Educational Gaps

1. The best approach within the neonatal intensive care unit (NICU) for using antimicrobial stewardship activities in a measurable way is still being studied.

2. Best practice of antimicrobial use is challenging in a population in which definitive infectious pathology is not always readily apparent.

Abstract

The neonatal intensive care unit (NICU) presents a unique challenge within hospitals. A neonate’s response to an infectious insult is challenging to differentiate from other pathologic processes, thereby making antimicrobial management more difficult. Antimicrobial stewardship programming has sought to combat this difficulty, relying on its core principles of appropriate antimicrobial selection, dose, duration, and route of administration. Increasing evidence suggests that imprudent and prolonged use of antimicrobials can lead to various undesirable health outcomes for neonates, including necrotizing enterocolitis, disseminated fungal infection, and even death. The need for empiric antimicrobial use is unavoidable, but there are ways in which concomitant antimicrobial stewardship and infection prevention efforts can allow for optimal clinical outcomes. Pharmacy-driven stewardship efforts of optimal neonatal dosing and therapeutic drug-level management of patients in our institution’s NICU serve as examples of NICU-specific stewardship initiatives. These types of stewardship efforts function as part of a larger effort to create a culture of conscientious and judicious antimicrobial use within our NICU.

Objectives

After completing this article, readers should be able to:

1. Provide definitions for antimicrobial stewardship as it applies to the neonatal intensive care unit (NICU).
2. Discuss the pitfalls of antimicrobial use in the NICU and the implications of misuse/overuse.
3. Highlight ways antimicrobial use is most effective in neonates.
4. Highlight infection prevention within the NICU as a key stewardship activity.

Introduction

The neonatal intensive care unit (NICU) is a distinctive place in any hospital due to the variability and fragility of its patients. Neonates have a limited repertoire of signs and symptoms to manifest in response to disease entities such as sepsis, congenital heart disease, and intra-abdominal pathology. It can be challenging for clinicians to determine which infants warrant empiric antimicrobial therapy for possible infection and which may benefit from an echocardiogram.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ASP</td>
<td>antimicrobial stewardship program</td>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<td>CLABSI</td>
<td>central line–associated bloodstream infection</td>
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<td>CVC</td>
<td>central venous catheter</td>
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<td>ELBW</td>
<td>extremely low birthweight</td>
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<td>EOS</td>
<td>early-onset sepsis</td>
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<td>IDSA</td>
<td>Infectious Diseases Society of America</td>
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<td>LOS</td>
<td>late-onset sepsis</td>
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<td>MRSA</td>
<td>methicillin-resistant Staphylococcus aureus</td>
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<td>NEC</td>
<td>necrotizing enterocolitis</td>
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<td>PICC</td>
<td>peripherally inserted central catheter</td>
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<td>VLBW</td>
<td>very low birthweight</td>
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to evaluate for cardiac pathology. This overlap between the presentation of infectious and noninfectious illnesses creates difficulty when developing clinical management algorithms, including selection and duration of antimicrobial therapy.

Antimicrobial stewardship programs (ASPs) are designed to confront this challenge in all areas of the hospital, and increasingly in the outpatient setting. Tailoring programming in the NICU requires significant consideration of the special needs of the neonatal population. The pharmacokinetic and pharmacodynamic parameters of neonates have substantial interindividual and intra-individual variability based on gestational age, day of life, weight, total body water, and skin and renal maturity, as well as the variability of their clinical presentations. In a health-care environment in which quality patient care, health-care cost, and bacterial resistance considerations are paramount, it is important not only to implement general stewardship principles but to tailor those efforts toward a specific population. The NICU is one such place requiring added scrutiny.

