Neonatal Sepsis

A Review of Pathophysiology and Current Management Strategies

Margaret A. Glaser, MSN, NNP; Lauren M. Hughes, MSN, NNP; Amy Jnah, DNP, NNP-BC; Desi Newberry, DNP, NNP-BC

ABSTRACT

Background: Early-onset sepsis, occurring within 72 hours of birth, and late-onset sepsis, occurring after this time period, present serious risks for neonates. While culture-based screening and intrapartum antibiotics have decreased the number of early-onset cases, sepsis remains a top cause of neonatal morbidity and mortality in the United States.

Purpose: To provide a review of neonatal sepsis by identifying its associated risk factors and most common causative pathogens, reviewing features of the term and preterm neonatal immune systems that increase vulnerability to infection, describing previous and the most current management recommendations, and discussing relevant implications for the neonatal nurse and novice neonatal nurse practitioner.

Methods/Search Strategy: An integrative review of literature was conducted using key words in CINAHL, Google Scholar, and PubMed.

Findings/Results: Group B streptococcus and *Escherichia coli* are the most common pathogens in early-onset sepsis, while Coagulase–negative staphylococci comprise the majority of cases in late-onset. The neonatal immune system is vulnerable due to characteristics including decreased cellular activity, underdeveloped complement systems, preferential anti-inflammatory responses, and insufficient pathogenic memory. Blood cultures remain the criterion standard of diagnosis, with several other adjunct tests under investigation for clinical use. The recent development of the sepsis calculator has been a useful tool in the management of early-onset cases.

Implications for Practice: It is vital to understand the mechanisms behind the neonate's elevated risk for infection and to implement evidence-based management.

Implications for Research: Research needs exist for diagnostic methods that deliver timely and sensitive results. A tool similar to the sepsis calculator does not exist for preterm infants or late-onset sepsis, groups for which antibiotic stewardship is not as well practiced.

Video Abstract available at https://journals.lww.com/advancesinneonatalcare/Pages/videogallery.aspx.

Key Words: diagnosis, immunity, implications, management, neonatal early-onset sepsis, neonatal intensive care, neonatal late-onset sepsis, neonatal sepsis, pathophysiology, risk factors

Neonatal sepsis is a systemic bacterial, viral, or fungal infection that poses a potentially fatal threat to both term and preterm infants. Sepsis affects 4 to 22 newborns per 1000 live births globally.[1,2] Although changes in intrapartum screening and antibiotic administration over the last 2 decades have significantly reduced risk and severity, sepsis remains a top 10 cause of neonatal death in the United States.[3-5]

Author Affiliation: *Neonatal Nurse Practitioner Program, ECU College of Nursing, Greenville, North Carolina.*

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Correspondence: *Lauren M. Hughes, BS, BSN, RN, CCRN, East Carolina University Neonatal Nurse Practitioner Program, 2205 W 5th St, Greenville, NC 27889 (Hughesla17@students.ecu.edu).*

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Neonatal sepsis is classified on the basis of the timing of presentation as early-onset or late-onset. Early-onset sepsis (EOS) is an infection acquired by vertical acquisition of a pathogen from mother to neonate that presents between birth and 72 hours of life. Late-onset sepsis (LOS) presents after 72 hours of life, and is typically acquired horizontally from the neonate's environment, though it can result from a delayed presentation of vertically acquired maternal pathogens.[5-7] Because of the more common horizontal acquisition, LOS is often considered a hospital-acquired infection.[5-7] The purpose of this manuscript is to provide a review of neonatal sepsis by identifying its associated risk factors and most common causative pathogens, reviewing term and preterm neonatal immune features that increase vulnerability to infection, describing previous and the most current management recommendations, and discussing relevant implications for the neonatal nurse and novice neonatal nurse practitioner.

RISK FACTORS

Risk factors for EOS and LOS vary by the nature of pathogen acquisition, though the primary characteristic that places neonates at greatest risk for infection is

decreased gestational age, regardless of the mechanism of transmission. Neonates of extreme prematurity and very low birth weight (VLBW), defined as less than 1500 g, are more likely than term infants to be diagnosed with sepsis.[2,8] In addition to gestational age, risk for EOS is associated with maternal factors. Historically, a diagnosis of maternal chorioamnionitis has been used to identify infants at risk. The relationship between chorioamnionitis and EOS is consistently observed in the preterm population; however, it is much less common in term infants.[5,9] More recently, the individual maternal features of peripartum fever and length of time from rupture of membranes to delivery have been used to better assess EOS risk, and thus there has been a shift from the use of chorioamnionitis to the term intra-amniotic infection (IAI).[3,4] Racial and ethnic disparities exist in the number of infants affected by EOS, though they are not independent predictors of disease. The relationship between race and neonatal sepsis is influenced by lack of prenatal care, substance abuse, and a 50% increase in premature birth among black women when compared with any other race.[3,10,11]

While maternal factors primarily influence risk of EOS, neonatal characteristics primarily influence risk of LOS. Neonatal factors include prematurity, VLBW status, and the presence of congenital anomalies. Infants with these factors often require invasive devices, delayed enteral feeding, medications, and complex management in a neonatal intensive care unit.[2,8] Central venous catheters and endotracheal tubes, both commonly required in these groups of neonates, allow for direct pathogen entrance. Delayed enteral feedings and the administration of certain medications (ie, antibiotics, histamine receptor antagonists, and proton pump inhibitors) affect the neonate's microbiome and contribute to pathogenic vulnerability.[2,6,8]

In addition to neonatal characteristics, external factors have been shown to contribute to the occurrence of LOS. A high acuity unit with increased workload can lead to decreased compliance with infection prevention measures and a significant elevation in LOS risk. A retrospective cohort study[12] found that for every 1% of infants younger than 32 weeks present in a unit census, there is a 2% increase in sepsis risk.

