Antibiotic Stewardship

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Introduction

Neonates, especially those who are premature or have congenital malformations, are at increased risk for serious bacterial infections. It is therefore unsurprising that antibiotics are the most-prescribed medications within neonatal intensive care units. Appropriate antibiotic use for proven infection can be lifesaving. However, their inappropriate or excessive use must be guarded against. Mounting evidence has associated exposure to antibiotics with numerous adverse outcomes (Box 1) [1–10]. Therefore, clinicians must balance the benefits of antibiotics against short-term and long-term risk of their use. This balance can be achieved through an antibiotic stewardship program (ASP) [11]. The goal of this chapter is to demonstrate how providers can optimize antibiotic use while minimizing toxicity and adverse effects.

Box 1 Adverse Outcomes Associated with Antibiotic Use in Early Infancy

Early	*Candida* colonization and invasive candidiasis
	Multidrug-resistant organism colonization
	Late-onset sepsis
	Necrotizing enterocolitis
	Bronchopulmonary dysplasia
	Mortality
Late	Asthma
	Eczema
	Obesity

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Establishing an Antibiotic Stewardship Program

Personnel. Antibiotic stewardship programs (ASPs) should be multidisciplinary. Most ASPs involve at a minimum an infectious disease specialist or a clinical pharmacist whose sole or primary role is to oversee the ASP. However, remote monitoring by ASP personnel is not nearly as effective as when nursery personnel are invested stakeholders. Evidence suggests that neonatologists are more receptive to feedback if it originates from another nursery provider than from infectious diseases or pharmacy [12, 13]. In addition, nursery stakeholders can guide the ASP as to which interventions are likely to meet with the most buy-in from other nursery providers.

Strategies. There are several approaches that ASPs can use in the nursery setting, including audit and feedback, prior authorization, and guidelines.

- *Audit and feedback*. Prospective audit of antibiotic prescribing combined with timely feedback to individual providers, the nursery as a whole, or both, is a staple of antimicrobial stewardship. Prospective audit may be comprehensive, evaluating every dose of every antibiotic administered in the nursery, or it may be restricted to certain antimicrobials such as those that are broad spectrum or those that are most commonly used [14, 15]. Audit and feedback has several advantages. First, it is the most "passive" of the three core strategies and may be viewed more favorably by providers as a result. Secondly, prospective audit allows ASP providers and the nursery stakeholders to identify emerging patterns in real time. Finally, when audit and feedback has been compared head-to-head with prior authorization, audit and feedback has consistently been shown to be more effective [16–18].
- *Prior authorization*. Prior authorization refers to specific antimicrobials that can only be used after being "authorized" by a member of the ASP. Alternatively, a given agent could be used empirically for 24 or 48 h, but then would be stopped unless authorization to continue is given. Use of a given antimicrobial usually drops quickly once it is placed under prior authorization. However, prior authorization has also been associated with provider push-back, increased use of unrestricted antimicrobials, and delays in therapy [19]. The use of antibiotic "time-outs," where antibiotics may be started but then are reviewed at a certain point (usually the 48-h mark), is an equally effective and better-tolerated approach compared with prior authorization [20].
- *Guidelines*. Guidelines for common infections can improve both diagnostic and antimicrobial stewardship by minimizing the number of unnecessary evaluations and optimizing the diagnosis and treatment of suspected infections. In the NICU setting, protocols for early-onset sepsis, late-onset sepsis, and necrotizing enterocolitis may be beneficial. Suspected sepsis accounts for the majority of antibiotic use in the NICU. Chapters "Early-Onset Sepsis," "Late-Onset Sepsis," and "Necrotizing Enterocolitis" highlight suggested approaches to early- and late-onset sepsis and necrotizing enterocolitis, respectively.

Metrics. Another issue is how to report antibiotic usage in the nursery setting. A commonly used term for ASPs is days of therapy per 1000 patient-days [21]. This metric counts each day (or partial day) of a given antibiotic separately. For example, 2 days of ampicillin and gentamicin therapy would count as 4 days of therapy—2 days of ampicillin and 2 days of gentamicin. This is in contrast to "length of therapy," which refers to the number of calendar days that an infant receives antimicrobial therapy and is more consistent with how providers speak. When using length of therapy, 2 days of ampicillin and gentamicin therapy is 2 days. Although days of therapy is preferred by ASPs, and length of therapy is used by providers, the optimal metric has not been identified and both have weaknesses [22]. For example, providers can decrease their nursery's days of therapy by changing all infants from ampicillin and gentamicin to meropenem—significantly broadening coverage but reducing the days of therapy to 2 to 1.

