Neonatal Antibiotic Use: What Are We Doing and Where Shall We Go?

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Education Gap
To properly assess the scope of the problem of unnecessary antibiotic use and monitor the impact of such efforts, there is a need to consistently characterize antibiotic usage in NICUs and nurseries, as well as among centers.

Abstract
Antibiotic stewardship aims to ensure that clinicians administer the right antibiotics, to the right patients, for the right reasons. These principles are being widely applied in medical care, but have been particularly challenging in the NICU. Infectious risk factors and clinical instability are common among neonatal patients, and lead to significant cumulative antibiotic exposures in the NICU setting. Both the frequency with which antibiotics are administered and the potential unintended consequences of antibiotic administration differ between preterm and term infants. Multiple metrics are available to measure antibiotic use, yet no single measure is universally applied to neonatal stewardship.

Objectives After completing this article, readers should be able to:
1. Review current rates of neonatal antibiotic use among preterm and term infants.
2. Recognize the potential risks of antibiotic therapy in preterm and term infants.
3. Describe measures of antimicrobial stewardship and identify advantages and limitations of applying these to the neonatal population.

INTRODUCTION
Antibiotic therapy is a mainstay of neonatal care, and antibiotics are the most commonly prescribed class of medications in the NICU. (i)(2) Antibiotics have...
clear benefits for infants with suspected or confirmed infection, but appropriate narrow-range coverage and treatment durations remain an issue. (1) However, there is increasing evidence pointing to the risks of adverse outcomes of antibiotic exposure among infants without culture-confirmed infection. Measures to improve both prevention of infection and accuracy in diagnosing infection should result in decreased antibiotic use. To measure and ultimately optimize antibiotic use, there is a need to consistently characterize antibiotic use in NICUs and nurseries, as well as across centers. A thorough understanding of current antibiotic use and reliable tools for measuring use are first and critical steps to appropriately applying the principles of antimicrobial stewardship to the neonatal population.

**ANTIBIOTIC USE AMONG PRETERM INFANTS**

Preterm infants frequently receive empirical treatment with antibiotics soon after birth because of the risk of early-onset sepsis (EOS). Preterm labor and/or premature rupture of membranes result from maternal infection in about a third of cases, (4)(5) and 1 in 90 very low-birthweight infants (VLBW; birthweight <1,500 g) is diagnosed with culture-confirmed EOS. (6) The infection-attributable mortality among VLBW infants with EOS is ~35%, and ranges as high as 50% for infants at the lowest gestational ages (22–24 weeks). (7) Given the relatively high prior probability of EOS and the staggering risk of mortality, combined with the clinical instability inherent among preterm infants at birth, (8) it is no surprise that the rates of empirical early antibiotic therapy among preterm infants are quite high.

Neonatal clinicians also frequently extend antibiotic therapy despite sterile cultures for various reasons. Clinicians express concern that maternal intrapartum antibiotics, inadequately blood volumes for neonatal culture, and/or neonatal antibiotics administered before blood culture may all result in false-negative findings. Perhaps most important, clinicians are reluctant to stop antibiotic therapy when preterm infants remain critically ill. In a study of 790 extremely low-birthweight (ELBW; birthweight <1,000 g) infants born in 2000, 94% received early empirical antibiotics and 59% received more than 3 days of therapy despite negative blood culture findings. (9) In a larger study including approximately 4,000 ELBW infants born in Neonatal Research Network (NRN) sites from 1998 to 2001, 96% received early empirical antibiotics and 53% received more than 4 days of therapy despite negative cultures. (10) Kuppala et al found that in VLBW infants without sepsis or necrotizing enterocolitis (NEC) who survived past day 7, 36% (130/365) received prolonged initial empirical antibiotics for 5 days or more. (11) A study from the Canadian Neonatal Network reported that of 8,414 VLBW infants without infection-related morbidities, 4,607 (55%) received antibiotics for 4 or more days in the first week of age. (12)

