to have meningitis caused by GBS because of the extremely high likelihood of disease as documented by the CSF white cell count. Empirical therapy is given when disease is suspected for brief preselected time frame (eg, 48 hours) while culture results are pending. Prophylaxis is given to a group of patients who are at risk of acquiring disease independent of culture results.

Note that as clinical management moves from definitive to presumptive to empirical therapy to prophylaxis, the proportion of infants with disease decreases. Thus, the number of infants without disease who are exposed to the antimicrobial agent increases. As clinical management moves from definitive therapy to prophylaxis, the proportion of infants who potentially benefit from therapy drops, and the proportion of infants who are potentially harmed by needless therapy rises. In the settings of empirical therapy and prophylaxis, because so many more infants potentially are harmed by therapy and so few will receive benefit, the conduct of prospective multicenter trials that document the safety, long-term outcomes, and rare adverse events is crucial to public health.

Empirical therapy and definitive treatment

Congenital infections

If congenital nonbacterial infection is suspected, it is often prudent to seek the advice of infectious disease specialists. Treatment for possible exposure to several agents (HIV, herpes virus, toxoplasmosis, and Treponema
pallidum) often is indicated. Transmission of HIV has been reduced from almost a third to less than 2% through a series of interventions including maternal antenatal and intrapartum and neonatal antiretroviral therapy and delivery by cesarean section. Recent cohort data have emerged regarding the safety of long-term treatment of toxoplasmosis with pyrimethamine and sulfadiazine [41]. Close follow-up is essential for infants with possible intrapartum exposure to ensure proper management (eg, parental acyclovir is given to all infants with suspected herpes virus infections). Active neonatal syphilis can occur in newborns who are asymptomatic at birth and in those with multi-organ involvement. Thus, no infant should be discharged from the hospital without confirmation of evaluation of mother’s serologic status for syphilis. Infants born to seropositive mothers need further evaluation and close follow-up.

Early- and late-onset infections

For newborns with suspected bacterial infections, ampicillin and an aminoglycoside are considered standard empirical therapy. Ampicillin provides coverage for gram-positive infections (GBS). Gentamicin provides gram-negative coverage (E coli and other Enterobactericeae) and also provides synergy with ampicillin against GBS. Cefotaxime, a third-generation cephalosporin with superior CSF penetration compared with gentamicin, may be considered in cases of documented gram-negative meningitis. Vancomycin, or nafcillin, sometimes is substituted for ampicillin for suspected nosocomial infections [35]. Duration of antibiotic therapy is generally 10 days for confirmed bacteremia, 14 days for meningitis caused by gram-positive organisms, and 21 days for gram-negative meningitis.

Empirical therapy for Candida can be considered in symptomatic late preterm neonates who have risk factors for fungal infections (thrombocytopenia, history of invasive surgical procedures, or exposure to broad-spectrum antibiotics). The safety and efficacy of this approach are unproven, however, and treatment should not be employed casually. Amphotericin B deoxycholate has a wide spectrum of activity, and it generally is tolerated well in neonates compared with adults; it should therefore be considered first line treatment of Candida infections in this population. Fluconazole is an alternative drug when treating an isolate known to be sensitive.

Isolation of Candida from the bloodstream warrants prompt removal or replacement of central vascular catheters. Removal has been defined as taking out the catheter at the time of positive blood culture and use of no vascular access or peripheral vascular access. Replacement has been defined as removal of the catheter that is in situ at the time of the acquisition of positive blood culture and placement of a new catheter at a different anatomic location [36,37]. Prompt replacement or removal following candidemia has been associated with more rapid clearance of organism, improved survival, and improved neurodevelopmental outcomes. Prompt removal or
replacement following bacteremia with *S aureus*, *Enterococcus*, and gram-negative organisms is probably ideal, but the data are not as consistent as those with candidiasis [37,38]. Following one positive culture, blood cultures should be performed daily to ensure sterility. Persistent bacteremia is an indication for catheter removal or replacement and suggests the possibility of accompanying infection in an intravascular thrombus or endocarditis.

**Prevention**

*Congenital infections*

Prevention of HIV infection in the exposed neonate has been a remarkable achievement. The neonatologist can help to ensure prevention of maternal–infant transmission by advocating for routine testing of pregnant women and follow-up of infected pregnant women, timely and appropriate therapy with antiretroviral drugs, collaboration with obstetrical and infectious disease colleagues for mothers in labor and infants in the peripartum period, and follow-up for the infant after discharge from the nursery. Syphilis can be prevented with thorough screening by means of antibody testing of the mother, documentation of administration of three doses of penicillin to the infected mother, and documentation of a fourfold decrease in maternal antibodies.

*Early-onset infections*

Early infection caused by GBS has been reduced with the use of intrapartum chemoprophylaxis. Using a strategy of universal prenatal cultures [24] at 35 to 37 weeks, intrapartum antimicrobial prophylaxis is indicated if:

- If the mother has had a previous infant with invasive GBS disease
- If GBS bacteriuria is present in the current pregnancy
- If there is a positive GBS screening culture during the current pregnancy (unless a planned cesarean delivery is performed in the absence of labor or membrane rupture),
- If GBS status is unknown and any if any of the following are present: delivery at less than 37 weeks’ gestation, membranes have been ruptured for at least 18 hours, intrapartum fever

Intravenous penicillin G to the mother is the drug of choice for GBS prophylaxis because of efficacy and narrow spectrum of activity. Alternatively, intravenous ampicillin may be provided. Detailed algorithms for the management of infants at risk of GBS infection are presented in Fig. 1.

*Late-onset*

Hand hygiene remains a key component of infection control in the nursery. So too are adequate staffing, avoiding overcrowding, nursery design,
workload capacity, appropriate staff-to-infant ratios, and catheter management teams [39,40]. Advantages of good infection control practices in the NICU include the avoidance of the pressing need for antimicrobial prophylaxis measures and subsequent medication-associated adverse events, drug dosing errors, and antimicrobial resistance.

Two products have been approved for prevention of severe respiratory syncytial virus disease in children younger than 24 months who have bronchopulmonary dysplasia or a history of premature birth. Of the two,
Palivizumab, a humanized monoclonal antibody that is given intramuscularly, is administered more commonly to at risk infants [24].

Summary

Evaluation of the infant with possible infection should include careful review of the maternal and perinatal history and an assessment of the symptoms of infection exhibited by the neonate. A diagnostic evaluation for congenital infections should be considered in neonates who have intrauterine growth restriction and multi-organ involvement. Evaluation for potential sepsis in neonates should include blood and CSF cultures and urine cultures in neonates older than 72 hours of age. Prompt empirical antibiotic therapy is necessary if bacterial sepsis is suspected, and this should cover the organisms to which the neonate is at highest risk. Good infection control practices remain the standard for prevention of invasive disease.

References


