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Principles and Strategies of Antimicrobial Stewardship in the Neonatal Intensive Care Unit

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Abstract

The judicious use of antibiotics is an important means to limit the emergence of antibiotic resistant organisms. While specific guidelines for neonates are often lacking, antibiotic stewardship principles can be applied to the neonatal intensive care unit. Principles include accurately identifying patients who need antibiotic therapy, using local epidemiology to guide the selection of empiric therapy, avoiding agents with overlapping activity, adjusting antibiotics when cultures results become available, monitoring for toxicity, and optimizing the dose, route, and duration of therapy. Neonatal intensive care units should develop interdisciplinary antimicrobial stewardship teams with the support of their institutions. Prescriber audit and feedback as well as preauthorization and formulary restriction of selected antibiotics are recommended antimicrobial stewardship interventions. Ancillary strategies include education and computerized decision support. Metrics to evaluate antimicrobial stewardship programs should include measurements of patient safety and quality, such as rates of adverse drug events, and appropriate dosing and timing of perioperative prophylaxis.

Antibiotic Use and the Burden of Antibiotic Resistance

The emergence of antibiotic resistant organisms (AROs) has been linked to the inappropriate use and overuse of antibiotics.^{1,2} Infants hospitalized in neonatal intensive care units (NICUs) are commonly prescribed antibiotics. As evidence, in a point prevalence study of 29 NICUs, 47% of 827 infants were receiving at least one antibiotic on the day of the survey.³

Broad spectrum antibiotic exposure has been associated with the emergence of multi-drug resistant gram-negative bacilli and development of invasive candidiasis.^{4,5} Prolonged duration of empiric antibiotic therapy for early onset sepsis in extremely low birth weight infants has been associated with increased risk of death and necrotizing enterocolitis (NEC).^{6,7} In addition, antibiotics can cause adverse events such as nephrotoxicity,

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hepatotoxicity, and hematological abnormalities, and necessitate blood draws for therapeutic monitoring.⁸

Infections with AROs are associated with increased morbidity and mortality and increased healthcare costs, likely related to increased virulence, delays in appropriate therapy, and fewer treatment options as few pharmacokinetic and clinical studies of antibiotic efficacy are available in the neonatal populations.^{9,10} Furthermore, infants infected or colonized with AROs can serve as reservoirs for other infants as well as for potential outbreaks.^{11,12}

Unique Challenges in Antibiotic Prescribing in the NICU

The signs and symptoms of sepsis in infants are non-specific and may represent the presentations of a non-infectious process, such as apnea of prematurity or gastroesophageal reflux. Adequate blood quantities may not be feasible to obtain for culture. When cultures reveal growth for coagulase-negative staphylococcal (CoNS) species, distinguishing between infection and colonization or contamination may be difficult. Treatment guidelines are often not established for infants, particularly for preterm neonates. Thus, NICU clinicians often treat infants with negative cultures for 'presumed late onset sepsis'. In a retrospective review of 754 patients from 2 NICUs, antibiotic therapy to treat presumed infection was shown to be 8.8-fold higher than antibiotic use to treat culture-proven infection.¹³

Antimicrobial Stewardship and the CDC Get Smart For Healthcare Campaign

Antimicrobial stewardship is recognized as a critical patient safety and quality imperative to combat the emergence of antimicrobial resistance (AMR) and preserve the activity of existing agents.¹⁴ The primary goal of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity and the emergence of resistance.¹⁵

The most important national antimicrobial stewardship initiative for acute care settings is the Centers for Disease Control and Prevention's (CDC) Get Smart Campaign.¹⁶ Initiated in 2011, this campaign's goal is to promote timely and appropriate antibiotic utilization for hospitalized patients. Inherent to its principles are the ongoing evaluation of the need for antibiotics, the appropriate selection of a regimen, and optimization of the dose, route (e.g., intravenous vs. oral) and duration of therapy. These principles can be applied to empiric use (when infection is suspected but cultures are pending), definitive use (when an organism has been identified), or for prophylaxis (e.g., prevention of postoperative infections). The Campaign's core principles of antibiotic use with relevant examples for the NICU are described in Table 1.