Definitions and Background

Antimicrobial stewardship has become an essential component of optimal antimicrobial use in the hospital. Antimicrobial stewardship, as defined by the Infectious Diseases Society of America (IDSA), includes interventions targeted toward the improvement and monitoring of appropriate antimicrobial use by selecting the most optimal drug regimen, including the type of drug used, the dose, duration of therapy, and route of administration. (1) Antimicrobial stewardship efforts strive to achieve clinical cure, limit toxicity and adverse events, decrease health-care–associated infections and cost, and reduce the development of resistant organisms. Several studies have demonstrated the implications of a health-care system without antimicrobial stewardship, including negative effects on three main areas: quality patient care, clinical outcomes, and cost. (2)(3)(4) Adverse events related to antimicrobials and their misuse, such as kidney and liver toxicity, diarrheal illness, and resistant bacterial infection, negatively affect all three of these areas. (2)

With the realization of the significant, persistent threats of antimicrobial misuse, the Centers for Disease Control and Prevention (CDC) and the IDSA have worked to promote more judicious use of antimicrobials. In 1995, the CDC started the National Campaign for Appropriate Antimicrobial Use in the Community, followed in 2003 by the Get Smart: Know When Antibiotics Work program, national campaigns both aimed at reducing antimicrobial use and the prevention of resistance. (5) In 2007, the IDSA set forth guidelines for the development and maintenance of formal ASPs in the inpatient setting. (2) In a 2013 report from the CDC (“Antibiotic Resistance Threats in the United States”), improvement in antimicrobial stewardship was highlighted as one of the main interventions. (6)

It is estimated that 50% of all antimicrobial use in the United States is inappropriate. (5) In response, we have seen the implementation of successful antimicrobial stewardship efforts, particularly within inpatient medicine. Hospitals with an active ASP have seen inappropriate antimicrobial use decline. ASPs vary among hospitals but are largely based on two methods of interventions (or combinations of these methods): prospective audit with feedback to providers and antimicrobial restriction with authorization requirement. (7) These systems are often supported by an ASP team, which includes, at minimum, an infectious diseases physician and clinical pharmacist and, if feasible, a microbiologist, infection preventionist (eg, infection control nurse), hospital epidemiologist, and information systems specialist. Hospitals have been able to achieve the goals of stewardship with measurable increases in quality patient care and appropriate antimicrobial use, concurrent with decreases in adverse events, cost of hospitalization, and bacterial resistance. (8)

Stewardship in the NICU

NICU-specific antimicrobial stewardship strategies were recently reviewed by Patel and Saiman (9) from Columbia University by using the principles of the CDC’s Get Smart programming to emphasize this NICU-tailored approach to antimicrobial stewardship. They highlighted the importance of optimal diagnostic strategies (eg, use of biomarkers), empiric antibiotic selection based on local antibiogram characteristics and risk factors, constant reevaluation of the antimicrobial regimen, monitoring of toxicity, and consideration of shorter antimicrobial courses as cornerstones of NICU stewardship. Some of the suggested tactics included obtaining two blood cultures of at least 0.5 mL of blood in the initial evaluation of late-onset sepsis (LOS) for improved recovery of organisms and avoiding concurrent use of redundant coverage (eg, meropenem and metronidazole) for the treatment of necrotizing enterocolitis (NEC).

How to encourage behavior change among providers is a constant challenge of stewardship activities in any setting. In an attempt to address this factor, Patel et al (10)(11) adapted the “model of actionable feedback” and evaluated its implementation in the NICU setting. Based on the stewardship mechanism of provider feedback, the
Reducing the Need for Antibiotics

Antimicrobial stewardship efforts directed at infection prevention and optimal drug dosing are two ways in which antimicrobial misuse can be abated in the NICU. Successful infection prevention efforts have focused on the appropriate insertion, maintenance, and timely removal of central venous catheters (CVCs), prevention of colonization and decolonization of potential pathogens, microbiology laboratory surveillance and local antibiogram use, and containment of isolated infections. (12)(13)(14) Decreasing the number of health-care-associated infections reduces the need for empiric antibiotic use.

Infection Prevention

CVCs are essential to the long-term care of neonates, particularly for those very low birthweight (VLBW) and extremely low birthweight (ELBW) infants requiring parenteral nutrition. CVCs are not without risk: central line-associated bloodstream infections (CLABSIs) are known to cause significant morbidity and mortality in the neonatal population. (13) Milstone et al (14) performed a retrospective cohort study at eight centers involving more than 4,700 peripherally inserted central catheters (PICCs) in ~4,000 neonates. They found that the daily risk of infection was higher in PICCs that were in place for more than 2 weeks compared with those that were in place for less than 2 weeks. The most common organisms isolated were gram-positive, coagulase-negative staphylococci and *Staphylococcus aureus*. Gram-negative organisms were seen more often in those PICCs in place for more than 50 days. Infection prevention efforts aimed at creating the optimal environment during insertion and maintenance/access serve to decrease this risk, particularly with long-term CVC dwell times. Other efforts aimed at timely CVC discontinuation allow for fewer total patients who have CVCs, thus decreasing the number of CVC infections and the need for antibiotic use.

