Antimicrobial Stewardship in the NICU

Joseph B. Cantey, MD\textsuperscript{a,b,*}, Sameer J. Patel, MD, MPH\textsuperscript{c}

INTRODUCTION: NATURE OF THE PROBLEM

Adverse Outcomes Related to Antibiotic Use

Antibiotics are the most commonly prescribed medications in neonatal intensive care units (NICUs).\textsuperscript{1} There is increasing evidence that inappropriate or excessive use of antibiotics in the NICU leads to serious adverse outcomes. These outcomes include the emergence of multidrug-resistant organisms (MDROs), linked to endemic or epidemic infections\textsuperscript{2–4}; increased rates of invasive candidiasis\textsuperscript{5–7}; necrotizing enterocolitis (NEC); late-onset sepsis (LOS); or death (\textit{Table 1}).\textsuperscript{8–10}

\textsuperscript{a} Division of Pediatric Infectious Disease, Department of Pediatrics, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, USA; \textsuperscript{b} Division of Neonatal/Perinatal Medicine, Department of Pediatrics, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, USA; \textsuperscript{c} Division of Pediatric Infectious Diseases, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago Northwestern University Feinberg School of Medicine, 225 East Chicago Avenue, Box 20, Chicago, Illinois 60611–2605, USA

* Corresponding author. Division of Pediatric Infectious Disease, Department of Pediatrics, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390. \textit{E-mail address:} Joseph.Cantey@UTSouthwestern.edu

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<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Antibiotic Exposure</th>
<th>Adverse Event</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotten et al, 8 2007</td>
<td>5693 ELBW infants in 19 centers (NICHD NRN)</td>
<td>≥5 d of initial empiric therapy despite sterile cultures</td>
<td>NEC or death</td>
<td>1.50 (1.22–1.83)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>NEC</td>
<td>1.34 (1.04–1.73)</td>
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<td>Death</td>
<td>1.86 (1.45–2.39)</td>
</tr>
<tr>
<td>Kuppala et al, 9 2011</td>
<td>365 VLBW infants, 3 centers</td>
<td>≥5 d of initial empiric therapy despite sterile cultures</td>
<td>NEC, LOS, or death</td>
<td>2.66 (1.12–6.30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LOS</td>
<td>2.45 (1.28–4.67)</td>
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<tr>
<td>Cotten et al, 5 2006</td>
<td>3702 ELBW infants in 12 centers (NICHD NRN)</td>
<td>Any receipt of third-generation cephalosporin or carbapenem</td>
<td>Invasive candidiasis</td>
<td>Hazard ratio 1.68</td>
</tr>
<tr>
<td>Saiman et al, 7 2001</td>
<td>370 ELBW infants in 6 centers</td>
<td>Any receipt of third-generation cephalosporin</td>
<td>Candida colonization</td>
<td>1.85 (1.24–2.77)</td>
</tr>
<tr>
<td>Lee et al, 6 2013</td>
<td>530,162 infants &gt;1500 g</td>
<td>Any receipt of third-generation cephalosporin, carbapenems, ticarcillin, or piperacillin</td>
<td>Invasive candidiasis</td>
<td>1.6 (1.10–2.40)</td>
</tr>
<tr>
<td>de Man et al, 4 2000</td>
<td>436 infants in 2 centers</td>
<td>Crossover trial of cefotaxime vs tobramycin for empiric therapy</td>
<td>Colonization with organism resistant to empiric therapy</td>
<td>18.0 (5.6–58.0) for cefotaxime exposure</td>
</tr>
</tbody>
</table>

