Strategies to improve antibiotic use in the neonatal ICU

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Purpose of review
Neonates are at a high risk of infection and may have nonspecific signs of sepsis. Accordingly, they are heavily exposed to antimicrobials. Neonates are also uniquely at risk of both short-term and long-term complications from antibiotic exposure. This review discusses advances in antibiotic stewardship in the neonatal population.

Recent findings
Antimicrobial utilization is highly variable among NICUs in excess of case-mix variation. Rates of early-onset sepsis because of Group B Streptococcus have decreased substantially with the introduction of intrapartum antibiotic prophylaxis. Recent epidemiologic studies have created evidence-based tools to more accurately estimate a newborn's risk of early-onset sepsis. Antibiotic selection and duration for late-onset sepsis and necrotizing enterocolitis are variable among centers, with inadequate evidence to guide practice. Novel diagnostic methods and biomarkers are increasingly used to assist with diagnosing infection, but inadequate specificity in many cases may result in excess antibiotic exposure. Published antimicrobial stewardship experiences in the neonatal inpatient setting have largely been successful and well tolerated.

Summary
Recent publications have identified many ways to safely reduce antimicrobial exposure and developed strategies to implement antimicrobial stewardship in the neonatal inpatient setting. However, new approaches are needed to further improve antibiotic use and to implement these interventions more universally in NICUs.

Keywords
antibiotic stewardship, antibiotics, neonatal ICU, sepsis

INTRODUCTION

Neonates, especially those born preterm or with major congenital anomalies, are at high risk of serious infection [1,2,3▪]. Sepsis is associated with high mortality [1,3▪] and the initial signs of sepsis are usually nonspecific. In addition, hospitalized neonates are at risk for nosocomial infections and complications, such as NEC(NEC). Accordingly, patients in the neonatal ICU (NICU) are heavily exposed to antibiotics [4▪,5]. This population is also at particular risk of adverse consequences of antibiotic exposure [6]. The NICU, therefore, represents a critical frontier for the antimicrobial stewardship movement. We review the common indications for antimicrobial administration in the NICU, the adverse events associated with antimicrobial exposure, evidence of opportunities and strategies to safely reduce antimicrobial exposure, and the effectiveness of published antimicrobial stewardship strategies.

ANTIMICROBIAL UTILIZATION IN NEONATAL INTENSIVE CARE

Some variation in antimicrobial prescribing among settings must be expected, based on factors, such as case mix and microbiologic resistance patterns. However, unexplained variation in healthcare practices without differences in outcomes represents an opportunity for improvement [7]. Among NICUs in California, antibiotic utilization varies 40-fold,

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Curr Opin Pediatr 2019, 31:127–134
DOI:10.1097/MOP.0000000000000716

KEY POINTS

- Neonates are frequently exposed to antibiotics in the NICU.
- There is substantial inter-hospital variation in antimicrobial prescribing practices in the NICU and antibiotic use is poorly aligned with the actual risk of infection in many circumstances.
- Antibiotic use in neonates may have adverse effects in the long-term including increased risk of allergies, asthma, and obesity.
- Effective strategies to decrease antibiotic use in the NICU have included the use of sepsis risk calculators, automatic stops for empiric antibiotics, and structured guidelines.
- Further research should focus on reliable and rapid identification of infected (and uninfected) neonates; determination of optimal treatment strategies for proven infections; and development and dissemination of effective and safe antimicrobial stewardship practices.

ranging from 2.4 to 97.1% of patient-days including antibiotic exposure [8]. Within the California sample, intermediate level NICUs (the lowest acuity level) used more antibiotics than higher acuity NICUs despite the majority not reporting any episodes of nosocomial infection or early-onset sepsis [8]. Updated data from the same set of NICUs from 2013 to 2016 did find a significant 21.9% decrease in gross antibiotic use, with much greater decreases among NICUs participating in an external antimicrobial stewardship effort; however, significant unexplained variation persisted [9▪▪]. In an international point-prevalence study of inpatient prescribing, substantial regional variation in antibiotic prescribing for neonates was observed. In some regions, particularly Asia and Latin America, use of broad-spectrum agents, such as meropenem and amikacin was far more common than in other regions. Encouragingly, however, the combination of gentamicin with amoxicillin, ampicillin, or penicillin dominated drug use [10].