COMMON PATHOGENS

Early-Onset Sepsis

Group B streptococcus (GBS) and *Escherichia coli* (*E coli)* together account for nearly 70% of cases of EOS.[11] In term neonates, GBS is the most common pathogen (40%-45% of cases), followed by *E coli* (10%-15% of cases).[4] These statistics are reversed in the preterm population, as *E coli* is responsible for 50% of cases, while GBS accounts for only 20% to 25% of cases.[5,13] Although GBS occurs more frequently overall, *E coli* is the leading cause of morbidity and mortality associated with EOS.[10,11,14] Other less common pathogens include *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Enterococcus spp*., gram-negative bacilli (*Enterobacter spp*. and *Haemophilus influenzae*), and *Listeria monocytogenes*.[11] Polymicrobial infections are rare.[10]

Late-Onset Sepsis

Late-onset sepsis is most often caused by gram-positive bacteria but can also be attributed to gram-negative bacteria, fungi, and viruses.[2,15,16] The most common gram-positive LOS agents include coagulase-negative staphylococci (50% of cases), *S aureus* (7% of cases), and GBS (1% of cases).[2,6,16,17] Gram-negative bacteria contribute to 20% to 42% of LOS cases and include *E coli*, *Klebsiella pneumonia, Serratia marcescens, Enterobacter spp.,* and *Pseudomonas aeruginosa*. *E coli* is the most common gram-negative species, and *P aeruginosa* the most fatal.[6,16,17] Rates of fungal LOS vary by institution, ranging from 5% to 28%, and typically affect VLBW infants.[2,6,16] The most common fungi are *Candida albicans* and *Candida parapsilosis*, which are becoming more prevalent in patients with central venous catheters.[2,6] Viruses are the least common agents attributed to LOS but can significantly impact the long-term outcomes of those affected. Of the viral pathogens, herpes simplex viruses are the most common agents, with manifestation of symptoms between 5 and 28 days of life.[2,16]

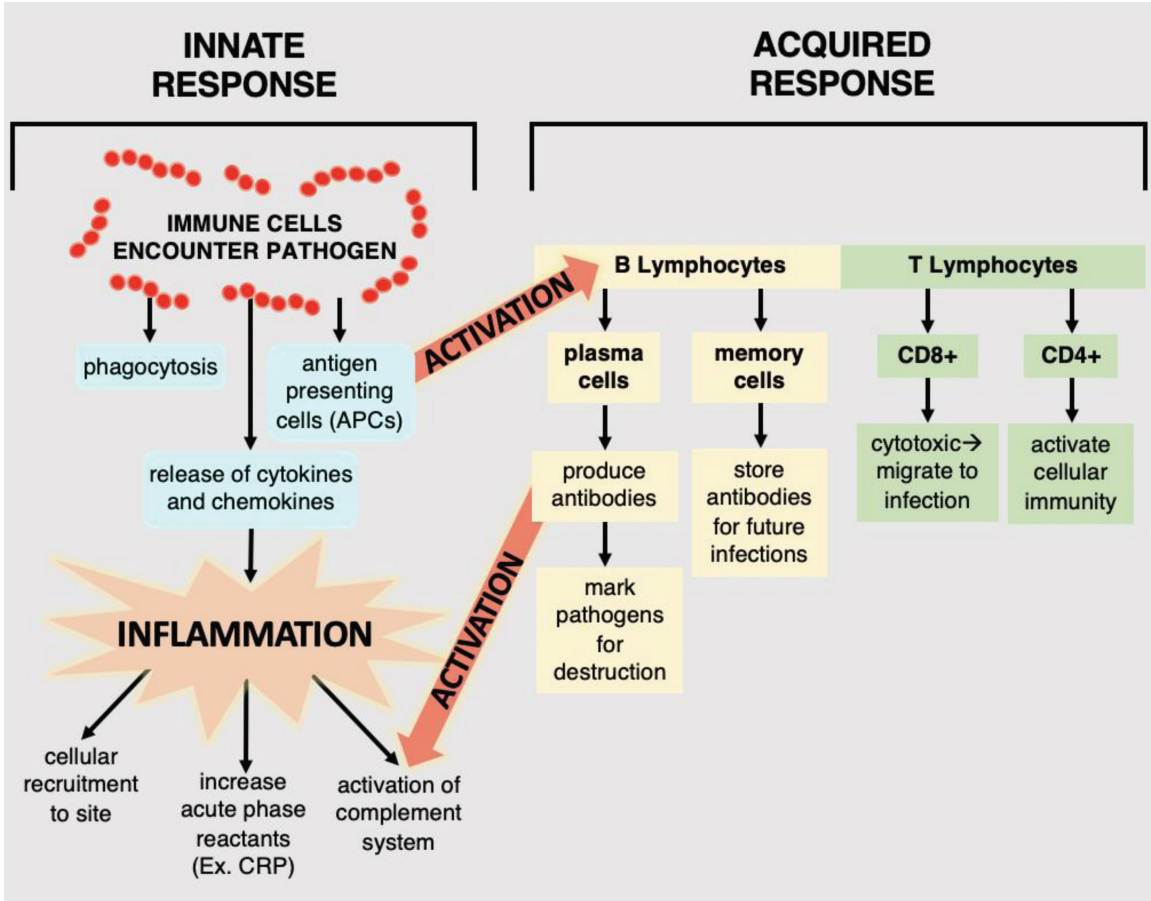
THE NEONATAL IMMUNE RESPONSE

Neonatal immunity comprises the innate and acquired immune systems (Figure 1). Innate immunity is the neonate's first-line response to infection and is driven by phagocytes and the complement cascade.[16] The innate system also regulates tolerance to self and interacts with T and B cells from the acquired immune system to generate memory responses to antigens that the body has previously encountered.[18] Acquired immunity is the slower but more directed immune response, driven by lymphocytes and maternally acquired antibodies.[16] See Table 1 for a description of the key cells in each of these systems. The neonate has a variety of immune deficiencies across both of these systems that increase vulnerability to infection.