A study performed by Bizzarro et al (15) found a significant decrease in the rate of CLABSIs (8.4 to 1.28 per 1,000 central line days) after an educational intervention was implemented aiming to improve the quality of clinical CVC practices. Several other studies have shown similar results after implementation of standard practice bundles for the management of CVCs not only in neonates but in all patient populations. (13) Infection prevention efforts are also important for timely discontinuation of CVCs. In a retrospective cohort study by Wirtschafter et al. (16) involving 754 neonates from two level III NICUs, antibiotic use (in days and courses) was much higher (ninefold to 14-fold) for presumed infection than for confirmed CLABSIs; many more infants received antibiotics based on suspicion rather than confirmed infection. Studies verify that there is a significant amount of antimicrobial use for suspected infection, with no microbiologic evidence of CVC infection. Neonates are often given antimicrobials for presumed CVC infection that is not confirmed during sepsis evaluation, and therefore they may not need continued antibiotics or possibly not even need the CVC. For stewardship efforts and CVC care programs to be successful, all stakeholders in a neonate’s management must participate and have access to the necessary equipment to accomplish appropriate CVC care and prompt appropriate discontinuation. In our NICU specifically, the CLABSI rate for the 4 years before implementation of our CLABSI bundle was 2.17 CLABSI episodes per 1,000 central line days. The rate for the 2 years after implementation was 0.88 CLABSI episode per 1,000 central line days, which was a significant decrease in the number of CLABSIs.

Routine infection prevention relies on continuous microbiologic surveillance, resources for health-care workers, and infection prevention team input. These are important aspects of antimicrobial stewardship related to rapid infection identification and containment. Continued staff education (eg, appropriate CVC management education), hand hygiene, and prompt initiation of appropriate isolation precautions all serve to prevent and contain isolated infections and/or outbreaks. (12) Availability of hand-washing stations and disinfectants and appropriate personal protective equipment, including gowns, gloves, and masks, are essential for the success of infection control efforts. Infection control efforts targeted toward colonization prevention and decolonization by using antifungal prophylaxis have been shown in various studies to reduce the incidence of invasive
fungal infections in ELBW and VLBW infants. (17) Screening for methicillin-resistant Staphylococcus aureus (MRSA) and decolonization by using intranasal and even systemic therapy have been successful in reducing the rates of invasive infection caused by MRSA. (12)

**Selecting Appropriate Empiric Antibiotics**

Despite the often large number of providers who have diverse clinical practices in NICUs, a limited number of antimicrobial agents account for the majority of antimicrobial courses, and their use can be anticipated under certain clinical presentations. Antimicrobial stewardship efforts and models of provider feedback in the NICU can be targeted toward these known high-use antibiotics, such as vancomycin. We know the most frequently isolated bacterial organisms in neonates who have early-onset sepsis (EOS) are group B streptococci and Escherichia coli, and among infants who have LOS, the most frequently isolated organisms are coagulase-negative staphylococci and S aureus. (18)(19) Based on these most frequently isolated organisms, ampicillin, gentamicin, and vancomycin are the most widely used antibiotics in the NICU setting. (20) This antimicrobial-specific approach was illustrated in a study by Chiu et al (21) in which a vancomycin clinical use guideline was published and implemented in two tertiary care NICUs in Boston. The study yielded a statistically significant reduction in vancomycin start rates (by 35%–62%), as well as an overall reduction (40%–49%) in the number of infants exposed to vancomycin at all. This reduction in vancomycin use occurred with no evidence of increased deleterious effects of untreated sepsis or other infections.