Variation in gross utilization and antimicrobial choices has also been demonstrated for specific conditions. Within a large consortium of freestanding children's hospitals, the proportion of neonates admitted to NICUs who received antibiotics within 3 days of birth for presumed sepsis ranged from 52.3 to 90.9% [4▪]. Furthermore, the mean treatment duration within individual hospitals ranged from 3.2 to 8.6 days, with some hospitals in the sample prescribing antibiotic courses for longer than 3 days to 20% of the infants and some giving these longer courses to over 80% [4▪]. Among infants with congenital diaphragmatic hernia, 89.9% received antibiotics within the first 3 days of life and 11.4% received at least 7 days, despite early-onset sepsis occurring in only 2 of 1085 infants (0.2%) [11].

COMMON INFECTIOUS SYNDROMES AND MANAGEMENT VARIABILITY IN THE NEONATAL ICU

Early-onset sepsis

Early-onset sepsis (EOS), defined here as an invasive bacterial infection occurring within the first 3 days of life, affects a significant proportion of neonates, and is associated with high mortality [3▪]. Blood cultures are generally sufficient for the diagnosis of EOS. The most common causes of EOS remain Group B *Streptococcus* and *Escherichia coli* [12–14]. The risk of EOS decreases significantly with increasing gestational age [2,3▪]. Despite a declining incidence in recent decades, [12,13,15▪▪] high-risk neonates are nearly universally exposed to empiric antibiotics for EOS [4▪].

Among full-term and late-preterm neonates, the risk of EOS is typically in the range of 0.3–0.6 cases per 1000 live births, but antibiotic exposure occurs in approximately 5–8% of these neonates [2,16▪▪,17▪▪] meaning that at least 100 neonates receive antibiotics for each one with EOS. The American Academy of Pediatrics (AAP) [18], the American Congress of Obstetricians and Gynecologists (ACOG) [19,20], and the Centers for Disease Control and Prevention (CDC) [21] protocols reflect the risk of EOS before the advent of intrapartum antibiotic prophylaxis [12,13]. Recent analyses of very large cohorts of infants resulted in the development of the Neonatal Early-Onset Sepsis Calculator, which incorporates objective data and the infant's clinical status to provide a precise estimate of the risk of neonatal sepsis [22▪▪]. Many infants who would receive antibiotics under existing protocols may safely avoid antibiotics using this approach. Results of implementation are reviewed below.

In accordance with their higher risk of EOS, most very-low-birth-weight (VLBW) infants receive empiric antibiotics [5,15▪▪]. There is substantial inter-hospital variation in the proportion of infants in this category who receive antibiotics [4▪]. Recent analyses have identified scenarios in which empiric antibiotics for EOS may not be necessary, such as in the absence of preterm labor or chorioamnionitis [15▪▪]. Within this population, antibiotic duration is highly variable despite the high reliability of blood cultures, assuming that an adequate sample is obtained [23,24,25▪]. Adverse effects putatively associated with prolonged

antibiotic exposure in this setting are reviewed further below.

Late-onset sepsis

Late-onset sepsis (LOS) is generally defined as invasive bacterial or fungal infection beginning after the first 72 h of life. LOS may manifest seemingly spontaneously or as a nosocomial complication, such as catheter-related bloodstream infection or ventilator-associated pneumonia. Diagnosis is made by prompt culture of sterile sites, including blood, urine, and CSF. Cultures of endotracheal aspirates should be considered when clinical and radiologic evidence suggests possible pneumonia. However, results of cultures from nonsterile sites must be interpreted with caution [24,26]. Strategies to prevent nosocomial infection are reviewed below. Meningitis is more common in LOS than EOS and should be ruled out in most cases in which LOS is suspected or diagnosed [27]. Among VLBW infants (birth weight <1500 g), incidence as high as 20% has been reported [1]. In addition to the typical pathogens of EOS, causative organisms include (but are not limited to) coagulase-negative staphylococci, *Staphylococcus aureus*, other Gram-negative bacilli, and *Candida* spp. [1].