We recently examined early antibiotic use among preterm infants over time and across both academic and community hospitals in the United States. (13) Of 40,364 VLBW infants, including 12,947 ELBW infants, the majority received antibiotics in the first 3 days after birth (79% of VLBW; 87% of ELBW) and no differences in antibiotic initiation were observed over time from 2009 to 2015. Rates of VLBW infants receiving more than 5 days of early antibiotics decreased slightly over time, but did not change among ELBW infants, with significant variation in practice observed across centers. Overall, rates of antibiotic treatment in preterm infants in the first days after birth are an order of magnitude higher than the actual incidence of culture-confirmed early infection, and little change has been observed over time. (6)(14)(15)

Current guidance on antibiotic use for preterm infants is to use antibiotics in all newborns with critical illness. (16) Recent studies suggest that EOS risk assessment strategies for preterm infants could be based on delivery characteristics and/or placental pathologic findings that correlate with culture-confirmed infection. (17)(18) Currently, no well-developed EOS risk assessment tools are available for VLBW infants as exist for term newborns. (19)(20)

Most studies of antibiotic use in preterm infants have focused on the first days after birth; there are fewer data regarding antibiotic use in preterm infants during the entire hospitalization because these infants are often grouped together with term infants in analyses of overall unit-specific antibiotic use. A 1998 to 2000 multicenter study from the United States reported that 56% of VLBW infants (3,459/6,215) received at least 1 antibiotic course after postnatal day 3. (21) Among 13,738 infants cared for in Canadian centers from 2010 to 2014, 11,669 (85%) received antibiotics at any point during hospitalization. This study did find a decline in antibiotic use over the entire NICU hospitalization: the overall annual antibiotic use rates (AURs), defined as number of days an infant was exposed to 1 or more antibiotics divided by the total length of stay, declined from 0.29 in 2010 to 0.25 in 2014. (12)

**ANTIBIOTIC USE AMONG TERM INFANTS**

Rates of antibiotic exposure for suspected EOS among term newborns vary by center. (22)(23) Although center variation could be related to differences in obstetric practice or in rates of maternal intrauterine infection, the primary
factor identified in a recent national survey of newborn practice is variation driven by evolving methods of EOS risk assessment. (22) Measurement of AURs among term infants may also be complicated by the fact that there is center-specific variation in how such infants receive care. For example, well-appearing newborns receiving antibiotic therapy in the NICU will be counted in NICU-specific AURs, while similar infants receiving these therapies in a nursery setting, or while rooming-in with the mother, will be missed.

As many as 400,000 uninfected newborns are administered empiric antibiotic therapy at birth for the risk of EOS every year in the United States. (19)(24) In a population-based study by Escobar et al, 15.2% (2,785 of 18,299) of infants with birthweights greater than or equal to 2,000 g were evaluated for EOS, and of these, 31% were treated with systemic antibiotics. (25) Another center using a local algorithm based on Centers for Disease Control and Prevention (CDC) 2002 guidelines found that 15% of well-appearing newborns of 35 weeks’ gestation or greater were evaluated for EOS. (26) After adjusting policies based on updated CDC 2010 guidelines, the same center found that 6.8% of all well-appearing infants born at more than or equal to 36 weeks’ gestation were evaluated for EOS and 5.2% were treated with empiric antibiotic therapy, while only 0.04% of the study cohort had culture-confirmed EOS. (26) Multivariable risk models may significantly decrease the number of EOS evaluations in term and late preterm newborns and decrease empiric antibiotic exposure in this population. (19) (20)(27) Prospective studies using a neonatal sepsis risk calculator based on these models demonstrated 40% to 50% decreases in empiric antibiotic administration to term and late preterm infants compared with prior practices, and found no safety concerns. (28)(29) Only 2.6% of all infants born at more than or equal to 35 weeks’ gestation in the perinatal centers of the Kaiser-Permanente Northern California healthcare system received empiric antibiotic treatment with the use of the sepsis risk calculator combined with locally derived care algorithms. (28)

