Neonatal Antibiotic Use: How Much Is Too Much?

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Antimicrobial stewardship efforts benefit the individual and the community by improving patient-specific outcomes as well as decreasing the overall burden of antimicrobial resistance. Antibiotic stewardship can also save the health care system substantial amounts of money through decreased pharmacy costs, decreased inpatient use for antibiotic-resistant infections, and decreased frequency of antibiotic-associated adverse events.[1] In NICUs, infants are frequently exposed to antimicrobial medications as prophylaxis against infection, as empirical treatment of suspected infection, and as targeted treatment of confirmed infection. Most neonatal antibiotic treatment is for suspected rather than proven infection, and researchers in several studies suggest that antibiotics are overused in both term and preterm infants.[2–8] Evolving concern for unintended harm from neonatal antibiotic exposures has energized interest in the general principles of antimicrobial stewardship.[3,5,9–13] Stewardship recommendations and quality collaborative programs support the appropriate use of antimicrobial agents in the NICU.[14–17] Single centers report variably successful impacts of neonatal antibiotic stewardship interventions on the use of antibiotics for term infants who are at risk for early-onset infection, on the overall use of antibiotics across gestational ages, and on appropriate choice and duration of antibiotic therapy.[18–21] In recent analyses using large multicenter data sets, researchers find small but significant declines in overall neonatal antibiotic use and in extended use in the absence of confirmed infection among preterm infants.[5,22]

Where do neonatal clinicians go from here to affect comprehensive national antibiotic stewardship? To understand how much antibiotic use is too much, we need to know where we are and determine where we should aim to go. Schulman et al[23] helped inform where we were starting in a report using a cohort of 52 061 infants cared for in 127 NICUs across California in 2013. The researchers reported the antibiotic use rate (AUR), which was defined as the total number of patient days that infants were exposed to at least 1 parenteral antimicrobial medication per 100 patient days. Their findings provided a wake-up call to the neonatal community: overall antibiotic use varied 40-fold, with a median site-specific AUR of 24.5% and a range of 2.4% to 97.1% of patient days. Regardless of the NICU level of care, the AUR was unrelated to rates of proven infection, necrotizing enterocolitis (NEC), surgical volume, or mortality. These findings have been widely interpreted to represent practice variation beyond biological patient variation. In this issue of *Pediatrics*, Schulman et al[24] revisit the AUR in a cohort of 223 196 infants cared for in 137 California NICUs from 2013 to 2016. Compared with 2013, the AUR declined by 21.9% in 2016. Declines in AURs were more robust in centers that participated in recognized external antimicrobial stewardship programs than in those centers that did not (28.7% vs 16.2%), and lower-acuity centers had more variation than centers that provide

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Opinions expressed in these commentaries are those of the authors and not necessarily those of the American Academy of Pediatrics or its Committees.

DOI: https://doi.org/10.1542/peds.2018-1942

Accepted for publication Jun 28, 2018

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Dr Flannery was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development of the National Institutes of Health (award T32HD060550). Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: Dr Puopolo is a faculty member of the Vermont Oxford Network's

To cite: Flannery DD and Puopolo KM. Neonatal Antibiotic Use: How Much Is Too Much?. *Pediatrics*. 2018;142(3):e20181942

complex quaternary care. Certain themes persisted in this study. Center-specific AURs still varied substantially, although the AUR range narrowed to a range of 5.6% to 57% of patient-days by 2016. The AUR remained unrelated to rates of proven infection and NEC. In contrast to their previous findings, post hoc analyses of 2016 data revealed that a higher AUR was correlated with higher surgical volume and higher mortality rates among quaternary-care centers, driven primarily by 3 centers with the highest AURs. Finally, the authors observe that the cut-point for the lowest AUR quartile among complex-care centers was 14.4%. With no explanation for higher AURs, they suggest that this might be the place we should aim to go.

These high-level statewide data are an essential first step in informing practice and policy and should motivate providers and neonatal centers to critically evaluate their own practices. Given the size and diversity of the cohort, these data do provide a reasonable context for centers to understand where they are starting. However, a more nuanced understanding of the AUR will be required before we can determine where to aim to go.

One important limitation of this study is that it is not used to address whether the observed changes in the AUR were associated with any particular positive or negative outcomes among individual infants, individual care units, or even within the entire cohort beyond the relatively blunt measure of overall mortality. The persistently wide range of AURs and the differences between NICU levels of care suggest that it is unlikely that 1 size AUR will fit all. The AUR might be better informed by detailed data on the center-specific patient case-mix, admission rates, and duration of hospitalization. It may be fruitful for future researchers to report comparisons of culture-mandated versus nonmandated AURs, broad versus narrow-spectrum AURs, and disease- and gestational age–specific AURs. In particular, site-specific surgical case load should not be offered as an explanation for AURs but should be viewed as an opportunity to examine the complex reasons for surgery-associated antibiotic use.

Nonetheless, it is likely that this study reflects persistent clinician uncertainty regarding the optimal use of antimicrobial agents for infants in the NICU. Some infants need antibiotics. The treatment of culture-confirmed bloodstream infections is informed by professional standards. To arrive at an ideal AUR, neonatal providers will need to come together on issues that currently lack consensus. The authors state that, "…in our experience such blood culture–negative conditions [meningitis and pneumonia] are not likely to be important AUR drivers at most NICUs."[23] We would disagree. Provider discretion in treating sepsis for which the culture result was negative and uncertainties in interpreting cerebrospinal fluid values and in diagnosing ventilator-associated pneumonitis, urinary tract infection, and gastrointestinal conditions short of NEC as well as variation in the use of surgical antibiotic prophylaxis all contribute to the NICU AUR.[25–29]

Variation should inform a search for ideal care; it cannot define it. Like their previous work, this study by Schulman et al is a vital contribution that should not be used to define AUR targets but serves as a renewed call for continued progress in neonatal antibiotic stewardship.

ABBREVIATIONS

AUR: antibiotic use rate
NEC: necrotizing enterocolitis

Internet-Based Newborn Improvement Collaborative for Quality "Choosing Antibiotics Wisely"; and Dr Flannery has indicated he has no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2018-0115.

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