Empiric antibiotic therapy for LOS appropriately varies by setting and is generally based on expert opinion [24,26]. In all cases, coverage of Gram-positive and Gram-negative organisms is warranted. Where the incidence of methicillin-resistant *S. aureus* (MRSA) is low, an antistaphylococcal penicillin, oxacillin or nafcillin, may provide sufficient Gram-positive coverage. Vancomycin is recommended when the risk of MRSA is high, such as during an outbreak or if the infant is known to be colonized. Most practitioners favor an aminoglycoside as Gram-negative coverage. Coverage should be tailored to the scenario: for example, a third-generation cephalosporin is recommended if meningitis is suspected. The antimicrobial regimen should be adjusted as culture results become available. Duration depends on the specific clinical situation. When appropriately obtained, cultures are negative after 48 h and other indications for antimicrobials, such as necrotizing enterocolitis (NEC) are not suspected, antibiotics can generally be discontinued [24].

Necrotizing enterocolitis

Antibiotics are a standard component of the management of NEC [28], but there is no consensus on the optimal antimicrobial regimen because of a striking lack of evidence. A Cochrane Database Systematic Review in 2012 identified two randomized controlled trials that enrolled a total of 62 infants, both during the 1980s [29]. One compared ampicillin and gentamicin to ampicillin and gentamicin along with clindamycin; [30] the second compared ampicillin and gentamicin alone to ampicillin and gentamicin along with enteral gentamicin [31]. There is, accordingly, no standard regimen [26], and practice has been shown to be highly variable even within a single center [32]. It is likely that there is significant variation in the antimicrobial spectrum deployed across centers. There is general agreement that Gram-positive, Gram-negative, and anaerobic coverage are warranted [26]. Cultures of blood and, whenever available, peritoneal fluid, if positive, can be used to guide antimicrobial therapy. In this area, further research is badly needed.

EFFECTS OF ANTIBIOTIC USE IN THE NEONATAL ICU

Broad-spectrum antibiotic use in the neonatal population has been associated with increased antibiotic resistance, death, candidemia, and NEC [33–36,37▪▪]. In the long-term, early-life antibiotic exposure also been associated with the development of allergies, asthma, and obesity [38–41,42▪▪]. Broad-spectrum antibiotics reduce infant gut microbial diversity and alter gut flora [43]. Tsai *et al.* [44] demonstrated that increased exposure to third-generation cephalosporins and carbapenems were independent risk factors for multidrug-resistant Gram-negative bacteremia [44], and infections with these organisms were associated with greater mortality. Several studies have found that exposure to broad-spectrum antibiotics increases the risk of candidemia and that infants with candidemia can have mortality twice that of infants without candidemia [45–47]. Although studies previously demonstrated an increased risk of NEC with increased antibiotic use [48–50], a recent case–control study demonstrated a decreased association between early use of antibiotics after birth and NEC [51▪▪]. Further research should be done to determine, which infants may benefit from early, empiric coverage and those who may be at increased risk of complications from antibiotics.

ADVANCES IN THE USE OF DIAGNOSTIC TESTING AS AN ADJUNCT TO ANTIBIOTIC STEWARDSHIP

Definition of 'diagnostic stewardship'

As advances in laboratory diagnostics and pathogen detection progress, it is increasingly important for healthcare providers and microbiology laboratories

to practice 'diagnostic stewardship.' The goal of diagnostic stewardship is to 'select the right test for the right patient, generating accurate, clinically relevant results at the right time to optimally influence clinical care and to conserve health resources' [52]. Improving the use and interpretation of diagnostic tests in the NICU may help with determining, which infants are at high risk and may benefit from empiric antibiotic therapy. This is particularly important because of the low likelihood of sepsis in neonates and the nonspecific signs of sepsis in this population.