Abbreviations: ELBW, extremely low birth weight (<1000 g); NICHD NRN, National Institute for Child Health and Human Development Neonatal Research Network.
Alteration of the neonatal microbiome by antibiotic exposure has been suggested as a mechanism for some of these adverse effects. Infants treated with antibiotics experience a decrease in genetic diversity of their microbiome and a surge in Proteobacteria along with a reduction in Firmicutes. Mai and colleagues demonstrated a similar bloom in Proteobacteria within 7 days of an episode of NEC in their case-control study of infants less than 32 weeks’ gestation. Although it is unclear whether altering the concentration of Proteobacteria or Firmicutes plays a causal role, it is becoming clear that changes to the microbiome are associated with an increased risk for NEC. Furthermore, serial genetic analysis of the infant microbiome has shown that the acquisition of resistant bacteria begins at birth and can be driven by systemic antibiotic therapy. These alterations to the infant microbiome can lead to poor outcomes not only for that infant but also other infants in the intensive care unit because of the horizontal transmission of pathogens.

**Diagnostic Challenges**

The predominant challenge to antibiotic stewardship in the NICU is that sepsis in the neonate can present with nonspecific findings, and many of these findings overlap widely with noninfectious causes. A normal physical examination does not exclude bacteremia, and at present there is no combination of laboratory testing with sufficient sensitivity to preclude infection. As a result, there is a very low threshold for neonatologists to obtain cultures and start empiric therapy for clinical signs that could be consistent with sepsis. Clinical signs including apnea, respiratory distress, tachycardia, and temperature instability are not very specific in diagnosing sepsis. Not surprisingly, uninfected infants with respiratory distress syndrome or transient tachypnea of the newborn are frequently treated with empiric antibiotic therapy pending their culture results. Hypotension is another finding that may lead to empiric antibiotic therapy. Up to 20% of infants who are less than 1500 g experience hypotension, a rate tenfold higher than their incidence of sepsis.

**Culture-Negative Sepsis**

A diagnostic dilemma occurs when cultures are sterile but the infant continues to have clinical signs or abnormal laboratory values that could be consistent with sepsis. There are 2 common situations that lead to the treatment of culture-negative sepsis. First, many preterm infants have clinical signs that are caused by their prematurity but are indistinguishable from sepsis, such as respiratory distress and hypotension. These infants are more likely to receive prolonged antibiotic therapy despite sterile cultures. Second, when mothers receive intrapartum antibiotic prophylaxis (IAP), some providers think that such antibiotic therapy might mask a true sepsis episode by making the infant’s blood culture falsely negative. Maternal IAP is highly effective in preventing neonatal sepsis and is intended to ensure that infants have sterile cultures. Therefore, these infants actually are at a lower, not higher, risk for sepsis because of maternal IAP.

The duration of therapy for culture-negative sepsis varies widely between and within centers, and studies have shown that the duration of therapy may not be related to the infant’s clinical findings or risk factors for sepsis. Cordero and Ayers performed a study of 790 infants who were less than 1000 g who received empiric antibiotics for early onset sepsis (EOS) and had sterile blood cultures. The duration of antibiotic therapy did not correlate with the number of risk factors for EOS or Clinical Risk Index in Babies (CRIB-I) scores, a validated severity score for preterm infants. Spitzer and colleagues reported a cohort of 998 term neonates treated for suspected EOS who, by 24 hours of age, were on full feeds and had normal vital signs and sterile blood
cultures. Infants with no risk factors received a median of 3.3 days of antibiotics; infants with 2 or more risk factors received a median of 3.5 days. Despite sterile cultures and no clinical signs of sepsis, greater than 20% of infants in the cohort received 5 or more days of therapy.