**Limiting Antibiotic Duration**

The use of antibiotics within the NICU is often unavoidable. In the setting of a culture-positive isolated bacterial infection, the administration of directed antimicrobial therapy is straightforward. However, the potential for neonates (particularly VLBW and ELBW infants) to have many other pathologic conditions with overlapping clinical presentations can make so-called “culture-negative sepsis” syndromes difficult to manage. (20)(22) These neonates warrant empiric antibiotic therapy during initial evaluation. However, beyond the initial evaluation and antibiotic coverage, further management differs greatly within and among NICUs and can have significantly negative adverse effects. Prolonged empiric antibiotic use for suspected EOS and LOS has been associated with the development of invasive candidiasis, increased risk of NEC and death, increased hospital length of stay, and bacterial resistance. (20)(23)(24)(25)(26)

A study by Cotten et al (23) examined the risk of invasive candidiasis in more than 3,700 ELBW neonates who survived past 72 hours. The neonates were treated in 12 different centers across the country, with varying prescribing practices seen among institutions. The investigators found that use of broad-spectrum antibiotics (most often a third-generation cephalosporin) was associated with increased risk of invasive candidiasis, the incidence of which ranged widely (2.4%–20.4%) across different centers. This risk was only seen in infants receiving antimicrobial therapy for longer than 5 days. This finding makes sense pathophysiologically, because we know that Candida gut colonization is promoted by long-term broad-spectrum antibiotic use, thus increasing the risk of invasive disease. (27)

In a more recent retrospective study, Cotten et al (24) examined a cohort of ELBW neonates surviving more than 5 days who received empiric antibiotic therapy within the first 72 after birth for presumed EOS. The authors’ goal was to determine whether there was a correlation between NEC and/or death and the duration of antibiotic use. They found that prolonged antibiotic therapy (>5 days) with sterile culture results was associated with an increased odds of death or developing NEC (4% increase with each additional day of initial empiric antibiotics). These data are replicated in other studies, with the caveat that more than 5 days of therapy in an ELBW neonate who has signs and symptoms of EOS may be warranted in some cases. For example, suboptimal blood culture volumes could yield falsely negative culture results, highlighting the stewardship principles related to appropriate utilization and interpretation of diagnostic strategies. Kuppala et al (25) similarly examined more than 300 neonates of less than 32 weeks’ gestation and less than 1,500 g birthweight who survived for 7 days with no NEC or sepsis. They found that prolonged (>5 days) initial empiric antimicrobial therapy was associated with a higher incidence of NEC, LOS, and death. In a related retrospective study, Clark et al (26) examined more than 24,000 neonates who received one of two antibiotic regimens within the first 72 hours after birth for presumed EOS; the study goal was to determine factors associated with death. The antibiotic regimens consisted of ampicillin + gentamicin or ampicillin + cefotaxime. Investigators found that neonates, regardless of age, who were treated with ampicillin + cefotaxime were more likely to die and less likely to ultimately be discharged from the NICU compared with those neonates treated with ampicillin + gentamicin.

Not only can the prolonged and broad-spectrum use of antimicrobials yield adverse outcomes in neonates, it can also promote bacterial resistance. Increasing resistance...
is one of the most important rationales for stewardship, particularly within the ICU setting, which harbors the highest prevalence of resistant organisms. (6)(12) The impact of resistance in the NICU is less well described than in other health-care settings. One European study by de Man et al (28) examined the use of empiric antibiotics on the emergence of bacterial resistance. The investigators assigned two identical NICUs to different empiric antibiotic regimens: NICU 1 received penicillin G + tobramycin for presumed LOS and fluoxacillin + tobramycin for presumed LOS; NICU 2 received intravenous amoxicillin + cefotaxime for both presumed EOS and LOS. Rectal and respiratory bacterial cultures were gathered weekly in all patients receiving empiric therapy. The relative risk for patient colonization with strains resistant to the empiric regimen per 1,000 patient-days was 18 times higher for patients receiving the amoxicillin + cefotaxime regimen compared with patients receiving the penicillin G + tobramycin regimen. *Enterobacter cloacae* was most commonly isolated in neonates undergoing the amoxicillin + cefotaxime regimen, whereas *E. coli* was most commonly isolated in neonates undergoing the penicillin G + tobramycin regimen. These findings highlight the fact that initial empiric antibiotic selection affects not only clinical outcomes but also resistance and the potential for initial or recurrent sepsis episodes. It is thus important to consider the spectrum of the empiric agents as well as the institutional antibiogram to effectively treat the most prevalent organisms in one’s NICU.