The relationship of microbiological testing and antimicrobial stewardship in the neonatal ICU

Adequate blood cultures may be difficult to obtain in extremely low birthweight neonates, given the volume of blood that is traditionally required. The sensitivity of blood cultures varies by the level of bacteremia present and the volume of blood obtained [53]. Lower blood volume obtained for blood culture may be associated with increased risk of contaminants leading to increased antibiotic exposure and increased risk of adverse effects of antibiotics [53]. Ensuring adequate blood volumes (0.5 –1.0 ml) that are collected for culture can improve diagnosis and treatment of neonatal sepsis [53]. As anaerobic bloodstream infections are uncommon in neonates and neonates have little blood volume, anaerobic blood cultures should only be performed in those patients who are at increased risk of anaerobic bacteremia (e.g. neonates with intraabdominal infections) [53].

Significant technological advances in clinical microbiology have accelerated the process of identifying pathogens in blood cultures through rapid molecular techniques. Rapid diagnostic tests for bacteria, such as fluorescent in-situ hybridization (FISH), microarray, multiplex PCR, and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF), can decrease time to species identification compared with conventional methods, and in some cases, provide preliminary susceptibility information. These newer technologies may help clinicians more rapidly optimize antimicrobials [53]. Studies in the adult population have shown that the routine use of a microarray technology lead to improved and timely treatment of Gram-positive bacteremia [54]. A prospective randomized controlled trial comparing rapid multiplex PCR with traditional blood culture demonstrated that rapid multiplex PCR was effective at improving antibiotic use and reducing duration of antibiotics for contaminants [55]. Additionally, when real-time antibiotic stewardship recommendations were combined with rapid multiplex PCR, further antibiotic de-escalation occurred. In the future, techniques, such as next-generation sequencing may allow detection of pathogens directly from blood components, without an incubation step, and may significantly decrease the time to pathogen detection and identification [56]; however, these techniques require further validation. These evolving technologies require expertise in application and interpretation in order to maximize the potential benefit [55].

Use of biomarkers to identify infection in the neonatal ICU

Biomarkers and markers of inflammation and infection, including absolute neutrophil count, C-reactive protein (CRP), procalcitonin, and various cytokines, have all been studied as predictors of early-onset and late-onset sepsis in neonates [57]. A biomarker for sepsis that is highly sensitive and specific for sepsis has yet to be discovered, however, some biomarkers may be helpful for risk stratification of infants. The immature to total neutrophil count (I:T ratio), for example, can be helpful in determining risk of infection but lacks the specificity to differentiate inflammation from infection [58,59]. CRP is one of the most studied biomarkers for neonatal sepsis, but CRP can be elevated in noninfectious, pro-inflammatory conditions [60]. Serial CRPs may improve the sensitivity and specificity. If serial CRPs are normal, then the likelihood of bacterial infection is low; however, the specificity of even serial CRPs is not high enough to differentiate between bacterial infection and inflammation [61]. Reliance on a single test with poor positive predictive value to identify sepsis will result in unnecessary antibiotic exposure [26].

Cytokines, in particular interleukin 6 (IL-6), have been studied in neonates as predictors of fungal and bacterial sepsis [62]; however, studies are limited making clinical interpretation of these markers challenging. IL-6 is a cytokine produced by mononuclear phagocytes, endothelial cells, and fibroblasts, which leads to further cytokine production, T-cell activation, B-cell antibody secretion, and differentiation of cytotoxic T cells [63]. IL-6 is elevated early in sepsis and has a short half-life, and may be useful as an early marker for sepsis and response to therapy [64]. IL-10, an anti-inflammatory cytokine released by monocytes and macrophages has been studied in conjunction with IL-6. Measurement of increased IL-6 and IL-10 improve the positive predictive value of these markers for sepsis [64]. Procalcitonin (PCT) is commonly used in the diagnosis of sepsis and bacterial

pneumonia in older patients but is less useful in the diagnosis of neonatal sepsis because PCT levels increase in healthy neonates after birth for physiologic reasons [60]. The sensitivity of PCT is 76% and the specificity is 76% for early-onset sepsis [60]. The use of combinations of biomarkers to assess risk of neonatal sepsis has been shown to increase the sensitivity, and in some instances, reduce the use of antibiotics [65].