Variation in Treatment Duration for Infections

Treatment variation in the NICU persists even if infection is diagnosed. In a study from Liem and colleagues, describing a survey of antibiotic use in the Netherlands, 10 units had 7 different empiric regimens for LOS, 6 for meningitis, and 7 for NEC. Antibiotic use in the highest-volume NICU was almost 3 times higher than the use in the lowest-volume NICU despite similar patient populations. It is clear that centers manage clinical scenarios in a variety of ways. For pneumonia, this problem is exacerbated by the challenge of differentiating pneumonia from other causes of respiratory distress in the newborn in a timely manner. Protocols that use objective risk factors in combination with culture results and clinical course are promising avenues to reduce unnecessary antibiotic use, but caution is warranted in interpreting abnormal laboratory values in the absence of clinical signs. Follow-up radiographs may help differentiate pneumonia from retained lung fluid or surfactant deficiency and allow discontinuation of antibiotic therapy. Once pneumonia is confirmed, there are limited clinical trials evaluating the optimal duration of therapy. One study suggests that 4 days of therapy may be sufficient in infants who are 35 or more weeks’ gestation who are asymptomatic by 48 hours of antibiotic therapy. Further trials are needed to determine the appropriate duration of therapy for preterm infants with pneumonia. Similarly, there is a paucity of treatment-duration studies on NEC, despite the higher inter-rater reliability of the Bell diagnostic criteria. Given the relative frequency of these conditions, multicenter trials to determine appropriate treatment durations are feasible and warranted.

Maternal Chorioamnionitis

Another clinical situation leading to a high volume of antibiotic use is the management of infants born to mothers with chorioamnionitis. Although chorioamnionitis is a clear risk factor for neonatal sepsis, the current recommendation for obtaining a complete blood count and a blood culture and starting empiric antibiotic therapy was developed before the widespread use of IAP. It remains unclear whether a laboratory evaluation with initiation of empiric therapy is warranted in well-appearing infants born to mothers with chorioamnionitis. Because up to 4% of pregnancies are complicated by chorioamnionitis, upwards of 150,000 infants a year in the United States will receive empiric antibiotic therapy that many providers view as controversial. Further data are needed to determine how at risk well-appearing infants are if the mother received appropriate intrapartum antibiotic therapy.

Dosing and Therapeutic Drug Monitoring

Dosing and therapeutic monitoring of antimicrobials in neonates can be difficult. Neonates have both reduced glomerular filtration and tubular secretion compared with older children, and hepatic metabolic activity may vary extensively between preterm and term infants. Even the ideal dosing strategy for vancomycin, an antibiotic invented more than 50 years ago, is unknown in neonates. In 2009, the Infectious Diseases Society of America (IDSA) and the American Society of Health-System Pharmacists recommended serum vancomycin troughs of 15 to 20 mg/L for the treatment of complicated methicillin-resistant Staphylococcus aureus infections (eg, bacteremia, meningitis) in adults. Although studies have demonstrated the need for initial
dosages between 60 and 70 mg/kg/d in hospitalized children, none of these studies included infants less than 2 months of age. Monitoring of therapeutic drug levels can be limited because of concerns of iatrogenic blood loss, which may require red blood cell transfusions, particularly in low birth weight infants.

**Perioperative Prophylaxis**

There is a significant knowledge gap regarding the optimal use of perioperative antibiotic prophylaxis for neonates. There are guidelines recommending one antibiotic agent for no more than 24 hours, or 48 hours for cardiac surgery; but these recommendations have not been extended to neonates. Therefore, many infants continue to receive prolonged perioperative antibiotic prophylaxis, sometimes with multiple agents. For abdominal wall defects, such as gastroschisis or omphalocele, some surgeons recommend antibiotic prophylaxis until closure, which is often delayed. Even less is known regarding the optimal approach to infants undergoing extracorporeal membranous oxygenation (ECMO); a recent survey of ECMO centers revealed tremendous variation in the use of antibiotic prophylaxis before or during cannulation as well as in the antibiotics used and the duration of prophylaxis. This variation is concerning as there is evidence that prolonged perioperative antibiotics do not prevent surgical site infections but may increase the risk of drug-resistant infections.

