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Neonatal sepsis: Progress towards improved outcomes

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Summary Neonates are predisposed to infections during the perinatal period due to multiple exposures and a relatively compromised immune system. The burden of disease attributed to neonatal infections varies by geographic region and maternal and neonatal risk factors. Worldwide, it is estimated that more than 1.4 million neonatal deaths annually are the consequence of invasive infections. Risk factors for early-onset neonatal sepsis (EOS) include prematurity, immunologic immaturity, maternal Group B streptococcal colonization, prolonged rupture of membranes, and maternal intra-amniotic infection. Intrapartum antimicrobial prophylaxis administered to GBS-colonized women has reduced the burden of disease associated with early onset GBS invasive infections. Active surveillance has identified Gram-negative pathogens as an emerging etiology of early-onset invasive infections. Late-onset neonatal sepsis (LOS) attributable to Gram-positive organisms, including coagulase negative *Staphylococci* and *Staphylococcus aureus*, is associated with increased morbidity and mortality among premature infants. Invasive candidiasis is an emerging cause of late-onset sepsis, especially among infants who receive broad spectrum antimicrobial agents. Prophylactic fluconazole administration to very low birthweight (VLBW) neonates during the first 6 weeks of life reduces invasive candidiasis in neonatal intensive care units with high rates of fungal infection. Prevention of healthcare associated infections through antimicrobial stewardship, limited steroid use, early enteral feeding, limited use of invasive devices and standardization of catheter care practices, and meticulous hand hygiene are important and cost-effective strategies for reducing the burden of late-onset neonatal sepsis.

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Introduction

The perinatal period is hazardous with multiple opportunities for exposures to virulent organisms. Potential sites of exposure include the uterus, the birth canal, the neonatal care unit, invasive procedures and devices, healthcare providers, family and visitors, and the community. In addition to these multiple sites of exposure and diverse modes of infection transmission, neonates are relatively immunocompromised. The impaired innate immune function of premature infants predisposes them to invasive infections. Because the fetal immune response begins at about 24 weeks of age and development occurs until term, premature neonates do not benefit from complete immune system development, making them more susceptible to infection with organisms that term infants may be able to suppress.[1] Prolonged hospitalization, invasive procedures and devices, lack of enteral feeding, and the utilization of broad spectrum antibiotics, due to increased risk of infections with multi-resistant pathogens, increase risk to already vulnerable neonates.

The recognition of neonatal sepsis is complicated by the frequent presence of non-infectious conditions that resemble those of sepsis, especially in very low birthweight (VLBW) preterm infants, and by the absence of optimal diagnostic tests. While the laboratory identification of an organism from a sterile site is optimal for definitive diagnosis, it is not always possible to isolate a causative pathogen. Invasive infections can also occur in seemingly asymptomatic neonates. Therefore assessment of history and risk factors in combination with diagnostic tests are used to identify neonates who are more likely to be infected.

Burden of disease and characterization

Worldwide, invasive neonatal infections are estimated to cause approximately 36% of the estimated 4 million neonatal deaths annually. Rates of infection vary by geographic region, resource endowment, maternal and infant risk factors. Early and late-onset neonatal sepsis is differentiated by timing of symptom onset, virulence of the infecting organism(s) and associated pathogenesis. Early-onset sepsis (EOS) is defined by infection in the first week of life. Many investigators, including those who participate in the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Network and the Vermont Oxford Network, define EOS by the onset of signs or symptoms and an associated positive culture at or before 72 h of life. Late-onset sepsis (LOS) is characterized by the onset of symptoms consistent with sepsis at greater than 72 h of life. These classifications of EOS and LOS reflect the differing etiologies and proposed pathophysiology of pathogens commonly associated with the timing of onset of these conditions.

Early onset sepsis (EOS)

EOS remains a serious complication of the post-partum period. Risk factors for EOS include prematurity and associated immunologic immaturity,[2] maternal Group B *streptococcal* (GBS) colonization, rupture of membranes greater than 18 h, and maternal intra-amniotic infection.[3,4] In the 1970's, Group B *streptococci* (GBS) emerged as the leading cause of neonatal meningitis and bacteremia in the United States. The association between maternal GBS colonization and neonatal infection resulted in the development of guidelines to administer intrapartum antimicrobials to GBS-colonized women in the United States to reduce invasive GBS in the newborn. Widespread implementation of these guidelines has resulted in substantial reduction in early-onset GBS disease. However, burden of disease continue and GBS remains the most frequently isolated EOS pathogen in the United States, particularly among term infants.

Epidemiologic surveillance has noted the emergence of *Escherichia coli* (*E. coli*) as an important pathogen associated with EOS, especially among VLBW infants. Increased rates of severe disease and death with Gram-negative EOS have been reported in some studies. To monitor changes over time, it remains important to continue active surveillance for rates of EOS and pathogens associated with infection.

Burden of EOS

The burden of EOS in the United States, assessed by the Centers for Disease Control and Prevention (CDC) through their Active Bacterial Core Surveillance (ABCs) in 4 states from 2005 to 2008 yielded an overall rate of EOS of 0.77 per 1000 live births and a case fatality rate of 10.9%. In the ABC surveillance, GBS was responsible for 0.29 infections per 1000 live births with a case fatality rate of 7% and *E. coli* was responsible for 0.19 infections per 1000 live births with a case fatality rate of 25%.[5] In comparison, the National Institutes for Child Health and Development (NICHD) Neonatal Research Network (NRN) assessed all live births from 16 university neonatal care units from 2006 to 2009. This evaluation resulted in an overall rate of EOS of 0.98 per 1000 live births with a case fatality rate of 16%; a rate of GBS infections of 0.41 per 1000 live births and case fatality rate of 9% and 0.28 *E. coli* infections per 1000 live births with a case fatality rate of 33%.[6] In both the CDC ABCs and NICHD NRN studies, rates of infection and case fatality increased with decreasing gestational age and birthweight. In both studies, the estimated burden of EOS in the United States was approximately 3300 cases and 400 deaths annually.

Group B streptococci (GBS)

The central challenge with the management of EOS GBS is identifying the 2% of infants born to GBS colonized women who will develop invasive disease (EOS, pneumonia, and/or meningitis). One-half of infants born to GBS colonized women will themselves be colonized.[7,8] Of these, 98% will be asymptomatic while 2% will have evidence of invasive disease. Studies in the United States have elucidated a number of risk factors for early onset (EO) GBS disease including maternal GBS carriage, GBS bacteriuria, prematurity, low birth weight, prolonged rupture of membranes