ANTIBIOTIC STEWARDSHIP INTERVENTIONS IN THE NEONATAL ICU

Published antibiotic stewardship interventions in the NICU have been largely effective (Table 1) [9▪▪]. Published stewardship interventions have generally been aligned with strategies recommended by the CDC [66] and Infectious Diseases Society of America [67]. Simple interventions, such as education regarding the risks of broad-spectrum antibiotic use and modifying empiric treatment algorithms, may be effective at reducing broad spectrum antibiotics and changing colonization patterns [36,68]. Structured guidelines for antibiotic use can also have an impact. In one institution, creation of guidelines for the empiric use of vancomycin reduced vancomycin use by 40% without an impact on patient safety [69].

Another effective stewardship approach is prospective audit and feedback. In this method, the

Table 1. Effective neonatal ICU antibiotic stewardship implementation strategies

Intervention type	First author, year [ref. no.]	Strategy	Outcomes
Modification of treatment guidelines	Chiu, 2011 [69]	Created guidelines for use of vancomycin based on culture data and clinical improvement	Decreased use of vancomycin in the NICU by 40%
	Calil, 2001 [68]	Educational efforts and changes in empiric antibiotic recommendations to decrease the use of third-generation cephalosporins	Decrease in the proportion of infants colonized by multidrug-resistant *Enterobacter cloacae* over the 4-year implementation period
	de Man, 2000 [36]	Limited antibiotics to either narrow-spectrum or broad-spectrum on two NICU units and monitored colonization	Predominant colonization patterns varied based on prescribed antibiotics; *Escherichia coli* was more common among those treated with the narrow spectrum antibiotics whereas *Enterobacter cloacae* was more common among those treated with the broad spectrum antibiotic regimen
Automatic stop dates for antibiotics	Cantey, 2016 [24]	Autostop at 48 h for empiric antibiotics	Antibiotics days of therapy decreased by 27% with no difference in safety outcomes
	Tolia, 2017 [72▪▪]	Autostop at 48 h for empiric antibiotics started in the first 7 days of life	Decrease in antibiotic days of therapy and lower proportion of patients on antibiotics for longer than 48 h
	Astorga, 2018 [71]	Autostop at 48 h for empiric antibiotics used at admission to NICU	Total antibiotic use significantly decreased by 35% after the autostop intervention, with the greatest impact on vancomycin days of therapy
Prospective audit and feedback	Nzegwu, 2017 [70▪]	Prospective audit and feedback of antibiotics prescribed in the NICU	Decrease in antibiotic utilization by 14.7 days of therapy per 1000 patient days during the stewardship period, with the most significant decrease in the days of ampicillin therapy
Sepsis risk calculator	Kuzniewicz, 2017 [16▪▪]	Creation of an evidence-based calculator to determine, which neonates greater than 35 weeks may be at the greatest risk of sepsis	Decreased blood cultures drawn in neonates more than 35 weeks from 14.5 to 4.9% and decreased antibiotic use or older from 5 to 2.6%
	Dhudasia, 2018 [17▪▪]	Implementation of neonatal sepsis risk calculator in routine neonatal care	Decreased overall laboratory testing by 82% and decreased antibiotic use in newborns by 42%
Use of biomarkers	Franz, 2004 [65]	Randomized infants less than 72 h of age who had signs of sepsis or obstetric risk factors to receive antibiotics according to protocol or to receive antibiotics when IL-8 was greater than 70 and/or CRP was greater than 10	Infants in the IL-8 group received fewer antibiotics than those in the standard therapy group (36.1 versus 49.6%). There were no significant differences in the number of missed infections between the two groups.