Recommendations regarding duration of antibiotic therapy for suspected EOS also continue to evolve. (30)(31) Kiser et al reported in 2014 that at their institution, based on American Academy of Pediatrics (AAP) practice guidelines at the time, 24.2% of term and late preterm infants at risk for EOS due to maternal chorioamnionitis received antibiotics for more than or equal to 7 days. (32) The vast majority of these infants were treated with prolonged antibiotics because of abnormal laboratory values alone. Later revisions to the AAP guidelines recommend against treating asymptomatic infants with sterile cultures born to mothers treated for chorioamnionitis longer than 48 to 72 hours. (33)

There are fewer data on AURs specifically for term infants after the EOS period. In a 2005 national point prevalence study of 29 American centers, 43% of NICU patients were receiving antimicrobial therapy on the date of the survey. (1) In a 2013 study of 127 NICUs across California, which included both term and preterm infants, a 40-fold variation in overall AURs was reported, and this variation was independent of burden of infection. (34)

**RISKS OF ANTIBIOTIC THERAPY FOR PRETERM INFANTS**

Multiple studies suggest that antibiotics have potential risks for preterm infants without culture-confirmed infection. Broad-spectrum antibiotic exposures, particularly cephalosporin use, have been identified as problematic. Cephalosporin use is associated with increased incidence of invasive fungal infections in preterm infants. (35)(36) with an attributable mortality of 13%. (37) In a multicenter study that included 128,914 newborns of all gestational ages, empiric early treatment with a combination of ampicillin and cefotaxime, compared with ampicillin and gentamicin, was associated with higher mortality rates. (38)

Perinatal and postnatal antibiotic exposures are also associated with subsequent colonization with resistant bacterial organisms and later infection. (39)(40)(41)(42)(43) Most studies conducted in preterm infants have focused on the potential link between overall antibiotic exposures and later morbidities and mortality. One study of 5,693 ELBW infants cared for in 19 NRN centers found an association between prolonged initial antibiotic therapy (defined as antibiotics initiated at <3 days of age and continued for ≥5 days) and subsequent risk of NEC or death. (10) Prolonged initial empiric antibiotic use in VLBW infants cared for at 3 sites in Cincinnati, OH, was associated with the combination of late-onset sepsis, NEC, or death. (11) In a single-center study of 1,140 VLBW infants, each additional day of antibiotic exposure in the first 14 days of age was associated with increased risk of death or bronchopulmonary dysplasia (BPD), as well as increasing severity of BPD. (44) The relationship between early antibiotic exposure and development of NEC or BPD has been reported in other settings (39)(43) and may have biologic plausibility in a link between antibiotic exposure and subsequent gastrointestinal and airway microbiome dysbiosis. (43)(46) The Canadian multicenter study of VLBW infants without culture-confirmed infection or NEC found an association between infants in the highest AUR quartile and a composite outcome of mortality or “major morbidity” including persistent echogenicity or echolucency on neuroimaging, stage 3 or higher retinopathy of prematurity, or BPD. (12)
The association between the higher AURs and the composite outcome in this study was largely driven by the substantial increase in mortality among these infants. The primary limitation in all of these studies is confounding by indication: sicker infants are more likely to receive antibiotics than infants who are less sick, though each study included statistical adjustment for factors associated with severity of illness. The consistent association of poorer outcomes with empiric antibiotic exposure across studies of various designs and study cohorts suggests that prospective studies of antibiotic administration in the absence of culture-confirmed infection may be justified.