Before Starting Antibiotics—Diagnostic Strategies

Antibiotics are frequently initiated for suspected infection, particularly in low birth weight infants.¹⁷ Biomarkers may be useful to identify infants with true infection and reduce unnecessary antibiotic use. In a multi-center study, Franz et al assessed the impact of measuring interleukin-8 and C reactive protein (CRP) versus CRP alone on the initiation of empiric antibiotics for early onset sepsis and found that the use of both biomarkers vs. CRP alone decreased antibiotic use (49.6% vs. 36.1%; $p < 0.0001$), and there was not an increase in missed infections.¹⁸ Urinary neutrophil gelatinase-associated lipocalin has been shown to be an early marker for culture-positive late onset sepsis in very low birth weight infants.¹⁹

However, comparisons of studies assessing the utility of biomarkers are difficult to make due to small sample size and different study designs.²⁰

Optimizing blood cultures can improve antibiotic use as detection of an organism can allow targeted antibiotic therapy. Prior to antibiotic initiation, 2 blood cultures of at least 0.5 ml each should be obtained. A larger volume of blood (1 to 2 mL) may further increase organism recovery.²¹ It has been noted that in practice blood culture volumes are often low; Connell et al demonstrated that the volume of blood was less than 0.5 ml in 35% of blood cultures obtained from infants less than one month of age.²²

Obtaining 2 blood cultures may help clinicians differentiate between contamination or colonization and infection, particularly if CoNS are isolated. This is particularly useful when a central venous catheter (CVC) is present. In a national survey of 278 neonatologists from 35 hospitals, respondents were less likely to treat a positive peripheral culture with a full antibiotic course if the CVC culture was negative, as compared to a single positive peripheral blood culture (85% vs. 47%, $p < 0.0001$).²³

Starting Antibiotics--Selecting Empiric Therapy

The selection of empiric antibiotic therapy should be guided by local data, available in cumulative antibiograms, and, if relevant, outbreak investigations. A cumulative antibiogram is the percentage of isolates of epidemiologically significant species obtained from a specified patient population over a defined period of time that are susceptible to clinically relevant antibiotics. At the institutional level, cumulative antibiograms inform empiric therapy (e.g., the proportion of gram negative organisms that are susceptible to gentamicin). However, it is likely that the frequencies of AROs are different in the NICU compared with other hospital units and therefore cumulative antibiograms should be unit-specific to be most useful.²⁴ At the regional and national level, cumulative antibiograms can be shared with public health agencies and can inform clinical practice recommendations by professional societies. Knowledge of outbreaks can inform the temporary modification of empiric regimens (e.g., use of linezolid rather than vancomycin for an ongoing outbreak of vancomycin-resistant enterococci).

Agents with overlapping spectrum of activity should be avoided because there is no evidence for increased efficacy and this practice could increase toxicity. In a multi-center survey of neonatal clinicians, 37% (52/137) of respondents indicated that they would use meropenem and metronidazole for suspected NEC.²⁵ In contrast, to increase the likelihood of adequate initial therapy, a beta-lactam agent paired with an aminoglycoside agent (e.g., piperacillin/tazobactam plus tobramycin) may have role in empiric therapy for critically ill patients at risk of infection with multidrug-resistant pathogens. Once susceptibility results are known, use of a single beta-lactam agent is preferred, since, in adults, combination therapy has not shown to reduce mortality, morbidity, or protect against the development of resistance for gram-negative pathogens.^{26,27}

Reevaluating the Antibiotic Regimen

As more clinical data are available, the prescriber should review the initial antibiotic regimen. The microbiology report with antibiotic susceptibility testing (AST) is an invaluable tool to determine if antibiotics should be continued, modified, or discontinued.