Innate Immunity

The innate immune system encompasses the epithelium, many different cell types, cytokines, and the complement cascade that are primarily relied upon during the first several postnatal days.[18] The skin and epithelial membranes of the respiratory and gastrointestinal tracts provide a physical barrier to protect against pathogen entry. If this barrier is breached,

FIGURE 1



Review of the connected efforts of the innate and acquired immune systems. This figure is a flowchart explaining the immune response cascade and how the innate and acquired systems interact.[15] CRP indicates C-reactive protein.

immune cells phagocytize the pathogen, interface with the acquired immune system as antigen presenting cells (APCs), and release cytokines to recruit additional immune cells.[16] Important cellular components of the innate response to infection include neutrophils, monocytes, macrophages, dendritic cells, and the complement system.[16,18]

Neutrophils are the primary responders in the innate immune response. They produce antimicrobial proteins and can directly phagocytize bacteria.[16,18] Monocytes differentiate into macrophages, which function similarly to neutrophils in their phagocytic abilities. Macrophages also release cytokines that stimulate the production of antimicrobial components such as C-reactive protein (CRP) and act as APCs to mark pathogens for destruction.[16,18] The dendritic cell is another specialized APC and is dually functional in the adaptive response through involvement in antibody production and memory cell responses.[18] The complement system marks pathogens for elimination, triggers inflammation to attract phagocytes to the site of infection, and destroys pathogens.[16] The complement system is activated by 1 of 3 enzymatic pathways and causes lysis of targeted cells.[19]

The neonate's innate immune system is underdeveloped and functionally distinct from the adult's innate immune system, placing the infant at an increased risk for sepsis. Skin development and barrier function are more immature with decreasing gestational age, and the frequent need for invasive devices, such as central venous catheters and endotracheal tubes, causes a breach of the physical barrier.[6,16,17] Neutrophils are diminished in number and have inhibited migratory and phagocytic ability in the neonate.[14,19,20] The number of monocytes increases with decreasing gestational age; however, their recruitment and chemotaxis are impaired, causing a dampened inflammatory response even in the face of an increased supply.[18,19] In addition, neonatal monocytes have decreased antigen-presenting abilities, which are further depressed with

TABLE 1. Immune Cells and Their Function[15]

Cell Type	Function
Neutrophil	Primary responders in the neonate's innate immune response Involved in phagocytosis and cytokine production
Monocyte	Differentiate into macrophages Phagocytic and cytokine production abilities similar to neutrophil Act as APCs.
Dendritic cell	Serve as APCs in innate response Involved in acquired responses of antibody production and memory cell action
T cell	Involved in cell-mediated immunity Effector cells produce cytokines for pro- or anti-inflammatory response Suppressor cells have cytotoxic role
B cell	Produce and store antibodies in the acquired immune response

Abbreviations: APC, antigen presenting cell.

prematurity.[14,18,19] While the number of macrophages increases after the first several postnatal days, counts are initially low due to impaired recruitment. The macrophages that are available have depressed proinflammatory abilities.[18,19] Dendritic cells are immature, have decreased expression of various chemical immune regulators, and are unable to effectively activate an adaptive response.[19,20] The proteins involved in the reactions of the neonatal complement cascade are only 10% to 80% of normal adult levels, resulting in decreased cellular recruitment, phagocytosis, and cell lysis.[19]

Acquired Immunity

The acquired immune system requires exposure for efficacy. In the extrauterine environment, the neonate's acquired immune system begins to develop a response by building cellular memory to encountered pathogens. This memory results in a stronger, more efficient immune response against the same pathogen if encountered in the future. Both cell-mediated and humoral mechanisms involving antibodies are components of the acquired response.[16]

Cell-mediated immunity is conferred by effector $CD4^+$ T cells that activate various immune cells via cytokine production, and suppressor $CD8^+$ T cells that serve a cytotoxic role.[14,16,19] $CD4^+$ cells, known as T helper or Th cells, are further classified as Th1 or Th2 cells. Th1 cells have an important role in the proinflammatory response against microbial pathogens. Th2 cells secrete cytokines and mount an anti-inflammatory response to parasites and allergens.[19]

Humoral immunity primarily involves B cells that function in antibody production, act as APCs to activate $CD4^+$ cells, and respond to familiar antigens in the event of repeat exposure.[16] Antibodies produced by B cells activate cellular components of the innate system, initiate a pathway of the complement system, and directly inhibit pathogens.[16] This type of immunity is initially acquired through transplacental immunoglobulin G (IgG) and secretory immunoglobulin A (IgA) in human milk. These maternally acquired antibodies are transient but give protection during a time when the infant has not yet created its own.[16,19]