**ESSENTIAL PARTICIPANTS**

**The Antimicrobial Stewardship Team**

In their 2007 guidelines, The IDSA and the Pediatric Infectious Diseases Society of America recommended creation of a multidisciplinary, interprofessional antimicrobial stewardship team for developing and implementing interventions in health care institutions. Although the members may vary by the size and resources of the institution, the authors recommend that key members of the NICU antibiotic stewardship team should include a neonatologist, an infectious diseases (ID) physician, a neonatal or ID–trained pharmacist, infection preventionists, a bioinformatician, and a neonatal nurse. At smaller community hospitals, at minimum the stewardship team should consist of a neonatologist or hospitalist to lead stewardship interventions, a pharmacist to assist in neonatal dosing and drug monitoring, and a nurse or nurse practitioner for education and implementation.

**Role of the Neonatologist**

When few guidelines exist to guide antibiotic use, clinicians may be more likely to be influenced by institutional protocols or their fellow neonatologists. Neonatologists may be more receptive to implementing changes in their practice if advocated by a well-respected peer rather than ID doctors or pharmacists. The neonatologist on the antibiotic stewardship team can help determine which stewardship metrics are meaningful to their peers and which interventions are preferred. He or she can coordinate with the NICU leadership to present data at division meetings and conferences. Ultimately, for stewardship efforts to be sustained, a paradigm shift is necessary from an ID physician restricting antibiotic use to the NICU and stewardship teams leading efforts to improve antibiotic use. This point is especially true in resource-limited settings, where the stewardship ID physician has other responsibilities, such as clinical care and infection control.

**Other Participants**

A bioinformatician can build computerized order entry tools that include dosing recommendations for gestational age and updated chronologic age and weight. Alerts
can be created for renal dysfunction, trends in inflammatory markers, and cultures positive for MDROs.\textsuperscript{52} Neonatal nurses regularly identify subtle symptoms or vital sign changes that indicate a new-onset infection or adverse events while on antibiotic therapy. Communication with the neonatal nurse is critical to determine whether the infants’ clinical changes are isolated and potentially related to noninfectious causes or are persistent or worsening, suggesting a new or evolving infection. Antibiotic stewardship policies, particularly those involving the collection of diagnostic blood cultures or other blood samples, should, therefore, involve nurses’ input. Microbiologists can assist in the review of institutional clinical microbiological data to guide empiric antibiotic recommendations for pathogens specific to the NICU.

**MANAGEMENT STRATEGIES**

A comprehensive approach to antibiotic use in the NICU, including accurate measurement of antibiotic use, improvement in diagnostic techniques, rational selection of empiric therapy, and continual re-evaluation and de-escalation or discontinuation when appropriate, is imperative to optimize clinical outcomes while minimizing the unintended consequences of antibiotic therapy.\textsuperscript{50}

**Measuring Antibiotic Use**

Accurate measurement of antibiotic utilization is vital to identify targets of antibiotic stewardship, establish utilization benchmarks amongst institutions, and measure progress of stewardship interventions. Days of therapy (DOTs) is a commonly used metric in pediatrics and reflects total days of antimicrobial therapy administered, irrespective of dosing by weight or renal function.\textsuperscript{50,53–55} DOTs are often adjusted for 1000 patient-days of hospitalization allowing benchmarking between children’s hospitals.\textsuperscript{56} Some considerations must be kept in mind when measuring antibiotic use with DOTs in the NICU setting. First, preterm infants may receive antibiotics in intervals less frequently than every 24 hours (e.g., gentamicin may be administered as infrequently as every 48 hours); thus, DOTs may underestimate true antibiotic exposure. Second, preterm infants are likely to require prolonged hospitalization for nutritional support, with a decreasing requirement for antibiotic use as they approach term weight. Thus, the use of patient-days as a denominator to compare DOTs between institutions may be difficult if the proportions of preterm infants differ substantially. Finally, DOTs cannot measure antibiotic use at referring institutions. Although this is a general limitation with antibiotic stewardship metrics, it is particularly relevant for free-standing children’s hospitals where most infants may be transferred from other institutions. Table 2 lists potential antibiotic stewardship metrics for the NICU.

