

Antibiotic Stewardship in the Neonatal Intensive Care Unit: Lessons From Oxygen

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The introduction of oxygen therapy was in many ways a panacea for clinicians caring for preterm infants in the early 20th century. These pediatricians (the term “neonatologist” was not coined until decades later) began to use oxygen supplementation to support preterm infants and achieved previously unthinkable survival rates. In 1934, Julius Hess,¹ who was widely credited with developing the first incubator for oxygen administration, reported the survival of 4 extremely low birth weight (<1000 g) infants via use of his eponymous incubator, which provided ~40% to 50% oxygen concentration. Within a decade, effective delivery of high oxygen concentration was widespread among NICUs, and survival rates climbed. But simultaneously, so did the incidence of retinopathy of prematurity (ROP), which was then called retrolental fibroplasia. In 1951, oxygen toxicity was identified as the cause of ROP.² The response from pediatric providers was both swift and tragic; oxygen concentrations were decreased, and ROP rates declined, but mortality increased. It has been estimated that >16 infants died of hypoxemia for each case of blindness that was prevented.³ As a result, research efforts in neonatal care have begun to shift toward stewardship of this potentially lifesaving intervention by finding the optimal amount of oxygen delivery. Oxygen targeting has become more sophisticated because our understanding of oxygen toxicity has improved.^{4,5}

The parallels between the history of oxygen use and antibiotic therapy in the NICU setting are striking. In the 1960s, before ampicillin and gentamicin were available for neonates, the case-fatality rate of neonatal sepsis due to group B streptococci or Gram-negative Bacilli exceeded 50%. By the mid-1970s, antibiotics had markedly reduced the morbidity and mortality of these common perinatal infections.⁶ For decades, as was the case with oxygen, the tremendous benefit of antibiotics along with a perception that they lacked substantial harm led to liberal use of empirical antibiotic therapy for newborns. Not only were antibiotics routinely administered to infants with overt clinical signs of illness (eg, respiratory distress), but many well-appearing infants received empirical treatment based on perinatal risk factors, such as prolonged rupture of membranes, chorioamnionitis, or group B streptococcal colonization. By 2006, ampicillin and gentamicin were the 2 most frequently used medications in the NICU, and >80% of infants were treated with at least 1 course of antibiotics.⁷

However, recent studies are changing perceptions of the relative costs versus benefits of antibiotics, especially when used empirically. In this issue of *Pediatrics*, Ting et al⁸ investigated antibiotic use in >20 000 very low birth weight infants (≤1500 g) and found an association between prolonged antibiotic exposure (4–7 days) and a composite outcome of

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mortality or major morbidity, including intraventricular hemorrhage, periventricular leukomalacia, ROP, necrotizing enterocolitis, bronchopulmonary dysplasia, and late-onset sepsis. This study is the largest study to link early antibiotic exposure with adverse long-term outcomes, has the broadest composite outcome, and includes a validated marker (version II of the Score for Neonatal Acute Physiology) to control for severity of illness. This report by the Canadian Neonatal Network joins a growing list of studies in which researchers have associated early antibiotic exposure with adverse outcomes in neonates, such as sepsis, necrotizing enterocolitis, and death, even after controlling for severity of illness.^{9–12} As with oxygen toxicity, our understanding of how antibiotics mediate these short- and long-term effects by disrupting the normal gut and lung microbiome continues to grow.^{13,14}

Where, then, do we go from here? As with oxygen, eliminating antibiotic use in the NICU is neither possible nor desired, but current prescribing rates are unacceptably high. Ideally, antibiotic use in the NICU could be targeted with precision so that only the infants with proven infection would receive antibiotics, and even then, only the narrowest-spectrum effective antibiotic. These are fundamental principles of antimicrobial stewardship. Achieving this level of specificity with antibiotic therapy would reduce total NICU antibiotic use by >90%.¹⁵ However, to achieve that goal, several barriers remain to be overcome. First, although pulse oximetry can detect hypoxemia in a sensitive and specific manner for guiding oxygen therapy, at present there is no highly sensitive and specific test that allows for confirmation of sepsis before antibiotic administration to an infant who appears ill. Instead, providers must obtain appropriate cultures and

initiate empirical antibiotic therapy for a minimum of 24 to 48 hours before sepsis can be reliably excluded. This approach with empirical antibiotic therapy accounts for the majority of NICU antibiotic use, most of which is ultimately unnecessary.¹⁵ Second, too many well-appearing infants receive empirical antibiotic therapy in the first place. Interventions that are designed to fundamentally change physician prescribing behavior are needed to help guide safe and selective observation without antibiotics for certain populations, such as low-risk preterm infants who are born via cesarean delivery for maternal indications without labor or well-appearing infants who are exposed to chorioamnionitis. Recent guidance from the American Academy of Pediatrics' Committee on Fetus and Newborn and Committee on Infectious Diseases highlights approaches to risk stratification in both term and preterm infants.^{16,17}

Finally, and most importantly, providers who are caring for newborns must shift their thinking on antibiotics. For a long time, the classic teaching was "better safe than sorry." However, as is highlighted by Ting et al,⁸ we are learning that prolonged antibiotic therapy is not safe at all. Instead, the safest thing for many of our most vulnerable infants may be thoughtful evaluation, careful risk stratification, and close observation.

ABBREVIATION

ROP: retinopathy of prematurity

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