The neonate lacks the prior exposure to initiate a memory response due to the sterility of the uterine environment; therefore, acquired immunity is deficient in the neonate. The anti-inflammatory pathway, dampened cytotoxic abilities of $CD8^+$ cells, and the preferential development of suppressor cells in the neonate reflect the fetus's need to avoid an immune response to maternal antigens.[14,18] While useful in utero, these anti-inflammatory characteristics increase the infant's susceptibility to infection. The number of Th1 cells, which are critical for mounting a proinflammatory response, is low. Th2 cells that mount an anti-inflammatory response to parasites and allergens are more plentiful.[19] This is especially true for the preterm infant, as suppressor T cells that generally decrease in number from the second to the third trimester remain elevated.[14,18] All neonates have low levels of IgG, which is also exaggerated in the premature infant. Transplacental acquisition of IgG slowly begins in the second trimester and continues to term with a surge in the final weeks of gestation, leaving those infants born prior to this surge of antibodies at an increased risk for infection.[11,16,18,19]

MANAGEMENT OF NEONATAL SEPSIS

EOS Recommendations: Past and Present

The Centers for Disease Control and Prevention first released guidelines for the management of EOS in 1996, recommending that providers choose a risk-based or a culture-based approach to identify mothers who should receive intrapartum antibiotic prophylaxis (IAP) to prevent EOS related to GBS.[13,21,22] In later years, the guidelines underwent further revisions. In 2002, they reflected that all pregnant women receive culture-based GBS screening between 35 and 37 weeks of gestation.[13,21,22] In 2010, they added the definition of adequate IAP and included an algorithm for the management of newborns with suspected sepsis.[13,21] In 2012, the Committee on the Fetus and Newborn (COFN) released a report including the first attempt for recommendations on empiric antibiotics in the setting of negative blood cultures, expanding the number of infants recommended for treatment.[21] Neonatal providers responded by calling into question the increase in antibiotic exposure under COFN recommendations

and suggested the utility of a novice EOS calculator tool in evaluating risk level.[21]

Following the COFN algorithm, Kiser et al[23] found that nearly a quarter of their infants received antibiotic therapy for more than 48 hours due to abnormal laboratory values. In response, a commentary by Polin et al[24] concluded that antibiotics be discontinued by 48 hours in well-appearing term newborns whose mothers were diagnosed with chorioamnionitis, abnormal laboratory tests in an otherwise well-appearing term infant should not be used as evidence to continue antibiotic treatment, empiric treatment may be extended to 72 hours in preterm infants, and lumbar punctures (LPs) should be reserved for cases in which the blood culture is positive, clinical condition does not show improvement, or there is a high probability of suspected sepsis.[13,21,24]

In July 2019, the most recent revisions from the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists were released.[13] To prevent the transmission of perinatal GBS infection and identify those women at highest risk of colonization, the American College of Obstetricians and Gynecologists currently recommends universal screening by culture at 36 0/7 to 37 6/7 weeks of gestation and in women presenting in preterm labor prior to this gestation.[13] Those receiving IAP at least 4 hours prior to delivery now include mothers with positive GBS colonization by culture or antenatal GBS bacteriuria, mothers of an infant previously infected with GBS, those in preterm labor, and those with an unknown GBS status at term gestation in the event of maternal temperature of 38°C or more, rupture of membranes (ROM) of 18 hours or more, or a positive point-of-care screen.[13] If the point-of-care test is negative but risk factors develop, IAP should be administered.[13] IAP may also be considered if a woman presents in labor with unknown GBS status but has previously been colonized, as the risk for subsequent colonization is 50%.[13]

Risk Assessment

Empiric therapy has been linked to the potential overuse of IAP with negative outcomes in the infant population, so it is critical for the neonatal provider to identify infants at high risk for infection and decide on clinical management. In the context of many revisions and much controversy surrounding EOS management, the AAP has outlined 3 acceptable approaches for identifying term and late-preterm infants at high risk for the development of EOS.

A categorical risk factor assessment identifies infants who espouse certain criteria and provides an evidence-based recommendation for that risk factor (Table 2).[5] According to the AAP, substantial evidence has been used to develop these risk categories and recommendations; however, definitions for clinical illness, IAI, and normal laboratory values remain elusive and inconsistent.[5] For the purpose of defining IAI, a maternal temperature of 38°C or more is used.[13] A limitation of this categorical approach is that many relatively low-risk infants will receive empiric antibiotic treatment.[13]

A second approach, the multivariate risk assessment, is an algorithm that individualizes a neonate's level of risk through consideration of risk factors and clinical condition during the first 6 to 12 hours of life.[5] This risk assessment combines the probability of a newborn's risk of EOS based on maternal risk factors with the infant's clinical examination according to the 3 clinical conditions (well-appearing, equivocal, and clinical illness) (Table 3), which produces a single value of EOS risk with associated management recommendations (Table 4).[25] This method appears to be superior to the categorical risk assessment because the algorithm is based on objective data and is individualized to the infant.[5] This method of risk assessment informed the development of the neonatal early-onset sepsis risk calculator, which has been endorsed by the AAP in their most recent publication, and has gained traction as an EOS management tool in neonatal intensive care units across the country.[5,13,25] This tool utilizes maternal data and national incidence of sepsis to determine an infant's likelihood of EOS and provides recommendations for obtaining laboratory data and starting empiric therapy in infants older than 34 weeks of gestation. This tool has been validated in many settings with varying results. The development of the EOS calculator has decreased the use of empiric antibiotics by

TABLE 2. Early-Onset Sepsis Risk Factors and Associated Management Recommendations[5]

Risk Category	Recommendation
Ill-appearing newborn infant	Empirical antibiotic therapy + laboratory testing
Mother diagnosed with chorioamnionitis	Empirical antibiotic therapy + laboratory testing
Mother colonized with GBS, and received inadequate IAP, with a duration of ROM >18 h OR birth before 37 wk	Laboratory testing
Mother colonized with GBS who received inadequate IAP, but no additional risk factors	Inpatient observation for at least 48 h

Abbreviations: GBS, group B streptococcus; IAP, intrapartum antibiotic prophylaxis; ROM, rupture of membranes.