To avoid prolonged empiric use of antibiotics, providers may now rely more on alternative modes of infection identification. Not all sepsis-like syndromes will yield a bacterial organism, and with a critically ill neonate, it can be difficult to discontinue antibiotics in the face of negative culture results. However, advances in rapid viral pathogen identification through the use of polymerase chain reaction microarray systems may make it possible to limit the amount of empiric antibiotics given for presumed bacterial sepsis. (7)(9)(12)

**Maximizing Safety and Efficacy**

The task of assessing antimicrobial misuse in a NICU overall can be a daunting one. Antimicrobial use and its true necessity will continue to be a challenge. There are ways in which manageable strategies of optimal drug dosing and monitoring can make a difference in a patient population in which antimicrobial dosing can be anything but straightforward.

At the University of Chicago, our NICU consists of 47 tertiary care beds (level III) and 18 convalescent beds (level II), averaging just more than 1,000 admissions per year. There is capacity for extracorporeal membrane oxygenation support in up to three neonates at one time. On average, there are 30% to 40% of neonates taking at least one antimicrobial at any given time. This statistic correlates with what is seen in other NICUs. In a point prevalence survey of 29 NICUs, it was found that 43% of patients were receiving at least one antimicrobial on the day of the survey. (29)

Gentamicin and vancomycin are two of the more frequently used antibiotics in NICUs; however, dosing of these agents can be challenging due to the altered physiologic characteristics of neonatal patients. (9)(12) These altered characteristics include increased extracellular fluid and decreased renal function compared with that found in older infants, children, and adults, resulting in larger volumes of distribution and longer half-lives of gentamicin and vancomycin. In general, larger doses with longer dosing intervals of gentamicin and vancomycin are needed to achieve similar serum levels compared with those in older pediatric patients. In addition, as neonates grow, antibiotic dosing will need to be adjusted to accommodate for changing physiologic characteristics. In our institution, we base vancomycin and gentamicin dosing on both the weight of the patient as well as postnatal age. We use an empiric dosing regimen based on a retrospective chart review of our neonatal population. This review showed that our initial empiric gentamicin dosing was only achieving therapeutic serum concentrations at steady state 59.4% of the time. We updated our empiric gentamicin dosing to target a goal peak serum concentration of 6 to 10 mg/dL and a goal trough serum concentration of less than 2 mg/dL. On the basis of calculations informed by our review, we anticipate that our new empiric gentamicin dosing regimen will achieve goal serum concentrations in 78% of our patients with the initial regimen without increasing the risk of trough levels to ≥2 mg/dL. Empiric vancomycin dosing is used to target a goal trough serum concentration of 10 to 20 mg/dL. If the patient has a complicated central line infection, presumed pneumonia, meningitis, or bacteremia, empiric vancomycin dosing is used, with a goal trough concentration of 15 to 20 mg/dL. For patients receiving more than 48 hours of antibiotic therapy, serum vancomycin and gentamicin concentrations are routinely monitored at steady state for efficacy and safety.

We have gained more knowledge about the optimal dosing of several parenteral antibiotics in the NICU, but enteral antibiotics continue to be a challenge. For infants requiring intravenous access solely for antimicrobial therapy but with a condition amenable to oral therapy
(eg, uncomplicated pneumonia, osteomyelitis), it can be difficult to achieve maximal therapeutic efficacy with enteral therapy due to all of the physiologic challenges of the neonatal population. Enteral therapy may not be reliably absorbed in neonatal patients because of alterations in gut motility, absorption, and gastrointestinal tract disease.

Conclusions
The NICU will continue to serve as a challenge for implementing antimicrobial stewardship programming and streamlining antimicrobial management. Antimicrobial stewardship in the NICU still relies on the core principles of stewardship used in various other areas of health-care, with customization to the neonatal population based on accumulating evidence. Some of the most important lessons we have learned relate to our growing understanding of the significant morbidity of antimicrobial use uniquely seen in the neonatal population. We have proposed some feasible stewardship efforts via infection control and pharmacy-driven mechanisms by which neonates can benefit from more judicious use of antimicrobial therapy.

References
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Antimicrobial Stewardship in the NICU: Lessons We've Learned
Colleen Nash, Elisabeth Simmons, Palak Bhagat and Allison Bartlett
Neoreviews 2014;15:e116
DOI: 10.1542/neo.15-4-e116

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