Antibiotic Stewardship

Reassessment of Guidelines for Management of Neonatal Sepsis

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KEYWORDS

• Antibiotics • Neonatal sepsis • Management • Guidelines

KEY POINTS

- The collective concerted efforts to reduce risk of early onset group B streptococcus since 1996, which have included use of antibiotics for large number of women and infants, have been successful.
- Information is emerging indicating that exposures to antibiotics may increase risk of future health problems, especially in preterm infants.
- Antibiotic stewardship is a current goal of the Centers for Disease Control and Prevention.
- Clinicians struggle with the decision to empirically treat well-appearing infants with risk-factors with antibiotics.
- Emerging large scale use of electronic health records may better inform the risk-benefit calculations that clinicians consider in deciding on use of empirical antibiotics for early onset sepsis.

DEFINING THE PROBLEM: EARLY ONSET SEPSIS

Epidemiologists define early onset sepsis (EOS) as culture positive infections occurring the first 3 postnatal days.[1,2] The Centers for Disease Control and Prevention (CDC) defines early onset group B streptococcus (GBS) disease as blood or cerebral spinal fluid culture-proven infection occurring in the first 7 postnatal days.[3,4] The National Institute of Child Health and Human Development's (NICHD) definition of EOS also requires that the infection be treated with antibiotics for 5 or more continuous days.[2] However EOS is defined, the obstetric and pediatric communities have collaborated to greatly reduce the risk of the major cause of EOS in term infants, GBS (*Streptococcus agalactiae*), since the CDC's first guidelines to reduce the risk were published in 1996.[3] At the time the first guidelines emerged, the incidence of

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EOS in the United States was 3 to 4 cases per 1000 live-born infants.[5] With guideline modifications in 2002 and 2010 strongly recommending universal screening, fine-tuning of culture methods, and intrapartum antimicrobial prophylaxis (IAP) drug choice when the mother is penicillin allergic, the incidence of EOS has decreased to 0.3 per 1000.[2,4,6] GBS remains the leading cause of EOS in term infants, whereas *Escherichia coli* is most prevalent among premature infants.[2,7]

At a population level, the 2- to 10-fold reduction in prevalence of EOS since 1996 is remarkable.[2,8,9] The guidelines have saved lives. However, the guideline-based strategies that have led to this reduction have contributed to 30% of mothers in the United States receiving antibiotics during labor.[8,10,11] On the neonatal side, single-center experiences and population estimates based on clinicians following the guidelines since the first were published indicate that 15% to 20% of term infants (more than 500,000 infants per year in the United States), most of whom are asymptomatic, are evaluated with screening blood tests for EOS and many also receive empirical antibiotics.[11–13]

RISKS OF ANTIBIOTICS: WHY BE CAUTIOUS?

Adherence to the CDC's guidelines has resulted in significant decreases in EOS; but antibiotic exposures, in the absence of an identified infection to treat, do not seem to be totally without risk. The emerging evidence for risk provides a rationale for identifying mechanisms to limit antibiotic exposure initiation to infants at highest risk while missing extremely few if any infants with evolving infection and limiting the duration of antibiotics for those whose evolving clinical picture indicates an extremely low likelihood of infection. Aminoglycosides are among the most commonly used antimicrobials for the prevention and empirical treatment of EOS and have the potential to cause renal and ototoxicity.[14,15] Among premature infants, the duration of the initial empirical course is associated with later-onset infection, necrotizing enterocolitis, and death.[16–18]

In a Swedish cohort, antibiotic exposure in the neonatal period was associated with almost triple the odds of later wheezing in infants 33 weeks of age and older.[19] In a Dutch cohort, the use of neonatal antibiotics was associated with changes to the microbiome, which in turn were associated with atopic symptoms (eczema and wheeze).[20,21] Although the information linking antibiotic exposure to wheezing and atopy via the microbiome is intriguing and biologically plausible, and animal studies have demonstrated the strong influence of neonatal antibiotics on later gut microbiome and respiratory outcomes,[22,23] the investigators of meta-analyses of the cohort studies associating neonatal antibiotic exposures with later wheezing in children find that the associations are subject to bias and recommend caution before justifying the limitation of antibiotics for the purpose of avoiding asthma at the current stage of evidence accumulation.[24,25] More immediately, clinicians and the community at large share the concern that overall use of antibiotics contributes to the development of resistant organisms, making careful and selective use of antibiotics to the highest-risk patients a universal goal. Antibiotic stewardship is the third of 4 core activities identified by the CDC to limit the development of antimicrobial-resistant organisms: (1) prevent infections, preventing spread; (2) tracking resistance patterns; (3) improving use of antibiotics; and (4) developing new antibiotics and diagnostic tests.[26]

REVIEW OF PAST AND CURRENT CENTERS FOR DISEASE CONTROL AND PREVENTION GUIDELINES

The third and most recent iteration of the CDC's guidelines to prevent GBS perinatal disease was published in 2010.[4] The CDC's initial and subsequent guidelines were the