TABLE 3. Signs and Symptoms of Clinical and Equivocal Illness in the Neonate[25]

Clinical illness
Persistent need for CPAP/HFNC/mechanical ventilation outside of delivery room
Hemodynamic instability requiring vasoactive drugs
Encephalopathy/perinatal depression (seizures, 5-min Apgar score of <5)
Equivocal illness
Persistent physiologic abnormality ≥4 h or 2 or more physiologic abnormalities lasting >2 h
Tachycardia >160 bpm
Temperature instability >100.4°F or <97.5°F
Respiratory distress not requiring supplemental oxygen (nasal flaring, grunting, retracting)
Well appearing
No persistent physiologic abnormalities

Abbreviations: CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula.

half and unnecessary blood cultures by two-thirds.[5,24] However, one study of mention was recently performed after the modification of the calculator that included a higher risk estimate of 4 of 1000 live births, a risk level that aligns with the estimated risk of sepsis for a neonate born to a mother with IAI.[26] The study found that when the risk level of 4 of 1000 live births is employed for neonates 35 weeks of gestation and older, the calculator missed no neonates with culture-positive sepsis but did lead to a threefold increase in empiric therapy and a fourfold increase in blood culture collection.[26] When using the national incidence of 0.5 of 1000 live births, 40% of neonates with EOS were not recommended for empiric treatment.[26] This exhibits the importance of the appropriate use of the tool and the need for continuing investigation and validation.

A third strategy for identification of at-risk infants simply involves a risk assessment based on the newborn clinical condition. The presentation of sepsis is often nonspecific and can vary according to the gestational age, the severity and location of infection, and the causative agent.[1,3,11,27] The clinical presentation of sepsis can be reviewed in Table 5. Several neonatal intensive care units have employed this strategy through serial newborn examinations every 4 to 6 hours and empirically treat infants who develop signs and symptoms of infection over the first 48 hours.[13] These centers have reported a decrease in the number of laboratory draws, blood cultures, and antibiotics used.[5,30,31] Many clinicians have reported that these physical examinations are at least as good as, if not better than, laboratory tests in ruling out sepsis.[24,30,31] Considerations for this approach include the burden clinicians may face in performing serial examinations, as well as the understanding that identification of infants with EOS who are initially well appearing is not a failure but rather the intended outcome of this approach.[5]

The risk assessment presents a challenge in the preterm neonate, specifically for the VLBW infant for whom the risk assessment cannot be applied.[4] This likely explains why nearly 90% of infants younger than 32 weeks have previously been treated with antibiotics.[7] The AAP has recently outlined the most current approach for determining indications of preterm birth that may pose a risk for EOS in this subset of the neonatal population (Table 6).[13]

TABLE 4. Early-Onset Sepsis Risk as Determined by Sepsis Calculator and Associated Management Recommendations[5,25]

EOS Calculator Risk Level	Recommendation
<1 per 1000 live births	Observation only
≥1 per 1000 live births	Blood culture + observation
≥3 per 1000 live births	Blood culture + Empiric antibiotics

Abbreviation: EOS, early-onset sepsis.

TABLE 5. Symptoms of Neonatal Sepsis on Examination by System[1,2,3,11,28,29]

System	Symptoms
General appearance	Temperature instability Pallor, mottling Jaundice Bruising/petechiae
Neurologic	Lethargy or irritability Hypertonia or hypotonia High-pitched cry Tremors, jitteriness
Cardiovascular	Tachycardia or bradycardia Hypotension Cyanosis
Respiratory	Apnea or tachypnea Desaturation Grunting Retractions
Gastrointestinal	Abdominal distension Emesis, feeding intolerance Diarrhea
Genitourinary	Oliguria

TABLE 6. Early-Onset Sepsis Risk Stratification for Preterm Birth and Associated Management Recommendations[4]

Indications for Preterm Birth	Management Recommendations
Low-Risk	
Maternal indications (preeclampsia, medical illness, placental insufficiency, IUGR) Cesarean delivery Absence of labor Labor induction ROM prior to delivery	• Monitoring with no laboratory testing • Monitoring and a blood culture • May initiate empiric therapy if unstable or clinical picture does not improve after initial hours of life
High Risk	
Chorioamnionitis or IAI Premature rupture of membranes Preterm labor Cervical incompetence Acute onset of NRFHT ROM + Maternal indication for IAP but inadequate treatment received	• Blood culture • Empiric antibiotics • CSF culture and analysis if strong suspicion for infection

Abbreviations: CSF, cerebral spinal fluid; IAI, intra-amniotic infection; IAP, intrapartum antibiotic prophylaxis; IUGR, intrauterine growth restriction; NRFHT, nonreassuring fetal heart tones; ROM, rupture of membranes.

Diagnostics

The diagnosis of neonatal sepsis can be challenging, given that many maternal infections are silent and symptoms are variable. In addition, a rapid diagnostic test with enhanced accuracy has yet to be developed.[32,33] Diagnosis and treatment of sepsis is a unique process that combines history, risk factors, examination findings, and laboratory results with clinical judgment to narrow the differential diagnosis.