antibiotic stewardship team reviews antimicrobial orders under prespecified rules and provides recommendations wherever indicated [67]. A recent study demonstrated a significant reduction in ampicillin days of therapy when educational efforts were combined with prospective audit and feedback [70▪]. Other institutions have employed automatic stops on empiric antibiotics at 48 h, with a new order required to continue antibiotics [24,71,72▪▪]. The SCOUT trial led by Cantey *et al.* [24] created an automatic stop for antibiotics at 48 h in the NICU and recommended a 5-day course of suspected pneumonia or culture-negative sepsis [24]. These interventions led to a 27% decline in total antibiotic days of therapy and was maintained through the 9-month intervention period. Specifically, the use of gentamicin, ampicillin, and oxacillin decreased significantly after the automatic stop was implemented. There were no differences in the rate of late-onset sepsis, NEC or death in the intervention period; however, neonates had a longer length of stay. A similar study by Tolia *et al.* [72▪▪] demonstrated that automatic antibiotic stop orders in the first 7 days of life reduced total antibiotic exposure by 38% and decreased the number of infants on antibiotics for longer than 48 h by 20% without any impact on the incidence of death or NEC. Length of stay was not analyzed in the Tolia study; however, this should be examined in further studies.

Although these institutional changes have made an impact on antibiotic use in the NICU, there has also been a paradigm shift in the workup and management of newborns, which may lead to a more global reduction in antibiotic use. As described above, the AAP [18], ACOG [19,20], and CDC [21] protocols for treatment of neonates at risk for EOS result in antibiotic therapy for many neonates who may not require them [16▪▪,73]. The Neonatal Early Onset sepsis Risk Calculator is a tool that accurately predicts the risk of early-onset sepsis for an infant using only objective variables, such as gestational age and highest maternal temperature [16▪▪,74]. When this calculator was first studied at a Northern California health system, the authors observed a decrease in blood culture use from 14.5 to 9.5%, a decrease in empiric antibiotic use from 5.0 to 2.6%, and a decrease in antibiotic days per 100 births from 16.0 to 8.5 days [16▪▪]. Those who have implemented the routine use of the Neonatal Early Onset Sepsis Risk Calculator or similar calculator [75] have demonstrated a decrease in antibiotic use by 40% or more without an impact on morbidity, mortality, or readmission [17▪▪,76▪,77–79]. One multidisciplinary group integrated the use of the of the calculator into their workflow and were able to reduce antibiotic use in newborns from 6.3 to 3.7% in over 6000 births [17▪▪]. The authors did not see any significant increase in the risk of readmission with the use of the calculator.

CONCLUSION

The relationship between antimicrobial overuse and patient harm because of antimicrobial resistance and direct adverse effects is more evident in the neonatal intensive care setting than most other contexts in the practice of medicine. In many circumstances, antimicrobial use is poorly aligned with the actual risk of infection, and there is substantial interhospital variation in antimicrobial prescribing practices. This scenario presents an ideal setting for antimicrobial stewardship intervention, yet implementation of antimicrobial stewardship in the NICU appears to have lagged behind other inpatient settings. In recent years, substantial progress has been made on several fronts to safely reduce the overuse of antimicrobials in this population, but these new findings have yet to broadly influence practice. There is sufficient evidence to recommend the practices of clinical protocol development, particularly for EOS, LOS, and NEC; prospective audit and feedback; and use of automatic stop dates for new antibiotic orders. Many of these activities can be integrated with hospital-wide antimicrobial stewardship efforts. The success of the Neonatal Early Onset Sepsis Risk Calculator in hospitals that have implemented it is particularly encouraging. Future research should focus on: reliable and rapid identification of infected (and uninfected) neonates; determination of optimal treatment strategies for proven infections; and development and dissemination of effective and safe antimicrobial stewardship practices.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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