RISKS OF ANTIBIOTIC THERAPY FOR TERM INFANTS

In many centers, term infants are admitted to the NICU when empiric antibiotic therapy is indicated. For well-appearing asymptomatic infants, there is a potential negative impact of maternal/infant separation on initiation and exclusivity of breastfeeding. (50)(47) In the NICU, newborns are also at increased risk of exposure to multidrug-resistant organisms and nosocomial infection. (48) These risks may be mitigated if infants requiring intravenous antibiotics can receive the therapy in the mother’s postpartum care setting. (49)

Early antibiotic exposure may initiate dysbiosis even among otherwise healthy term infants. There is evidence that early life antibiotics alter gut and airway microbiota. (46)(50)(51) The widespread use of antibiotics during the peripartum (eg, intrapartum and immediate neonatal) period and the demonstration that such exposures alter the initial composition of the newborn gut microbial composition raises the possibility that intrapartum preventive therapies may have later health consequences. (52) These concerns are supported by studies of early infancy and childhood antibiotic exposures. Canadian infants receiving antibiotics in the first year of age were more likely to be overweight in childhood. (53) In a Finnish population based-cohort, antibiotic exposure before 6 months of age or repeatedly during infancy was associated with increased body mass in early childhood, with a distinct relationship between broad-spectrum antibiotic exposure and subsequent increased body mass. (54)

Studies also suggest a relationship between early antibiotic exposure and subsequent development of asthma. (55)(56)(57) Asthma is the most common childhood chronic illness, with increasing prevalence over the last 4 decades. (58) Using a longitudinal birth cohort of infants in British Columbia born between 1997 and 2003, investigators found that use of antibiotics in the first year of age was associated with increased risk of developing asthma and that the risk increased as the number of antibiotic prescriptions increased. (58) A systematic review of multiple studies addressing antibiotics administered in infancy and risk of childhood asthma found a pooled odds ratio of 1.52 (95% confidence interval [CI], 1.30–1.77). (55) Multiple confounding factors may influence the relationships between early antibiotic exposure and subsequent obesity, asthma, or allergic disease. Prospective studies of maternal, preterm, and term infant antibiotic exposures and the impact on childhood outcomes are ongoing and will better inform the true risks and benefits of empiric antibiotic use in the perinatal and early life period. (59)

NEONATAL ANTIMICROBIAL STEWARDSHIP

In 2002, the CDC proposed 12 steps to prevent antimicrobial resistance, based on 4 key strategies: preventing infection, diagnosing and treating infection effectively, using antimicrobial agents wisely, and preventing transmission of drug-resistant pathogens. (60) The antimicrobial stewardship elements of this campaign are relevant to NICU settings, yet are infrequently applied. (61) The Table summarizes the core elements of antibiotic stewardship recommended by the CDC and applicable to NICU settings. Antimicrobial stewardship efforts and national quality improvement initiatives have started to focus on neonatal settings, but there is continued uncertainty among neonatal clinicians about the optimal application of antimicrobial stewardship principles. (62)(63)(64)

Longitudinal accounting of antimicrobial use is a particularly important part of stewardship. To assess antimicrobial use in NICUs and nurseries and track change over time, there is a need to consistently characterize antibiotic use in these units and among certain populations. A detailed understanding of how antibiotics are used among specific categories of newborns may help optimize stewardship efforts. Currently, there are no uniformly accepted metrics of neonatal antimicrobial usage. For instance, some studies report proportions of infants who are started on antibiotics soon after birth, some report number of antibiotic courses during hospitalization, and others simply report proportions of infants in the NICU receiving antibiotics at a given point in time. Prolonged duration of empiric antibiotic treatment after a blood culture specimen is obtained may be defined as beyond 48 hours, 72 hours, 5 days, or even 7 days in different studies. Some studies report any exposure to any antimicrobial drug and some delineate by specific drug, class, or combination.
Measures and metrics to study the impact of antimicrobial stewardship programs have been reported for other populations. (64) The most commonly used measures evaluate drug consumption. Among studies conducted in adult patients, a widely accepted measure is “defined daily dose,” which is the amount of drug that a typical patient might receive on any day for therapeutic purposes. This measure is impractical in pediatric and neonatal populations because of the weight-based dosing required in these patients. Another method commonly used in antimicrobial stewardship research is to evaluate drug consumption by days of therapy (DOT). DOT is defined as overall days of antimicrobial therapy, usually reported per 1,000 patient days. DOT accounts for multiple drugs, for example, an infant receiving 2 antibiotics for 7 days contributes 14 DOTs. This measure may indirectly incentivize providers to use broad-spectrum monotherapy (ie, an infant receiving 1 broad-spectrum antibiotic for 7 days only contributes 7