Diagnostic Laboratory Data

The blood culture remains the diagnostic criterion standard for sepsis.[4,5,11,32] Most positive blood cultures initially result in less than 24 hours when using contemporary techniques with 1 mL of blood. Although previously considered adequate, specimens of 0.5 mL have demonstrated false negatives in infants with low levels of bacteremia.[4,5,11] As specimens incubate, pathogens and their sensitivities are identified and used to guide antibiotic treatment. Although considered the criterion standard, blood cultures have disadvantages including poor sensitivity in neonates, inadequate volume collection leading to false negatives, possibility for contamination during collection, and significant delay to specimen result.[2,34,35]

While the blood culture is standard, providers often order the collection of additional body fluids for culture, including but not limited to, urine and cerebral spinal fluid (CSF). The decision to include these additional cultures is based on the clinical picture and the timing of presentation. Urinary tract infections are not reported in EOS but are common in LOS, and therefore urine cultures are obtained only as part of the LOS workup.[2,36] Sensitivity of up to 95% is reported with urine specimens collected for culture by catheter insertion.[11] Thirty percent of all neonates with positive blood cultures also have positive CSF cultures; therefore, if not obtained prior to initiation of therapy and blood cultures are positive, a CSF culture is indicated.[5,11,37] Cerebral spinal fluid is obtained by LP for culture, Gram staining, and analysis. The priority of the LP should be weighed against the practicality of obtaining it, and antibiotic administration should never be delayed for the procedure.[5,11] A positive CSF culture is diagnostic for meningitis, but other parameters from atraumatic LPs, including an elevated leukocyte count, elevated protein level, and low glucose, can be supportive.[37] While body fluid cultures are the current standard to confirm neonatal sepsis, other diagnostic methods are under development to address the shortcomings of traditional culture methods.

Molecular testing with polymerase chain reaction and deoxyribonucleic acid microarray can detect sepsis with improved sensitivity and specificity when compared with blood culture. Microarray methods have been reported to deliver 100% sensitivity and 97.9% specificity.[11] These testing methods show promise in terms of rapid detection of bacterial deoxyribonucleic acid at lower concentrations than are present in typical samples.[11] Theoretically, this could eliminate the need for excessive empiric antibiotic treatment, as positive polymerase chain reaction results are available in as little as 30 seconds, and microarrays are able to quickly detect the specific pathogen and antibiotic sensitivities. The main

concern with these methods is that false negatives could delay necessary treatment; however, their utility as adjunct tests to optimize treatment in those who are positive in the rapid detection window is evident.[32] These methods are promising, but they are not currently approved for routine use in the United States.

Supportive Laboratory Data

There are a number of other supportive tests that may offer valuable information to providers while they await culture results, though sole reliance on results is not recommended because of poor predictive ability.[13] Results may be abnormal in scenarios unrelated to infection due to gestational age, asphyxia, preeclampsia, and many others.[5] These tests include complete blood cell count (CBC) with manual differential and a variety of inflammatory biomarkers. Laboratory results suspicious for neonatal sepsis can be viewed in Table 7. Traditionally, the CBC is collected and analyzed as part of the routine sepsis workup. A low absolute neutrophil count (ANC) and an elevated immature to total neutrophil ratio (I/T ratio) generally raise suspicion for infection.[42] Advantages of CBC include a low-volume specimen and short duration to result, though utility is greatest if obtained 4 to 6 hours after birth. Platelet count has not been found to be a reliable predictor of infection at any age or time point, but white blood cell counts and ANCs are shown to improve significantly between 1 and 4 hours and even more after 4 hours. The I/T ratio has been shown to provide some information in the first hour, but it is also more useful after 4 hours, demonstrating the need to obtain CBC after 4 hours, or at least repeat this laboratory test if obtained shortly after birth.[42] The characteristics of the CBC have been less studied in the early preterm population, though poor sensitivity is generally observed, and the best ability to predict EOS is associated with extreme values and from specimens collected more than 4 hours after birth.[5] Thrombocytopenia seems to be a more sensitive indicator of infection in the VLBW population, as it is reported in 3 of every 4 culture-confirmed, gram-negative cases of sepsis.[1,2] Recently, the I/T squared (I/T^2), the I/T ratio divided by the ANC, has been found to exhibit enhanced early prediction with better specificity (78%) compared with the I/T ratio (73%) and ANC (63%).[38,43] However, 2 large multicenter trials found little relationship between white blood cell count, I/T ratio, ANC, and culture-confirmed sepsis in the term population.[5,11,42,44] While 97% of symptomatic infants had abnormal CBCs, 99% of asymptomatic infants also had abnormal values, suggesting that they may not be useful in the diagnosis of EOS, with specifically poor prognostic ability for GBS EOS, and its use alone in the diagnosis of sepsis is unjustified by the AAP.[13,21]

There is debate over the inclusion of other biomarkers to guide management in the case of suspected sepsis with negative culture results. The most extensively investigated biomarkers are CRP and procalcitonin, which are serially resulted and trended for change. Some researchers have found sensitivity and specificity percentages up to 96% for CRP and procalcitonin, though this finding is inconsistent between studies.[11] Serial normal CRP or procalcitonin levels during the first 48 hours of life (commonly assessed at 8, 24, and 48 hours) are associated with high negative predictive value, but it is important to consider that both CRP and procalcitonin increase in response to factors unrelated to infection. Procalcitonin rises naturally after birth, making it especially unreliable for the diagnosis of EOS.[2,4,11,39,45] C-reactive protein begins to rise 10 to 12 hours after pathogen exposure and peaks by 48 to 72 hours.[28,45] Procalcitonin has higher sensitivity in the early stages of sepsis than CRP because it is detectable by 3 hours after exposure and peaks by 6 hours.[2,45] Normal serial CRP trends guide treatment duration when results steadily decline; however, neither CRP nor procalcitonin can be recommended to reliably detect infection.[2,4,11,15,46]