**Adjudicating Antibiotic Use**

The measurement of appropriate and inappropriate antibiotic use should be practical and useful to the prescribing neonatologists and should use institutional data when possible. Although some stewardship interventions are readily agreed on between the AS team and prescribing neonatologists (e.g., targeting MDROs effectively), others such as the interpretation of colonization versus true infection and duration of treatment may be more difficult. For areas of disagreement, an initial first step could be to educate the NICU team on their own prescribing practices (e.g., variation in the duration of culture-negative sepsis) to engender a discussion on best practice. It must be kept in mind that rotating on-service neonatologists have different durations of service time; thus, assigning individual responsibility for specific antimicrobial usage may not be possible. Thus, the presentation of the prescribing data as a team effort may be
most useful. Institutional clinical microbiology data should be used to guide the selection of empiric antibiotic therapy. Although the creation of NICU-specific antibiograms may not be possible because of a limited number of infections per genera, instances of a bug-drug mismatch can help determine if existing practices need to be altered. If possible, stratification by age younger than 7 days versus older than 7 days would be helpful as the pathogens and empiric antibiotic regimens differ between these 2 groups. Table 3 lists possible stewardship interventions.

### Maximizing Culture Yields

Procurement of adequate volume of blood for cultures can improve sensitivity. In clinical studies, most infants with sepsis have well more than 5 colony-forming units (CFU) per milliliter in their blood; up to 33% may have more than 1000 CFU/mL. Schelonka

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Useful antimicrobial stewardship metrics for the NICU</th>
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<tr>
<td><strong>Primary Drivers</strong></td>
<td><strong>Secondary Drivers</strong></td>
</tr>
<tr>
<td>Avoid redundant antibiotic use</td>
<td>Reduce concurrent use of antibiotics with anaerobic spectrum of activity</td>
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<tr>
<td>Reduce broad spectrum antibiotic use</td>
<td>Reduce use of broad-spectrum perioperative antibiotic prophylaxis for clean surgical procedures</td>
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<td></td>
<td>Reduce use of vancomycin</td>
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<td></td>
<td>Reduce use of third-generation cephalosporins</td>
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<tr>
<td>Reduce duration of antibiotic use</td>
<td>Avoid prolonged duration of postoperative prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Avoid prolonged duration of culture-negative sepsis</td>
</tr>
<tr>
<td>Avoid inadequate therapy</td>
<td>Reduce episodes of bug-drug mismatch for treatment of late-onset sepsis</td>
</tr>
</tbody>
</table>

### Table 3

Suggestions for stewardship in the NICU

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Examples of Stewardship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Institutional guidelines for obtaining and interpreting respiratory tract cultures, to avoid treatment of colonization</td>
</tr>
<tr>
<td>Empiric therapy</td>
<td>Develop NICU-specific antibiograms for Gram-negative infections as a group</td>
</tr>
<tr>
<td>Dose optimization</td>
<td>Use automated pharmacy alerts to identify infants who are receiving inadequate dosing for suspected meningitis</td>
</tr>
<tr>
<td>Prescriber audit and feedback</td>
<td>Use prospective audit and feedback to identify opportunities to target pathogens in infants with positive cultures</td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>Establish institutional protocols for the duration of treatment of NEC and culture-negative sepsis</td>
</tr>
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</table>
and colleagues demonstrated that inoculation of 1 mL of blood could detect neonatal pathogens at blood concentrations as low as 4 CFU/mL. The most recent American Academy of Pediatrics’ guidelines on the management of neonates with suspected sepsis recommend obtaining a minimum of 1 mL of blood for culture when sepsis is suspected. Audits of blood cultures obtained from NICUs show that the median volume is often less than 1 mL but can be improved with education of the providers responsible for the blood draw. Finally, cultures obtained from nonsterile sites, including endotracheal tubes, should be interpreted with caution to avoid treatment of colonization rather than infection.