Diagnostic Stewardship

Proper approach to the diagnosis of infection can ensure that antibiotics are used properly. This includes obtaining proper microbiologic studies when infection is suspected, interpreting the results correctly, and using ancillary tests properly to help guide cessation of antimicrobial use.

Cultures. The vast majority of antibiotic use within the NICU comes from the empiric or directed treatment of sepsis. Bacterial blood cultures remain the gold standard for diagnosing neonatal sepsis and are extremely sensitive when obtained properly. Studies have shown that septic neonates tend to have high bacterial concentrations in their bloodstreams, with a median value of 500 colony-forming units/mL [23]. Inoculation of 1 mL of blood is able to recover bacteria at concentrations as low as 4 colony-forming units/mL [24]. Sensitivity is lower at extremely low bacterial concentrations (<4 colony-forming units/mL), but the clinical significance of such low-level bacteremia is unknown. The recommendation is that a minimum of 1 mL of blood be obtained for culture when sepsis is suspected; unfortunately, collected volumes are frequently <1 mL [25, 26]. This issue could be improved with simple education of the providers obtaining the cultures.

Another major stewardship challenge is that clinicians may not trust sterile blood cultures. Reasons for this are multifactorial and include concern for improperly drawn specimens, institutional practices and habits, suspicion that intrapartum antibiotic prophylaxis may have "masked" a positive culture, and continued signs consistent with sepsis in an infant with sterile cultures. Whatever the reason, these behaviors may lead to treatment of "culture-negative" sepsis, often for prolonged periods [27]. The median course of therapy for culture-negative sepsis is 7–10 days. ASPs should evaluate the frequency of "culture-negative" sepsis courses and focus on timely discontinuation of antibiotics. This includes ensuring that appropriate blood cultures are drawn and then educating providers to trust those results [28].

Finally, cultures of non-sterile sites (e.g., trachea, skin, mucous membranes, etc.) must be interpreted cautiously. The infant's clinical state, imaging studies if

applicable, and culture results should be interpreted together to determine whether a positive culture represents infection or asymptomatic colonization.

Ancillary tests. A variety of ancillary blood tests have been evaluated against the gold standard of cultures to determine their sensitivity and specificity for detection of sepsis in infants. These biomarkers include complete blood cell counts with differential, C-reactive protein, procalcitonin, presepsin, interleukin-6, and more [29]. Although the particulars of the frequency, intervals, and cutoff values have varied between studies, the overall pattern is quite clear. The positive predictive value of these tests is generally poor. A variety of clinical scenarios can make these biomarkers abnormal even when cultures are sterile, including chorioamnionitis, perinatal asphyxia, preeclampsia, and even delivery itself [30, 31]. However, their negative predictive value is generally good, approaching 99% for serial neutrophil values. Therefore—if used at all—these studies are best used for their negative predictive value. Clinicians who are anxious about stopping antibiotic therapy in an infant with sterile blood cultures but continued signs of illness (e.g., hypotension, respiratory failure) may be reassured if biomarkers are also normal. However, it cannot be overstated that cultures are the gold standard, and properly obtained, sterile blood cultures should be trusted on their own merits. Additionally, these biomarkers do not have sufficient specificity or sensitivity to preclude the need for cultures or empiric antibiotic therapy.

Risk prediction models. Risk prediction models, also known as sepsis calculators, show tremendous promise in helping guide initiation of antibiotic therapy for early-onset sepsis. The best-studied model to date is the Kaiser sepsis calculator (available at https://neonatalsepsiscalculator.kaiserpermanente.org). This calculator uses the local epidemiology of early-onset sepsis, gestational age, maternal temperature, duration of rupture of membranes, and maternal group B streptococcal colonization status in combination with the infant's clinical appearance to recommend observation or cultures ± empiric antibiotic therapy. Large cohort studies have demonstrated that the use of these prediction models can safely reduce sepsis evaluations and empiric antibiotic use by 30–50% [32, 33]. However, these models have not yet been validated in more preterm infants.