Presepsin is a biomarker that has recently exhibited higher reliability in the diagnosis of neonatal sepsis, as it is less influenced by external factors, such as the birthing process, than CRP and procalcitonin.[34,35,46,47] Presepsin has high sensitivity and, similar to CRP, an ability to predict response to treatment

TABLE 7. Suspicious Laboratory Results[11,15,35,37-41]

Test	Value of Suspicion
CBC	
Platelets	<150,000/μL
ANC	<1500/μL (mild)
	<1000/μL (moderate)
	<500/μL (severe)
I/T ratio	>0.2
I/T^2	>0.02
CSF	
WBC	>20 mm^3
Protein	Term >100 mg/dL
	Preterm >290 mg/dL
Glucose	<70%-80% serum level
Biomarkers	
CRP	>1 mg/dL
Procalcitonin	>1 ng/mL
Presepsin	>850 ng/mL

Abbreviations: ANC, absolute neutrophil count; CBC, complete blood cell count; CRP, c-reactive protein; CSF, cerebral spinal fluid; I/T, immature to total neutrophil ratio; WBC, white blood cells.

through a decline of serial results.[35,47] Kumar et al[46] compared CRP, procalcitonin, and presepsin for predictive ability in neonatal sepsis. Researchers found that presepsin yielded a 94.1% overall sensitivity rate with 100% sensitivity in culture-positive cases.[46] Presepsin was also significantly more reliable with regard to negative predictive value (97.37 %) than CRP (82.61%) or procalcitonin (79.49%). Ahmed et al[34] compared these same biomarkers in EOS, reaffirming the previously mentioned findings that presepsin has higher sensitivity (88.9%) and specificity (85.7%) than CRP (66.7%, 73.8%) and procalcitonin (72.2%, 80.9%), respectively. This research strongly suggests that presepsin may be a more reliable biomarker, though still no method offers 100% sensitivity and specificity.[34,46]

Treatment

Empiric Therapy

Empiric treatment for sepsis involves the administration of broad-spectrum antibiotics with the goal of covering the most likely causative pathogens until culture sensitivities are resulted. Traditionally, a combination of a β-lactam aminopenicillin and an aminoglycoside is used, most commonly ampicillin and gentamicin.[11] An important consideration of aminoglycoside use is the need for therapeutic drug monitoring due to the concentration-dependent killing effect and the potential for nephrotoxicity and ototoxicity. Trough levels should be obtained prior to the second or third dose, depending on frequency of administration, to ensure levels of 10 to 15 μg/mL for bacteremia and 15 to 20 μg/mL for meningitis.[11] A glycopeptide antibiotic, often vancomycin, can be substituted in place of ampicillin for empiric gram-positive coverage in the context of LOS in an effort to cover the most likely causative agent, coagulase-negative staphylococci. However, due to increased vancomycin resistance, alternatives such as nafcillin, a β-lactam antibiotic, are being used to offer antistaphylococcal coverage.[2] Cohen-Wolkowiez et al[48] support the addition of an antifungal (amphotericin B or fluconazole) to the empiric regimen for LOS in units with high percentages of systemic fungal infections. When contemplating the use of an antifungal in empiric therapy, it is important to consider that invasive candidiasis is rare in term infants and is more common in premature infants and those who recently received antibiotics.[14]

In the context of strong clinical suspicion for severe sepsis or gram-negative meningitis, a third-generation cephalosporin, often cefotaxime, can be added to the empiric regimen. This addition optimizes therapy against ampicillin-resistant gram-negative organisms and offers enhanced central nervous system penetration. However, routine empiric use of cephalosporins is not recommended because of an increased risk for opportunistic *Candida* infection and the potential for antimicrobial resistance, especially with *Enterobacter* and *Klebsiella*.[4,5,11,14,27] In addition, Clark et al[49] conducted a large-scale retrospective cohort study that found a strong association between risk of death from EOS and substitution of cefotaxime for an aminoglycoside. Members of the cohort treated with ampicillin and cefotaxime had a 4.7% mortality rate prior to discharge, and those treated with ampicillin and gentamicin had a 2.3% mortality rate (adjusted odds ratio: 1.5; 95% confidence interval, 1.4-1.7).[49]

Antibiotics should be discontinued by 36 to 48 hours in a well-appearing infant with negative blood cultures.[4,5,11,14,27] Maternal intrapartum antibiotics may cause cultures to remain falsely negative, and thus a symptomatic neonate whose mother received antibiotics may complete a 10-day empiric course. A repeat blood culture with a standard empiric course of antibiotics may also be considered if therapy was never initiated; however, the AAP maintains that continued empiric regimens are rarely justified when laboratory data are normal.[4,11]

Narrowed Therapy

If a culture is positive, pathogen-directed therapy should be initiated on the basis of sensitivities (Table 8). Side effects of antibiotic administration are possible but are generally rare in neonates. It is important to consider the neonate's changing physiology over the first few weeks of life when planning doses and intervals, since many anti-infectives rely on hepatic and renal biotransformation and elimination.[14] Dosages and time intervals for medications vary according to gestational age, postnatal age, and weight.[27,50] Preterm infants typically require higher but less frequent doses related to an increased volume of distribution and decreased renal clearance.[27] In addition, doses and duration of the antibiotic regimen are often increased with central nervous system involvement.[50] Infants will typically respond to treatment within a day, and follow-up cultures should be drawn at this time to document pathogen clearance.[11] Duration of treatment can be guided by the presence of negative cultures upon repeat collection, serial trends of biomarkers, and the neonate's general appearance.