First, the body site from which the positive culture was isolated should be reviewed. Growth at non-sterile body sites (such as tracheal aspirates) may be colonizing flora, particularly when the clinical course is not suggestive of infection.

Second, susceptibility results provide the opportunity to treat with a narrow spectrum, less toxic, and more efficacious antibiotic. For example, highly relevant to the NICU, oxacillin is more effective than vancomycin for the treatment of methicillin susceptible *Staphylococcus aureus* (MSSA) infections and oxacillin should be used if a patient is infected with MSSA. Empiric antibiotics should be promptly stopped if the pathogens are resistant to that agent (e.g., discontinue vancomycin when gram negative bacilli are isolated). In a retrospective review of antibiotic use in 4 tertiary care NICUs, failure to narrow and discontinue antibiotics were the most common reason for inappropriate use and represented 9% of all antibiotic use.²⁸

Third, the minimum inhibitory concentration (MIC) can guide treatment for infections at sequestered sites, such as lung or the central nervous system. At these sites, decreased antibiotic penetration is expected. Thus, use of agents with MICs near the clinical breakpoint (the transition from susceptible to intermediate or resistant) would not be recommended, as adequate tissue levels may not be achieved. In addition, if treatment failure occurs, the MIC of subsequent isolates should be examined to determine if selection of resistant subpopulations has occurred while on therapy.

Finally, the date and time of the microbiology report, provide an opportunity for timely discontinuation of therapy when infection is not suspected. Nearly all blood cultures (>97%) with clinically meaningful bacterial growth will be positive within 48 hours.²⁹ Cultures with growth after 48 hours are more likely to be contaminants or colonizing organisms as these microbes are generally present at a lower inoculum.³⁰ Timely review of microbiology results may decrease antibiotic use. When compared with standard of care (periodic lab updates and clinician initiated phone calls), availability of real-time blood culture results via a computer link between the clinical microbiology automated blood culture system and the NICU reduced the mean number of antibiotic doses from 8.8 to 6.8 for infants undergoing a sepsis evaluation who had negative blood cultures.³¹

Monitoring for Toxicity

In the NICU population, dosing schedules should be appropriate for gestational age, chronological age, and current weight. Infants should be monitored for toxicity, particular if renal function is changing, or if prolonged courses of therapy are administered. For certain antimicrobials such as vancomycin, therapeutic drug monitoring should be performed to ensure the optimal trough level is obtained, and to detect toxicity, particularly if concurrent nephrotoxic drugs are used.³² New guidelines for methicillin resistant *Staphylococcus aureus* (MRSA) infections at sequestered sites (e.g. meningitis, pneumonia) recommend vancomycin serum trough concentrations of 15–20 mg/L.³³ While the optimal trough concentration in neonates has not been studied, these recommendations should be considered for infants with persistent MRSA bacteremia or MRSA infections at sequestered sites.

Implementing Shorter Duration of Perioperative Prophylaxis

Standardizing perioperative prophylaxis offers an additional antimicrobial stewardship opportunity. Perioperative prophylaxis recommendations for adult patients have been crafted by the Surgical Care Improvement Project (a partnership of 10 national organizations) and recommend use of one agent and discontinuation of antibiotic prophylaxis within 24 hours of surgery end time (48 hours for cardiac surgery).³⁴ Prolonged antibiotic prophylaxis is common in pediatrics, including the NICU. In a point prevalence survey of 32 hospitals from 21 European countries, 67% of pediatric patients received perioperative antibiotics for more than 1 day.³⁵ Further, 24% of these patients received combinations of antibiotics, most commonly metronidazole and a beta-lactam/beta-lactamase inhibitor. In an international

survey of 50 pediatric cardiac surgical units, 40% continued antibiotics for 72 hours.³⁶ Although the optimal duration of perioperative prophylaxis remains yet to be determined for infants hospitalized in the NICU, considerable practice variation could be reduced with the implementation of institutional guidelines.