Antimicrobial Stewardship

Once properly obtained cultures are obtained, antibiotics should be initiated, modified, and discontinued based on the results of those cultures and the infant's clinical status. Detailed recommendations for early-onset and late-onset sepsis, focal infections, and necrotizing enterocolitis are given in chapters "Early-Onset Sepsis," "Late-Onset Sepsis," and "Necrotizing Enterocolitis," respectively. However, antimicrobial selection should be tailored to a given center's antibiogram, which is available through the hospital microbiology lab and will inform nursery providers about rates of resistance seen locally.

Empiric selection. Empiric antibiotics provide adequate coverage for the likely pathogens while cultures are pending (Table 1).

Table 1 General empiric and definitive therapy guidelines for infants with suspected infection

Condition	Empiric therapy	Alternatives	Duration
Suspected infection			
Early-onset sepsis	Ampicillin and gentamicin		36–48 h pending culture results
Late-onset sepsis	Oxacillin and gentamicin	Vancomycin and gentamicin	
Meningitis	Cefotaxime and vancomycin		48 h pending culture results
Proven infection			
Necrotizing enterocolitis	Piperacillin/tazobactam	Ampicillin, gentamicin, and metronidazole	7–14 days depending on Bell's staging
Gram-positive	GBS—ampicillin CoNS—vancomycin MSSA—oxacillin MRSA—vancomycin *Enterococcus*—ampicillin		7–10 days for uncomplicated sepsis 10–14 days for meningitis
Gram-negative	Varies		10–14 days for uncomplicated sepsis 14–21 days for meningitis

CoNS coagulase-negative staphylococci, *GBS* group B streptococci, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-susceptible *Staphylococcus aureus*

Early-onset sepsis. Common pathogens include group B streptococci and gram-negative *Enterobacteriaceae* such as *Escherichia coli*. Ampicillin and gentamicin are widely used and cover virtually all commonly encountered pathogens. However, if the proportion of gentamicin-resistant *E. coli* is high (>10–15%), an alternative aminoglycoside should be considered.

Late-onset sepsis. The range of pathogens capable of causing late-onset sepsis is broad, making it difficult to cover all the possibilities. In general, coagulase-negative staphylococci, *S. aureus*, and gram-negatives (primarily the *Enterobacteriaceae*) account for the majority of cases. A semisynthetic penicillin such as oxacillin, in combination with gentamicin or another aminoglycoside, is appropriate in most cases. For infants who are colonized with methicillin-resistant *S. aureus* (MRSA), or for NICUs who do not perform prospective surveillance for MRSA, vancomycin may be necessary in lieu of oxacillin. However, vancomycin reduction strategies have been shown to be safe and effective (see chapter "Late-Onset Sepsis") [34].

Necrotizing enterocolitis. Pathogens responsible for necrotizing enterocolitis include aerobic and anaerobic gram-negatives as well as the anaerobic gram-positives found in the infant gut. These organisms can be empirically covered with piperacillin/tazobactam monotherapy. Alternatively, ampicillin, gentamicin, and metronidazole can be given in combination, but this achieves the same general coverage as piperacillin/tazobactam at the expense of more line entry for dosing and more nephrotoxicity due to the inclusion of an aminoglycoside.

Definitive therapy. Once empiric therapy has been started, the selection and duration of therapy depend on culture results and the infant's clinical status. If sepsis is suspected but cultures are sterile, antibiotics should be stopped promptly within 48 h; 36 h may be sufficient for early-onset sepsis [35]. Positive cultures should be treated with definitive therapy that is the narrowest possible regimen that reaches the infected compartment (e.g., blood, urine, cerebrospinal fluid) and treats the responsible organism(s). General guidelines are shown in Table 1 but will vary depending on the clinical circumstances and the infant's response to therapy.

Reporting

Effective ASP programs use the strategies listed in 27.2 to improve antibiotic use. However, effective stewardship requires ongoing communication and reporting of data between the nursery and the ASP. This reporting serves as feedback and education and can also help to identify new or emerging areas that need to be addressed. Antibiotic stewardship can feel a little bit like Sisyphus rolling the boulder up the hill over and over again. However, antibiotic stewardship efforts are viewed favorably by nursery providers and ultimately can be remarkably effective in reducing unnecessary or unwarranted antibiotic exposure in vulnerable infants [12, 15].

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