### TABLE. Interventions to Improve Neonatal Antibiotic Use

<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>DESCRIPTION</th>
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<tbody>
<tr>
<td><strong>Broad interventions</strong></td>
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<tr>
<td>Antibiotic “time outs”</td>
<td>Review of antibiotics 48 hours after initiation to actively determine extension or discontinuation</td>
</tr>
<tr>
<td>Prior authorization</td>
<td>Restricted use of certain antibiotics based on spectrum of activity, cost, or toxicities</td>
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<tr>
<td>Prospective audit and feedback</td>
<td>External review of antibiotic appropriateness by an expert in antibiotic use</td>
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<tr>
<td>Facility-specific treatment</td>
<td>Development and implementation guidelines based on site-specific patient characteristics and local antimicrobial susceptibility data</td>
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<tr>
<td>recommendations</td>
<td></td>
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<tr>
<td><strong>Pharmacy-driven interventions</strong></td>
<td></td>
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<tr>
<td>Dose adjustments and</td>
<td>Guidance based on gestational and/or postnatal age, organ dysfunction, therapeutic drug monitoring, resistance profile, etc</td>
</tr>
<tr>
<td>optimization</td>
<td></td>
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<tr>
<td>Automatic alerts</td>
<td>Reminders often embedded in electronic order entry systems</td>
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<tr>
<td></td>
<td>For example, alerts may flag unnecessarily duplicative therapy, drug-drug interactions; or warnings based on patient characteristics (eg, renal or liver dysfunction)</td>
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<tr>
<td>Time-sensitive automatic stop</td>
<td>Stop orders useful for specified antibiotic prescriptions and indications, especially antibiotics administered for surgical prophylaxis</td>
</tr>
<tr>
<td>orders</td>
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<tr>
<td><strong>Tracking and reporting antibiotic use and outcomes</strong></td>
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<tr>
<td>Antibiotic use measures</td>
<td></td>
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<tr>
<td>Defined daily dose</td>
<td>Estimation of antibiotic use in hospitals by aggregating the total number of grams of each antibiotic purchased, dispensed, or administered during a period of interest divided by the World Health Organization–assigned daily defined dose; not appropriate for neonatal settings</td>
</tr>
<tr>
<td>Days of therapy</td>
<td>Aggregate sum of days for which an antibiotic is given to a patient (numerator) divided by a standardized denominator (eg, patient days)</td>
</tr>
<tr>
<td>Antibiotic use rate</td>
<td>Number of days an infant was exposed to 1 or more antibiotics divided by the total length of stay</td>
</tr>
<tr>
<td>Variation in use</td>
<td>Comparison between institutions combined with information on infection burden and case mix</td>
</tr>
<tr>
<td><strong>Outcome measures</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical outcomes</td>
<td>Specifically, outcomes that measure the impact of interventions to improve antibiotic use (eg, duration of bacteremia, metastatic complications of infection, mortality)</td>
</tr>
<tr>
<td>Antibiotic resistance</td>
<td>Systematic accounting and display of local antimicrobial resistance data for both colonizing and infecting pathogens</td>
</tr>
<tr>
<td>Annual drug cost savings</td>
<td>Comparison of pre- and post-implementation costs of stewardship programs and/or interventions</td>
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</table>

One limitation of this metric is that it is in-centrally been used as a metric of antibiotic use in the NICU. Agents divided by the total length of hospital stay, have recently been used as a metric of antibiotic use in NICUs. Variation as a measure of antibiotic use in NICUs may be helpful, particularly when information on infection burden and case mix are available. Variation in the absence of infection among centers with similar morbidity and mortality profiles suggests that some proportion of antibiotic use may be unnecessary and may be used to identify target interventions for potentially modifiable prescribing behaviors. In addition, general AUR studies do not discriminate between narrow- and broad-spectrum antibiotics. Variation as a measure of antibiotic use in NICUs may be helpful, particularly when information on infection burden and case mix are available. Variation in the absence of infection among centers with similar morbidity and mortality profiles suggests that some proportion of antibiotic use may be unnecessary and may be used to identify target interventions for potentially modifiable prescribing behaviors.

