Empirical Antibiotic Therapy for Suspected Early-Onset Bacterial Sepsis

We are writing in response to the recently published article, “Management of Neonates With Suspected or Proven Early-Onset Bacterial Sepsis” by Richard Polin and the American Academy of Pediatrics Committee on the Fetus and Newborn (COFN).1

We agree with Dr Polin and the committee that empirical antimicrobial initiation and cessation are based on scientific principles modified by art and experience. The review is thorough and well referenced. However, we are concerned that the algorithms provided in this report may lead to increased use and duration of empirical antibiotics. Universal screening for maternal group B streptococcal (GBS) colonization and use of intrapartum antibiotic prophylaxis have resulted in substantial reduction in early-onset GBS among newborns. Despite this progress, GBS remains the leading cause of early-onset neonatal sepsis in the United States, with continued burden of disease.2 In 2010, the Centers for Disease Control and Prevention issued revised Guidelines for the Prevention of Perinatal Group B Streptococcal Disease.3

The algorithm included in the 2010 Centers for Disease Control and Prevention guidelines identifies only 2 categories of infants for empirical treatment: those with signs of sepsis and those with maternal chorioamnionitis. Well-appearing infants <37 weeks’ gestation with inadequate intrapartum antibiotic prophylaxis and infants >37 weeks with rupture of membranes >18 hours are to receive limited evaluation and observation for at least 48 hours. Because the consequences of missing early-onset sepsis can be grave, it is difficult to fault clinicians for initiating empirical antibiotics in preterm infants with risk factors. This may be the reason for the alternative strategy depicted in Fig 1 of the clinical report by Polin et al,1 which suggests treating all well-appearing infants <37 weeks’ gestation with inadequate intrapartum antibiotic prophylaxis with empirical antibiotics. Although Polin and the COFN state that “Antimicrobial therapy should be discontinued at 48 hours in clinical situations in which the probability of sepsis is low,” Figs 1 and 2 in the report may lead clinicians to prolong empirical antibiotic courses. For example, Fig 1 indicates that if cultures are negative and infants appear well, but laboratory data are abnormal, antibiotics are to be continued. Duration of empirical therapy is not discussed, and the only laboratory tests listed on the algorithms are from the first 12 postnatal hours. We are concerned that only using laboratory results obtained in the first 6 to 12 postnatal hours to determine duration of empirical therapy does not provide adequate positive or negative predictive value in most situations and will lead to increases in duration of antimicrobial courses, despite sterile cultures. For example, would a test with abnormal results be defined as one with elevated C-reactive protein, or one with elevated band count, or one with elevated white blood cell count? In a report of >800 well-appearing near-term and term infants exposed to suspected chorioamnionitis, 99% of the infants had at least 1 abnormal finding on the complete blood cell count, whereas only 0.5% had a positive blood culture.4 Thus, following the algorithm outlined in Fig 1, as many as 99% of infants with suspected chorioamnionitis might be candidates for empirical antibiotic courses >48 hours, despite sterile cultures. Guidance on definitions and timing of tests such as C-reactive protein after the first 12 hours that can provide reassurance regarding the very low likelihood of sepsis would be helpful for clinicians.5

The COFN suggestions could be strengthened with recent guidance from the Centers for Disease Control and Prevention to “Take an Antibiotic Time Out” when culture results are available at 24 to 48 hours: “Stop and reassess therapy. Antibiotics are generally started before a patient’s full clinical picture is known. Now that additional information is available, including microbiology, radiographic, and clinical information, clinicians should ask themselves if the antibiotic is still warranted or, more importantly, is this antibiotic still effective against this organism? It is the time to reevaluate why the therapy was started in the first place and to gather all of the evidence on whether there should be changes in the course of therapy or the antibiotics should be stopped altogether if an infection no longer appears likely.”6

Unfortunately, no antibiotic is without risk. Every time we administer antibiotics, especially prolonged antibiotics, we expose each infant to increased risk of subsequent infection with resistant organisms, invasive candidiasis, necrotizing enterocolitis, late-onset sepsis, and death.7,8 The risk for each infant of iatrogenic harm from prolonged antibiotic therapy is admittedly small (<1%). However, the risk of culture-proven early-onset bacteremia is 0.1%, and the risk of culture-negative early-onset bacteremia (false-negative blood culture) is also likely <1.2%. Thus, continued antibiotics as outlined in the algorithms proposed by the COFN may well harm more infants than they will protect.

The proposed algorithms have potential public health implications as well. When we administer surfactant or caffeine to infant A, there is no potential risk to infant B located in the
same nursery. Antibiotics are different. Every time we provide prolonged antibiotics to 1 infant, we expose every infant in the nursery to a small increased risk of resistant infection.\(^9\)

We agree that clinicians face difficult choices in initiation and duration of empirical antibiotics for early-onset sepsis. Too little use may result in preventable neonatal deaths from infection; too much use, especially prolonged use, may lead to increased mortality and morbidity.\(^7,8\) We agree that clinicians should have a low threshold for starting antibiotics in high-risk infants, but timely discontinuation of antibiotics in the face of negative blood cultures is necessary to reduce the risks associated with prolonged use of empirical antibiotics.

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Urinary Neutrophil Gelatinase Associated Lipocalin Identifies Neonates With High Probability of Sepsis

The diagnosis of “suspected sepsis” in neonates in the ICU is challenging given the nonspecific signs of sepsis and the poor diagnostic performance of currently used laboratory markers and the unfortunate delay in bacterial culture data.\(^1,2\) In this excellent review, Polin reports that, although sepsis screening panels and scoring systems that include multiple laboratory values may help exclude neonatal sepsis, their positive predictive value is very poor, <30%.\(^5,4\) Although the negative predictive value is of great importance, this review identifies the importance of identifying a marker of “high likelihood” of early-onset sepsis in neonates who require antimicrobial agents soon after birth, in short, a marker with a useful positive predictive value.\(^4\) Neutrophil gelatinase associated lipocalin (NGAL) is a member of the lipocalin superfamily expressed by neutrophils and kidney tubular epithelia in response to ischecmia, hypoxia, sepsis, and drug toxicity. NGAL acts as an iron scavenger preventing bacterial growth and, hence, is a critical component of the defense against infection.\(^5\) NGAL is a robust marker of acute kidney injury in adults\(^6\) and children, and we have identified it as a marker of sepsis in adults and in very low birth weight (VLBW) infants.\(^7\) We studied NGAL as an early biomarker of late-onset blood culture positive sepsis in VLBW infants and found 75% sensitivity, 84% specificity, 67% positive predictive value, and 89% negative predictive value, in comparison with VLBW infants without sepsis. The sensitivity and positive predictive value of this single urinary biomarker far exceeded even panels of biomarkers used to detect sepsis.\(^4\) Although the test characteristics may be different in early-onset in comparison with late-onset bacterial sepsis and in term compared with very low birth weight infants, we believe that NGAL may offer not only a robust negative predictive value, but also improved positive predictive values, and hence may be able to identify infants at high risk of being infected. NGAL deserves further investigation in neonatal populations.

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