

# Antibiotic Use in Neonatal Intensive Care

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The Centers for Disease Control and Prevention estimates that >2 million people in the United States become ill every year due to antibiotic-resistant infections, and at least 23 000 die as a result.<sup>1</sup> In India, newborn infants develop bacterial infections that are resistant to most known antibiotics; such infections led to the deaths of 58 000 infants in 2013.<sup>2</sup> These problems seem distant to your typical NICU here in the United States. However, in this month's issue of *Pediatrics*, Schulman et al<sup>3</sup> demonstrate that there is fertile ground for the United States to also experience such a disaster.

Our understanding of the negative effects of antibiotic exposure is expanding. New techniques for studying the human microbiome, as well as traditional epidemiologic studies, raise concerns about the negative effects antibiotics may have by altering healthy bacterial colonization.<sup>4</sup> Connections have been made between antibiotic exposure and risk of necrotizing enterocolitis and nosocomial infection in neonates,<sup>5</sup> as well as an understanding that alterations in the gut microbiome may be linked to longer term outcomes such as childhood obesity.<sup>6</sup>

There is no doubt that infectious diseases remain a major cause of morbidity and mortality in neonates and that antibiotics are life-saving. Early-onset sepsis and nosocomial sepsis persist, despite the remarkable progress in prevention over the last decade.<sup>7</sup>

Antibiotics are the most-prescribed medications in neonatal intensive care.<sup>8</sup> These agents are begun

empirically based on risk factors such as maternal chorioamnionitis or nonspecific signs and symptoms of hospital-acquired infection.<sup>9</sup> Some antibiotics (particularly antifungal agents) may be used prophylactically.<sup>10</sup> Our ability to discern the need to initiate or terminate antibiotic use is limited. Results of blood cultures (the most definitive of diagnostic tests for sepsis) may be negative due to previous antibiotic exposure, low colony count sepsis, and difficulty obtaining an adequate volume of blood for culturing. In the absence of positive culture results, continuation of antibiotics is often based on concern regarding the consequences of inadequate treatment, a judgment call that can easily lead to varied opinions among qualified neonatologists.

In this complex environment of uncertainty, variation in antibiotic use among NICUs is not surprising. Schulman et al<sup>3</sup> have demonstrated that not only is variation present, but, in NICUs in California, there is a remarkable 40-fold variation in antibiotic use. This study represents the largest and most diverse examination of antibiotic use in neonatal intensive care, involving 127 NICUs, 52 601 infants, and almost three-quarters of a million patient-days. The median antibiotic exposure was close to one-quarter of all patient-days, with a range from 2.4% to 97%. At all levels of care, from intermediate to those units that provide the most critical care, antibiotic use was independent of proven infection, necrotizing enterocolitis, surgical volume, or mortality. These findings are similar to other reports in pediatric

intensive care.<sup>11</sup> In 40 children's hospitals, antibiotic days ranged from 36.8% to 60.1%, a variation that could not be explained by patient- or hospital-level factors associated with antibiotic treatment.

It is hard to know what actions could be taken to reduce this extreme variation. Clearly, most of the antibiotic use is empirical, initiated for suspected infection rather than proven infection. The threshold, both for initiating or continuing antibiotics for suspected infection, needs to be evaluated further. In well-appearing term infants who have negative blood culture results, antibiotics can be discontinued after 48 to 72 hours even when their mothers are treated for chorioamnionitis.<sup>12,13</sup> In 1 study, 24% of infants born to mothers with chorioamnionitis were treated with prolonged (>48-hour) antibiotics, but 84% of these infants received prolonged treatment based solely on abnormal data from laboratory tests, which are known to have poor specificity.<sup>14</sup>

We can potentially curtail unnecessary use of antibiotics through improved diagnostic and clinical approaches. New bacterial gene identification methods may enhance our use of standard blood cultures, particularly in excluding systemic infection.<sup>15</sup> More sophisticated approaches to identifying infants at risk for early-onset sepsis by using a Bayesian approach could decrease empirical antibiotic treatment in as many as one-quarter million newborns nationwide.<sup>16</sup> Use of prophylactic antimicrobial agents (eg, fluconazole for prevention of candida sepsis) should be carefully considered and not serve as a replacement for other

unit-based infection control strategies.

Given the huge variation in antibiotic use with little evidence of clinical benefit from liberal compared with conservative antibiotic use, this issue is ripe for major quality collaborative approaches. Sources of variation in the use of antibiotics need to be identified and understood, including unit culture and beliefs about infection, variation in thresholds for starting and stopping therapy and emphasizing the importance of using potentially harmful therapies only when there is clear benefit. There is great potential to substantially reduce both risk and cost for this vulnerable population through more judicious use of antibiotics.

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