An important component of neonatal antimicrobial stewardship is to report the incidence of antimicrobial resistance among colonizing and infecting pathogens. A common approach involves reporting rates of specific resistant organisms such as methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus. A broader approach involves reporting and communicating antimicrobial-sensitivity data to inform stewardship interventions. Finally, clinical outcomes including rates of early-onset and late-onset infection as well as short-term infection-related morbidity and mortality must be considered in designing and assessing the impact of local antimicrobial stewardship interventions.

CONCLUSIONS

- Antimicrobial stewardship efforts have started to focus on neonatal settings.
- Multiple recent studies suggest that antibiotics have potential risks as well as benefits for both term and preterm newborn infants.
- To properly design and monitor neonatal antimicrobial stewardship efforts, there is a need to consistently characterize antibiotic use in NICUs and nurseries, as well as across centers.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know how infectious agents are transmitted to the neonate.

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1. Early-onset sepsis (EOS) is a common concern for preterm infants because preterm labor and/or premature rupture of membranes results from maternal infection in about a third of cases. What is the proportion of very low-birthweight (VLBW) infants who are diagnosed with culture-confirmed EOS?
   
   A. 1 in 20.
   B. 1 in 50.
   C. 1 in 90.
   D. 1 in 120.
   E. 1 in 200.

2. The rates of antibiotic exposure for suspected EOS among term and late preterm newborn infants vary by center. The use of multivariate risk models such as a neonatal sepsis risk calculator has been shown to decrease empiric antibiotic exposure in this population. In prospective studies using the neonatal sepsis risk calculator, rates of empirical antibiotic administration decreased by:

   A. 10%–20%.
   B. 20%–30%.
   C. 30%–40%.
   D. 40%–50%.
   E. 50%–60%.

3. Multiple studies suggest that antibiotics have potential risks for preterm infants without culture-confirmed infection. The use of cephalosporin, in particular, has been identified as problematic. Of the following, what risk is specifically associated with cephalosporin use?

   A. Increased risk of subsequent necrotizing enterocolitis.
   B. Increased risk of death or bronchopulmonary dysplasia.
   C. Increased risk of asthma.
   D. Increased incidence of invasive fungal infections.
   E. Increased risk of stage 3 or higher retinopathy of prematurity.

4. Antimicrobial stewardship is a critical element in preventing antimicrobial resistance. One of the metrics used to study the impact of antimicrobial stewardship programs is the drug consumption by days of therapy (DOT). DOT is defined as:

   A. The overall days of antimicrobial therapy per 1,000 patient days.
   B. The number of days an infant was exposed to 1 or more antimicrobial agents divided by the total length of hospital stay.
   C. The sum of days for which any amount of a specific antimicrobial agent is administered per 1,000 days present.
   D. The number of days an infant was exposed to a specific antimicrobial agent divided by the length of stay.
   E. The overall days of antimicrobial therapy per length of stay.

5. Measures and metrics are important considerations when studying the impact of antimicrobial stewardship programs. Metrics traditionally used in adult populations do not always apply to neonatal populations. Annual antibiotic use rates (AURs) have recently been used as a metric of antibiotic use in the NICU. Which of the following statements is correct regarding the limitations of AURs?
A. This measure may indirectly incentivize providers to use broad-spectrum monotherapy.
B. This measure is impractical in neonatal populations because of the weight-based dosing required in these patients.
C. This metric is influenced by mortality rate, because shorter time to death will result in a lower AUR.
D. This metric discriminates between narrow- and broad-spectrum antibiotics.
E. Optimal AURs are not well defined in NICU populations.