Early Antibiotic Therapy and Adverse Outcomes in Preterm Infants: Time for a Trial!

For decades, antibiotics have been prescribed after delivery to preterm infants cared for in the neonatal intensive care unit. Given the risks of early-onset sepsis, particularly during the peak of group B streptococcal disease, a "better safe than sorry" approach to empiric antibiotics became commonplace. Like Thetis dipping her newborn Achilles into the river Styx to confer invulnerability, neonatologists would routinely administer ampicillin and gentamicin for days or even weeks, often in the absence of any objective evidence for infection. As recently as 2008, approximately one-half of extremely low birth weight (ELBW; <1000 g) infants received >5 days of empiric antibiotic therapy after delivery.[1] Unfortunately, as with Achilles, a critical weakness in that strategy was identified. In 2009, Cotten et al associated prolonged early antibiotic therapy with an increased risk for necrotizing enterocolitis (NEC) and death in ELBW infants (OR, 1.04 [95% CI, 1.02-1.06] per day of antibiotics).[2] A variety of other study groups in different centers and countries have since found similar associations.[3-7] Over the last 10 years, prolonged empiric antibiotic use among preterm infants has decreased, although more than a third of ELBW infants still receive prolonged empiric antibiotics.

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In this volume of *The Journal*, Li et al report their very different experience with early antibiotic therapy and subsequent development of NEC in 2831 very low birth weight (<1500 g) infants from the NEOMUNE-NeoNutriNet cohort.[8] Using a logistic mixed methods analysis to control for a wide variety of confounders—including gestational age, birth weight, sex, study center, mode of delivery, use of antenatal steroids, Apgar scores, and timing and mode of enteral feeding—the authors found a 43% decrease in NEC incidence for infants who received empiric antibiotics in the first 72 hours of life compared with those who did not (OR, 0.25; 95% CI, 0.14-0.47). Interestingly, the duration of early antibiotic therapy did not correlate with NEC incidence (eg, additional days of antibiotics were neither protective nor harmful in their models). It is worth noting that the average duration of treatment was prolonged (>5 days) in the majority of the study centers. The average duration of empiric antibiotic treatment for the 2 largest centers in the study were 10 and 14 days, and 1 center treated newborns for an average of 19 days after delivery. The major limitations cited by Li et al include first, the significant disparities between the 2 groups, with the no early antibiotic group being more mature and more likely to be small for gestational age; and second, the inability to capture numerous confounders that occurred between age 72 hours and the onset of NEC, including subsequent antibiotic treatment, patent ductus arteriosus, transfusions, and countless other factors that may be associated with the development of NEC.

When it comes to dealing with measured and unmeasured confounders, Li et al have my unreserved sympathy.[8] No cohort study can possibly be designed to account for the myriad potential confounders that impact multifactorial outcomes such as NEC, late-onset sepsis, and death. In our group's study of early antibiotic use among very low birth weight infants, we used the Clinical Risk Index in Babies-II score to try to control for severity of illness.[5] We found that sicker babies received more antibiotics and then went on to have worse outcomes. Is that confounding by indication, or proof that antibiotics are harmful to the developing infant microbiome? The answer depends a lot on your a priori beliefs. Cotten et al used logistic regression stratified by the need for >7 days of mechanical ventilation to control for severity of illness.[2] Kuppala et al used a predictive scoring model that used clinical data from the first week after delivery.[3] Ting et al used the Score for Neonatal Acute Physiology-II.[6] All of these approaches are reasonable; all of these approaches are flawed.

The strategies available to investigators performing cohort studies are to either try to control for as much as possible, to the point where the model runs the risk of being overfitted or colinear, or to build a simpler, more intuitive model that will by definition miss potential confounders. This inevitable problem causes a form of biostatistical whack-a-mole, where fixing 1 problem causes another to pop up, with the end result being that any conclusions the reader disagrees with can be ignored or rationalized away owing to the inherently flawed study design. Because no cohort study can be designed perfectly to control for unmeasured confounders, I argue that it is time for a randomized controlled trial. A trial is the optimal way to control for confounders, measured and unmeasured alike.[9] The ability to balance unmeasured confounders is critical for NEC, because our understanding of the complex pathophysiology continues to evolve in real time.[10]

There was a time when a randomized controlled trial of early antibiotic therapy for preterm newborns was not seen

ELBW Extremely low birth weight
NEC Necrotizing enterocolitis

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as feasible. How could we safely randomize an at-risk infant to the placebo arm, when the chance of missing even one infant with early-onset sepsis was considered too great a risk? However, recent changes have shifted the landscape in neonatology. In addition to the growing body of evidence for early and late adverse outcomes following prolonged or unnecessary antibiotic use, there has also been an overall decrease in the rate of early-onset sepsis and a better understanding of how to stratify risk for early-onset sepsis, even among preterm infants.[11] In addition, the results of the SUPPORT and BOOST-II trials, although not without controversy, have demonstrated the feasibility and importance of finding the optimal approach to a medication (in those cases, oxygen) once viewed as uniformly life saving and safe but now known to have toxicity when used incorrectly.[12,13]

The NICU Antibiotics and Outcomes (NANO, NCT03997266) trial is a randomized controlled trial aimed at evaluating the adverse or beneficial outcomes of early empiric antibiotic therapy for ELBW infants.[14] The trial will randomize 802 infants born at 23-28 weeks gestation in a 1:1 to early empiric antibiotics or placebo. Infants whose risk for sepsis is too high (eg, infants born to mothers with chorioamnionitis or infants who are critically ill) or those who are at minimal risk for sepsis (eg, infants born via cesarean delivery for maternal indication, with rupture of membranes at delivery) will be excluded. The primary outcome will be the composite incidence of late-onset sepsis, NEC, or death; a priori secondary outcomes include sepsis, NEC, and death individually as well as microbiome diversity. Hopefully, the NANO trial and other well-designed, randomized controlled trials can define with precision the risks and benefits of early antibiotic therapy, and provide the definitive evidence neonatologists have been waiting for since 2009.

Li et al are to be congratulated for their ambitious undertaking. The 2831 very low birth weigh infants cared for across 5 continents represent an impressive cohort. The authors' conclusions are thought provoking and challenge the current paradigm of early antibiotic exposure leading to increased risk for NEC, and they and *The Journal* should be lauded for ensuring that their findings were published. This study highlights the complexity of studying the effects of early antibiotic therapy on neonatal outcomes and emphasizes the need for well-designed randomized controlled trials to answer these burning questions. The time has come for a trial. ■

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