**Ancillary Laboratory Tests**

In the absence of a test with sufficient sensitivity to prevent the initiation of antibiotic therapy, investigators have focused on non–culture-based diagnostics as a supplement to culture. The complete blood count and differential has been used in sepsis evaluations for decades, and the negative predictive value of serially normal immature-to-total neutrophil ratios approaches 100% when the blood cultures are sterile. However, the positive predictive value of serial blood counts is poor. Other evaluated biomarkers include C-reactive protein, procalcitonin, and cytokines, such as interleukins 6 and 8. There has been increased interest in developing risk-prediction models that may allow clinicians to withhold antibiotics in the lowest-risk infants, but these models have not been evaluated rigorously and may lack the sensitivity needed for clinicians to feel comfortable withholding antibiotic therapy. Heart rate monitoring as a physiologic predictor of impending sepsis shows promise, although what its effect on antibiotic stewardship will be is unclear. In general, these biomarkers may be able to improve the negative predictive value of a sterile culture; their use in combination with appropriate blood cultures can lead to reduced antibiotic use. The improved accessibility and speed of these tests, including their availability on a point-of-care microarray, may increase their clinical utility and allow further studies on their impact on antibiotic stewardship. Although promising, these tests are at present ancillary at best to appropriately drawn cultures. Making antibiotic decisions based on properly obtained cultures will help to decrease unnecessary or prolonged antibiotic therapy.

**Choosing Empiric Therapy**

Once appropriate cultures are obtained, empiric therapy that covers the most likely pathogens should be initiated. Group B Streptococcus and Enterobacteriaceae, such as Escherichia coli, remain the most common causes of EOS (<7 days of age); other Gram-negative bacilli, Candida spp, and Staphylococcus are additional causes of LOS. A combination of ampicillin and gentamicin remain the appropriate therapy for EOS, despite the increase in ampicillin-resistant pathogens. Third-generation cephalosporins should be avoided in the absence of meningitis because of concerns for resistance and increased rates of invasive candidiasis, particularly in low birth weight infants.

Appropriate empiric therapy for LOS includes a semisynthetic penicillin, such as oxacillin or nafcillin, in combination with an aminoglycoside. Alternatively, piperacillin-tazobactam or cefepime can be used for Gram-negative coverage, especially in infants known to be colonized with resistant Gram-negative organisms. Whether these agents are associated with increased rates of invasive candidiasis has not been well studied. Third-generation cephalosporins are best reserved for cases when meningitis is suspected. Coagulase-negative Staphylococcus (CoNS) is not routinely covered by oxacillin or nafcillin, but there is evidence suggesting that
CoNS infection is not associated with increased mortality. Therefore, some units have implemented vancomycin-reduction guidelines (Box 1) that reserve vancomycin use for infants with persistent CoNS bacteremia or those with methicillin-resistant *Staphylococcus aureus* infection.

**Reevaluating Antibiotic Use Once Initiated**

Using the culture results and the infant’s clinical course, providers should continually review the initial antibiotic regimen. Antibiotics should be discontinued if the cultures remain sterile by 48 hours, provided the infant is improved. If a pathogen is recovered, antibiotics should be changed to the narrowest-spectrum agent that has activity against the pathogen and distributes to the infected body site. Failure to narrow or de-escalate therapy based on culture results is one of the most common causes of inappropriate antibiotic use in the NICU. An electronic medical record hard stop is an effective means of reducing inadvertent use of antibiotics beyond 48 hours of sterile cultures.

