Early-Onset Neonatal Sepsis: A Continuing Problem in Need of Novel Prevention Strategies

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Early-onset neonatal sepsis (EOS) remains a feared cause of severe illness and death among infants of all birthweights and gestational ages, with particular impact among preterm infants. Centers for Disease Control and Prevention investigators have studied the changing epidemiology of invasive EOS for several decades. The Active Bacterial Core surveillance (ABCs) network, a collaboration between the Centers for Disease Control and Prevention, state health departments, and universities, was established in 1995 to address emerging infectious diseases of public health importance, including infections due to major neonatal pathogens.[1,2] ABCs data are remarkable because of the geographic distribution and size of the population-based network, laboratory-based identification of cases, linked epidemiologic and laboratory data, and surveillance over many years. In this issue of *Pediatrics*, Schrag and colleagues[3] present ABCs data on the epidemiology of early-onset neonatal sepsis collected over a recent 10-year period, with special attention to group B streptococcal (GBS) and *Escherichia coli* infections.

Invasive GBS infection among neonates, identified in the 1960s,[4] emerged as the most common cause of EOS, with high risk of morbidity and mortality. National guidelines for the prevention of perinatal GBS, first issued in 1996, recommended either antenatal screening for GBS colonization and intrapartum antimicrobial prophylaxis (IAP) for colonized women or targeted IAP for women with obstetrical risk factors in labor known to increase GBS transmission.[5] Revised guidelines in 2002 recommended universal antenatal screening for GBS at 35 to 37 weeks' gestational age to identify colonized women who should receive IAP.[6] Guidelines were additionally refined in 2010 to provide neonatal management recommendations based on maternal risk factors and clinical condition of the infant at birth, with an attempt to reduce unnecessary evaluations of well-appearing infants without risk factors.[7] Widespread adherence to national guidelines resulted in a remarkable decline in early onset GBS disease, but a concomitant increase in exposure to intrapartum antibiotics.[8] Several studies have reported missed opportunities for GBS prevention.[9] At the same time, clinicians and investigators voiced concerns about increased exposure to IAP with potential for an increase in non-GBS invasive pathogens and emergence of antibiotic resistance in GBS and other pathogens.

Schrag et al[3] describe trends in EOS sepsis due to GBS and *E coli* and compare clinical and epidemiologic characteristics of these infections. Their findings once again document missed opportunities for GBS prevention; 37% of women with an indication did not receive IAP. The vast majority of neonates have bacteremia, with only a minority diagnosed with meningitis. Rates of EOS overall and of

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E coli are stable, with some continued decline in GBS, easing concerns about potential increase of *E coli* infection in the face of increased IAP. Although GBS remains the most common EOS pathogen overall, the relative incidence of GBS and *E coli* varied by state, with some states having more *E coli* than GBS cases for at least one of the years studied. Rates of infection, morbidity, and mortality continue to be highest among preterm, especially very low birth weight, infants and among black infants. Eleven percent of infected infants died. Although mortality was higher among very low birth weight infants infected with *E coli*, birth weight, pathogen, and mortality are interconnected. Although ABCs collects limited neonatal clinical information, 6% of survivors were reported to have sequelae at hospital discharge.

This study underscores the need for continued adherence to national GBS guidelines: universal antenatal screening and attention to the special cases of women in preterm labor who should be screened at delivery and women with presumed penicillin allergy. The identification of infants with possible EOS is based on obstetrical and neonatal risk factors and the condition of the infant at birth. In particular, evaluating the infant's condition is challenging and depends on clinical experience. The relative severity of clinical symptoms with different pathogens deserves additional study, especially because pathogen and neonatal complications may impact neurodevelopmental outcomes among survivors.[10] Although not specifically addressed by this study, neonatal management of well-appearing term infants born to mothers with risk factors for infection, particularly chorioamnionitis, remains controversial. Risks of prolonged early neonatal antibiotics, including increases in late-onset sepsis, necrotizing enterocolitis, and death,[11,12] as well as worrisome changes in the microbiome,[13] support efforts to prevent unnecessary therapy. The global epidemic of antimicrobial resistance demands continued surveillance of susceptibility patterns as well as evidence-based guidelines for antibiotic stewardship in high-risk newborns.

Unlike GBS, there are no evidence-based strategies to reduce the risk of early-onset Gram-negative infections, particularly *E coli*. Additional studies to delineate specific risk factors for non-GBS EOS might lead to novel preventive interventions. Maternal immunization against invasive pathogens could prevent disease in the triad of mother, fetus, and newborn, a worthy goal.[14] GBS immunization would prevent both early- and late-onset neonatal disease and might have an impact on other adverse outcomes of pregnancy, including stillbirth, prematurity, and culture-negative clinical sepsis. More than 50 years after neonatal GBS was first described, it is time to see GBS vaccines in the clinical arena preventing disease in mothers and infants.

ABBREVIATIONS

ABC: Active Bacterial Core surveillance
EOS: early-onset neonatal sepsis
GBS: group B streptococcus
IAP: intrapartum antimicrobial prophylaxis

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