Developing an Antimicrobial Stewardship Team

Ideally, the antimicrobial stewardship team consists of a physician and clinical pharmacist with infectious diseases expertise, as well as key stake holders in clinical care, infection control, and patient safety and quality.¹⁵ The proposed members of a stewardship team in the NICU are shown in Table 2. While infectious disease fellows have commonly been employed to implement pre-approval strategies for antibiotics, fellows are less likely to provide appropriate advice when compared with dedicated ID pharmacists.³⁷ While not directly involved in providing stewardship to prescribers, advisory members include a clinical microbiologist, hospital epidemiologist, and nursing leadership. Support of both the NICU leadership and general hospital administration, particularly those involved, in patient safety and quality, is essential. For institutions with fewer resources, a pharmacist or motivated neonatologist ‘physician champion’ can lead antimicrobial stewardship efforts.

Implementing Antimicrobial Stewardship Strategies

Stewardship interventions should be sustainable and aligned with the available human resources and informational technology infrastructure. The Infectious Diseases Society of America and the Society for Healthcare Epidemiology, along with other professional organizations, have published evidence-based guidelines for stewardship programs in acute care settings.¹⁵ The two core strategies which provide the foundation of an antimicrobial stewardship program include: formulary restriction and preauthorization and prospective audit and feedback to prescribers. These, as well as other ancillary strategies, are listed with relevant NICU examples in Table 3.

In prescriber audit and feedback the antimicrobial stewardship team reviews antibiotic prescribing for select antimicrobials and provides real-time feedback to prescribers ideally at both initiation and continuation of therapy (48–72 hours later). Such strategies have proven successful for pediatric populations. In a study describing a hospital-wide program, prescribers contacted the stewardship team for prior approval of restricted antibiotics and re-approval after 48 hours of use.³⁸ To make recommendations to optimize therapy, the stewardship team reviewed relevant clinical data, including culture reports. Recommendations could include narrowing antibiotic therapy, dose adjustment, and formal consult with the infectious diseases service. During a 4-month study period, there were 652 calls to the pediatric stewardship team of which 45% lead to recommendations to optimize therapy. Savings in drug acquisition costs alone were \$50,000. Over a 3-year period, Newland et al demonstrated an sustained 18% decline in select antimicrobials after implementations of an AS program using prescriber audit and feedback.³⁹

Formulary restriction and preauthorization strategies exist in most hospitals, including those with tertiary care NICUs.⁴⁰ Restriction strategies may be more straightforward to implement as the restricted agents can simply be removed from the hospital formulary. One limitation of this strategy is that a compensatory increase in the use of non-restricted antimicrobials may occur. Another limitation is that, once approved, further prescribing advice is typically not sought or provided. The impact of the exclusive use of restrictive strategies on antimicrobial use in pediatric populations has not been well studied.

Additional stewardship strategies include prescriber education, guidelines and clinical pathways, biomarkers, and antimicrobial order forms. Education is the most frequently

employed intervention and is a component of other interventions. However, effective education is difficult to sustain and clinicians may 'burn out' and/or have competing demands for their time.⁴¹ Antibiotic cycling, defined as the scheduled rotation of preferred antimicrobials in a unit, is not currently recommended. While there may be decreased selective pressure for the antibiotic when it is off-cycle, reintroduction of the antibiotic would likely result in selection for the resistance determinant. Treatment guidelines for common conditions may help reduce inappropriate antimicrobial use,⁴² but should be updated regularly, if appropriate. Clinical pathways and prescriber education may be less costly to implement than prescriber feedback in institutions with fewer financial resources.