NEONATAL IMPLICATIONS

In term infants, long-term implications of sepsis primarily result from untreated or inadequately treated GBS infection.[11] The long-term outcomes of infants with sepsis have been studied most in the premature and VLBW populations, since they have the most significant burden. It remains unknown as to whether these complications are caused by sepsis or prematurity, though studies do show a strong association between neonatal sepsis and increased risk for complications. Infants with a history of sepsis exhibit poor growth and have increased risk of

TABLE 8. Directed Therapy for Confirmed Neonatal Bacteremia[43,50]

Medication	Indication	Dose and Duration	Side Effects
Ampicillin	Gram-positive and negative agents; important in empiric therapy related to action against *L monocytogenes*	50-100 mg/kg/dose Every 6-12 h 10-14 d	Fever Hives or rash Vomiting, diarrhea
Cefotaxime	Synergistic with gentamicin for severe gram-negative sepsis; gram-negative meningitis	50 mg/kg/dose Every 6-12 h 10-14 d	Fever Phlebitis, Rash Vomiting, diarrhea Eosinophilia
Gentamicin	Empiric therapy for gram-negative agents; synergistic with ampicillin or cephalosporin in confirmed gram-negative sepsis	4-5 mg/kg/dose Every 24-48 h 10-14 d	Ototoxicity Vomiting, diarrhea Nephrotoxicity Anemia Thrombocytopenia
Meropenem	Gram-positive and negative cephalosporin-resistant strains	20-30 mg/kg/dose Every 8-12 h 10-14 d	Rash Convulsions Vomiting, diarrhea
Nafcillin	Empiric antistaphylococcal; confirmed *S aureus*	25 mg/kg/dose Every 6-12 h 10-14 d	Fever Phlebitis Cholestasis Nephritis Neutropenia
Penicillin G	Confirmed GBS	25,000-50,000 units/kg/dose Every 8-12 h 10 d	Allergic reaction Phlebitis, rash Colitis Neutropenia
Piperacillin/tazobactam	Gram-positive and negative β-lactamase–producing bacteria; synergistic with gentamicin for *P aeruginosa*	100 mg/kg/dose Every 8-12 h 14 d Dosing based on piperacillin[a]	Fever, flushing Rash Vomiting, diarrhea Elevated liver enzymes Anemia
Vancomycin	Empiric antistaphylococcal; confirmed CoNS and MRSA	10-15 mg/kg/dose Every 6-24 h CoNS: 7 d MRSA: 10-14 d	Ototoxicity Red man syndrome Phlebitis Nephrotoxicity Neutropenia

Abbreviations: CoNS, coagulase negative staphylococci; GBS, group B streptococcus; MRSA, methicillin resistant Staphylococcus aureus.
[a]Dose and duration strategies are increased in cases of meningitis.

developing cerebral palsy (16.3%), bronchopulmonary dysplasia (53.6%), seizures (21%), and stage 3 or 4 retinopathy of prematurity (22.8%) when compared with unaffected neonates.[10,27,51] Other potential consequences include oxygen requirement at discharge (51%), cognitive deficits (35.9%), visual impairment (13.3%), hearing impairment (3.6%) or loss (35%), and motor delays (27%).[10,27,51]

Mortality rates of neonatal sepsis vary by gestational age and pathogen. In term infants, rates are low: 2% to 3% for EOS and 0.3% for LOS.[5,52] For infants born between 22 and 24 weeks, the mortality rate is higher and approaches nearly 50% for EOS and 4% for LOS.[4,11] Gram-positive infections have a 10% mortality rate.[52] Gram-negative infections are associated with a worse prognosis and carry a 45% mortality rate, causing 60% of all LOS fatalities.[1]

CONCLUSION

Despite the introduction of IAP, advances in diagnostic methods, and more targeted treatments, sepsis

Summary of Recommendations for Practice and Research	
What we know:	• Sepsis is a leading cause of morbidity and mortality in neonates even with modern advancements. • The neonate has multiple immune deficiencies making it more susceptible to infection. • Diagnosing neonatal sepsis is challenging because of the often nonspecific presentation and laboratory methods that offer poor sensitivity and specificity in the neonate. • The misuse of antibiotic therapy carries risks and contributes to resistance.
What needs to be studied:	• Continued efforts similar to intrapartum antibiotic prophylaxis and central line bundles to prevent the occurrence of neonatal sepsis. • A predictive model similar to the EOS calculator for neonates <34 weeks of gestation and for LOS. • Diagnostics for neonatal sepsis with improved sensitivity and specificity.
What we can do today:	• Promote antibiotic stewardship through the use of the EOS calculator. • Practice infection prevention to decrease the occurrence of LOS. • Utilize empiric therapy judiciously with consideration of the entire clinical picture.

continues to be associated with significant risk of morbidity and mortality in the neonatal population. The diagnosis and management of sepsis remain complicated and involves the integration of what we know about the neonatal immune system with the best available evidence on how to identify infants at high risk. Continued research is needed to develop diagnostic methods that yield rapid results with enhanced sensitivity and specificity. It is crucial that nurses understand neonatal sepsis. They must acknowledge the deficiencies of the neonatal immune system, be familiar with symptoms in order to detect small changes in their patient's clinical presentation, assist in the interpretation of laboratory data suspicious for infection, and recognize correct antibiotic administration practices when needed. In addition to this, APRNs must be familiar and up-to-date with the most current diagnostic and treatment recommendations. This article provides the staff nurse and the novice advanced practice nurse with a foundational understanding of neonatal immune system deficiencies and the management of neonatal sepsis, as efficiency in diagnosis and early initiation of treatment will improve outcomes for neonatal patients.

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