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**Box 1**

**Vancomycin reduction guideline**

For infants more than 3 days of age with suspected late-onset sepsis, provided that they are not known or suspected to be colonized with methicillin-resistant *Staphylococcus aureus*

1. Obtain blood cultures and consider obtaining cerebrospinal fluid (CSF) culture; obtain adjunctive diagnostic markers (complete blood count with differential, C-reactive protein) at provider discretion

2. Begin therapy with oxacillin (or nafcillin) and gentamicin

3. If the initial cultures are sterile at 48 hours
   a. Consider discontinuing antibiotic therapy.
   b. If the infant is clinically improved and the provider thinks that continued therapy is warranted, continue the current therapy.
   c. If the infant is deteriorating, obtain a second set of blood cultures and consider changing to vancomycin and gentamicin empirically.
   d. If the second set of blood cultures is sterile at 48 hours, again consider discontinuing antibiotic therapy.

4. If the initial cultures grow oxacillin-resistant coagulase-negative *Staphylococcus*
   a. Draw a second set of blood cultures, obtain CSF culture if not already collected, and change antibiotic therapy to vancomycin alone. The clinical scenario should guide the duration of therapy.
   b. If the second set of cultures is sterile at 48 hours, consider discontinuing all antibiotics on the basis that initial cultures may represent contamination.
   c. If the second set of cultures also grow oxacillin-resistant coagulase-negative *Staphylococcus*
      i. Verify with microbiology that they are the same species.
      ii. Continue therapy with vancomycin.
      iii. Consider removing indwelling catheters.

AREAS WHERE MORE WORK IS NEEDED

Coordinating Stewardship with Obstetricians

Collaborations with obstetricians are necessary to reduce antibiotic exposure in the perinatal period. Failure to follow antibiotic prophylaxis recommendations during pregnancy may lead to an unnecessary empiric antibiotic during evaluations for sepsis in neonates.\(^8^1\) This practice is particularly concerning for preterm infants as their mothers are less likely to receive IAP than mothers of term infants.\(^8^2\) Even when IAP is initiated, guidelines for the selection of IAP may not be followed. For example, despite the recommendation that pregnant women with penicillin allergies at low risk for anaphylaxis receive cefazolin for IAP,\(^2^3\) Van Dyke and colleagues\(^8^2\) demonstrated that women were more likely to receive clindamycin (70%) than cefazolin (14%), a more efficacious agent. Approximately 15% of invasive group B streptococcus isolates in the United States are resistant to clindamycin.\(^8^3\)

Organizing with Other NICU Quality Efforts

The most important measures to decrease antibiotic use in the NICU may be preventative. Prevention of preterm delivery logically will decrease the amount of antibiotic administered to preterm infants. Administration of progesterone to mothers at risk for recurrent preterm delivery is an encouraging strategy that is currently being evaluated further.\(^8^4\) Within the NICU, adherence to infection-prevention strategies, including hand hygiene and appropriate central line care, will limit horizontal transmission of infectious agents.

Building a Research Infrastructure

Generalizable metrics of antibiotic utilization, readily obtainable from the electronic health record, are necessary for benchmarking between institutions. Multicenter collaborations can provide the number of patients needed to conduct comparative effectiveness studies. Large neonatal clinical databases can be used for comparative effectiveness research.\(^8^5\) Possible areas of investigation include the brief versus prolonged perioperative prophylaxis for prevention of surgical site infections following cardiac surgery, comparison of antimicrobial regimens for the treatment of NEC, and comparison of agents and durations of therapy for EOS and LOS. Reports of adverse events with new antimicrobials can be shared between centers. Pooling of microbiological data can be used to create NICU-specific regional and national antibiograms to guide empiric therapy.

SUMMARY

Neonatologists care for a population at high risk for sepsis who present with very nonspecific signs. Neonates often receive prolonged antibiotic therapy for treatment of culture-negative sepsis. Multidisciplinary collaboration and meaningful antibiotic stewardship metrics for neonatologists are necessary. Key stewardship interventions include collection of appropriate blood cultures, use of ancillary laboratory tests, avoidance of unnecessarily broad empiric therapy, and de-escalation or discontinuation of therapy. Future efforts should include coordinating with other quality-improvement efforts and building a national research infrastructure.

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