Monitoring Success of Antimicrobial Stewardship

Antimicrobial stewardship programs should develop metrics to measure successful implementation and safety rather than exclusively focusing on cost saving. Initial efforts could include monitoring antimicrobials that are used most frequently or incur the most pharmacy costs. Alternatively agents with the greatest risk of toxicity or the greatest risk of inducing antibiotic resistance could be monitored. In pediatric populations, days of therapy, are the preferred metric to quantify antibiotic use.⁴³

The availability of the electronic medical record (EMR) can greatly facilitate the implementation of stewardship activities. The EMR can be queried for redundant drug combinations, prolonged duration of therapy, and prolonged perioperative prophylaxis. Integration with the clinical database, including AST results, current hepatic and renal function, drug-drug interaction, and known drug allergies can further facilitate stewardship efforts.

Metrics for appropriate antibiotic use should be developed with key stakeholders as prescriber acceptance of the metrics is paramount. Focus groups and understanding the work flow of the NICU can be useful to develop metrics that are meaningful to the prescribers.⁴⁴ Table 4 provides potential metrics that emphasize patient quality and safety. To monitor the effectiveness of the interventions, trends in antibiotic prescribing should be analyzed using times series analysis with multiple data points before and after the intervention to ensure that secular trends are not accounting for the observed differences.⁴⁵

Conclusion

The rise of antimicrobial stewardship programs in pediatric populations is promising. While there are fewer studies in NICU setting, the principles of effective stewardship are broadly applicable to this population.

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Table 1

Get Smart For Health Care Campaign with examples for the NICU

Get Smart Principles	Examples
Accurately identify patients who need antibiotic therapy	Obtain two blood cultures for evaluation of late onset sepsis prior to starting antibiotics
Utilize local and regional antibiograms	Avoid use of meropenem for empiric treatment of suspected late onset sepsis if rates of multi-drug resistant gram-negative bacilli are low.
Avoid therapy with overlapping activity	Avoid simultaneous use of metronidazole and meropenem to treat necrotizing enterocolitis.
Give the right dose and interval of drug	Target vancomycin trough to 15–20 mg/L to treat pneumonia caused by MRSA.
Review culture results and adjust antibiotics	Review microbiology results at transitions of care (e.g. sign out, weekend cross-coverage) and narrow antibiotic coverage promptly.
Monitor for toxicity and adjust therapy accordingly	Adjust antibiotic dose for patients with deteriorating renal function.
Stop therapy promptly if indicated by culture results	Discontinue antibiotics after 48 hours if blood cultures are negative and ongoing infection is not suspected.

Table 2

Potential NICU antimicrobial stewardship team

Team Members
Infectious diseases physician
Clinical pharmacist with infectious diseases training
Neonatologist
Clinical microbiologist
Information system specialist
Infection control professional
Hospital epidemiologist
Nurse

Table 3

Examples of antimicrobial stewardship strategies

Strategy	Examples
Prescriber audit and feedback	Review of microbiology results and patient record by antimicrobial stewardship team within 48 – 72 hours of initial approval of vancomycin with recommendation to continue, change or discontinue antibiotics
Formulary restriction and prior authorization	Require prior authorization from the antimicrobial stewardship team prior to the use of meropenem
Education	Provide lecture series about stewardship principles and antibiotic options for the treatment of gram-negative pathogens.
Guidelines and clinical pathways	Develop consensus guidelines for the duration of treatment of presumed 'culture-negative' sepsis
Antimicrobial order forms	Use automatic stop orders to provide the correct duration of perioperative prophylaxis
Dose Optimization	Target vancomycin trough levels between 15–20 mg/L for treatment of persistent MRSA bacteremia.
Computer surveillance and decision support	Automated alerts for redundant antibiotic combinations

Table 4

Examples of patient safety and quality metrics for evaluating antimicrobial stewardship interventions.

Potential Safety and Quality Metric
Episodes of ineffective empiric antibiotic therapy (organism/antibiotic mismatch)
Mean time to target vancomycin trough concentration for infants with known MRSA infection
Proportion of infants receiving appropriate dosing and timing of perioperative prophylaxis
Rates of infections with multi-drug resistant gram negative infections
Episodes of antibiotic-associated adverse events
Duration of treatment for culture negative presumed late onset sepsis