Antimicrobial Report

Prospective Surveillance of Antibiotic Use in the Neonatal Intensive Care Unit: Results From the SCOUT Study

Joseph B. Cantey, MD, Phillip S. Wozniak, and Pablo J. Sánchez, MD

Background: Prolonged or unnecessary antibiotic use is associated with adverse outcomes in neonates. Our objectives were to quantify all antibiotic use in a Level-III neonatal intensive care unit and to identify scenarios where their use could be reduced.

Methods: Surveillance and evaluation of all antibiotic use provided to every infant admitted to a Level-III neonatal intensive care unit from 10/3/11 to 11/30/12 was performed. Types of antibiotics, reasons for their initiation, discontinuation and duration, as well as clinical, laboratory and outcome data were recorded. Antibiotic use was quantified by days of therapy (DOT) per 1000 patient-days (PD).

Results: A total of 1607 infants were included. The total antibiotic use was 9165 DOT (343.2 DOT/1000 PD; 5.7 DOT/infant). Seventy-two percent of infants received 1 (43%) or more (29%) courses of antibiotics. Gentamicin (46%), ampicillin (39%) and oxacillin (8%) were the most frequently used agents. Ninety-four percent of antibiotic use (323 DOT/1000 PD) was empiric therapy for suspected infection. Thirty-six percent (216.2 DOT/1000 PD) was empiric therapy for suspected late-onset sepsis (>72 hours of age). Twenty-six percent of all antibiotic use (89.4 DOT/1000 PD) was therapy for ≥5 days despite sterile cultures; pneumonia (16%) and “culture-negative” sepsis (8%) were the major contributors. Five percent (17.4 DOT/1000 PD) of antibiotic use was for culture-proven sepsis, 5% (16.6 DOT/1000 PD) was penicillin prophylaxis for group B Streptococcus and 1% (3.5 DOT/1000 PD) was preprocedural prophylaxis.

Conclusions: Narrow-spectrum therapy accounted for >92% of antibiotic use and would not be monitored by most stewardship programs. Only 5% of antibiotic usage was due to culture-proven infection. Pneumonia and “culture-negative” sepsis were frequent reasons for prolonged therapy; further study of these conditions may allow reduction in treatment duration.

Key Words: neonate, stewardship

Pediatri Infect Dis J 2015;34:267–272

Antimicrobials are the most prescribed medications in neonatal intensive care units (NICUs) in the United States. When used appropriately, antibiotics are life-saving, but their overuse in NICUs has been associated with an increased risk for infection due to multidrug resistant organisms, invasive candidiasis, necrotizing enterocolitis, late-onset sepsis and even death. For this reason, pediatric infectious disease specialists and neonatologists have urged development of antibiotic stewardship programs aimed at reducing overall antibiotic consumption and curtailing their unnecessary use in NICUs. Before such programs can be designed and implemented successfully, prospective surveillance is needed to inform how and why antibiotics are being used locally. Thus, antibiotic stewardship in the NICU will require a thorough understanding of the clinical decisions driving their use. Currently, data regarding why and how antibiotics are used in the NICU is limited to retrospective observational data suggesting that inappropriate or unnecessary antibiotic use may be common. Therefore, the objective of the SCOUT (Surveillance and Correction of Unnecessary Antibiotic Therapy) study was to inform future antibiotic stewardship strategies in a Level-III NICU by (1) performing surveillance and evaluation of all antibiotic use during a 14-month period, (2) determining areas where antibiotic use could be reduced safely and then (3) implementing those interventions and monitoring for safety. The results of the initial surveillance are presented here.

Materials and Methods

Setting and Study Population

The NICU at Parkland Memorial Hospital (PMH, Dallas, TX) is a Level-IIIC, 90-bed, predominantly inborn unit that admits approximately 1400 infants annually. Staffing is provided by 22 neonatologists from the University of Texas Southwestern Medical Center, along with neonatology fellows, neonatal nurse practitioners and pediatric residents. Per protocol, all infants <35 weeks gestation or <2100 g birth weight are admitted to the NICU. Infants born to mothers with prepregnancy diabetes of any class are admitted for 4 hours of observation and glucose monitoring. Infants with surgical conditions are cared for in the NICU before and after surgery; infants with critical heart disease requiring surgical intervention are transferred to Children’s Medical Center Dallas.

Empiric therapy for early-onset sepsis (<72 hours of age) is ampicillin and gentamicin; oxacillin and gentamicin are initiated for suspected late-onset sepsis (<72 hours of age). Since 1997, there has been a vancomycin reduction protocol in the PMH NICU whereby oxacillin is the preferred empiric agent and vancomycin is initiated only if the infant is colonized with methicillin-resistant Staphylococcus aureus or the cultures of normal sterile body sites yield bacteria susceptible only to vancomycin. All infants receive a minimum of 2 blood cultures when evaluated for sepsis, and coagulase-negative Staphylococcus is considered a pathogen only when recovered in ≥2 cultures drawn within 2 days of each other. Third-generation cephalosporin agents are reserved for the treatment of Gram-negative meningitis, while piperacillin–tazobactam is the preferred second agent for complicated Gram-negative infections that do not involve the central nervous system. Decisions regarding specific antimicrobial agents and duration for pneumonia, necrotizing enterocolitis and other clinical scenarios are at the discretion of the attending neonatologist, with pediatric infectious disease consultation available.

Accepted for publication August 8, 2014.
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This work was supported by a Gerber Novice Researcher Award through the Gerber Foundation, #5200762201. The Gerber Foundation had no role in the design or conduct of the study, collection or analysis of data, writing of this manuscript, or in the decision on where to submit the manuscript.
The authors have no other funding or conflicts of interest to disclose.
This study was presented in part at the Pediatric Academic Society Annual Meeting; May 4–7, 2013; Washington, DC.
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ISSN: 0891-3668/15/3403-0267
DOI: 10.1097/INF.0000000000000542

The Pediatric Infectious Disease Journal  • Volume 34, Number 3, March 2015 www.pidj.com  |  267
Antibiotic Surveillance

The 14-month surveillance ran from October 3, 2011 to November 30, 2012 and consisted of 2 periods, 1 prospective and 1 retrospective. We performed prospective surveillance of all antibiotics provided to every infant who was admitted to the PMH NICU from March 1, 2012 to November 30, 2012 (9 months). Each infant’s electronic medical record (EMR) was reviewed; evaluation and analysis of all antibiotic use was continued until discharge. Specifically, the following information was obtained for each antibiotic course: the agent(s) prescribed, including dose and frequency, as well as the reason(s) for its initiation, discontinuation and duration. Pertinent clinical, laboratory, microbiologic and outcome data also were collected. For infants ≤32 weeks gestation, the Clinical Risk Index in Babies-II score was calculated as a marker for severity of illness. Antibiotics initiated after the infant had not received any for >48 hours were considered a new course of therapy. Antibiotics used for surgical prophylaxis always were considered to be a new course. The neonatology faculty and fellows were aware of the study. To control for the observer (Hawthorne) effect, we also performed a retrospective analysis of all antibiotic use from October 3, 2011 to February 29, 2012 (5 months). The start date was selected because on October 2, 2011, the “K” Nursery—a Level-II area staffed by the newborn nursery providers—was closed, and infants who would have been admitted to this nursery subsequently were cared for in the NICU.

At PMH, a combined maternal and neonatal chemoprophylaxis protocol is used for prevention of early-onset group B streptococcal infection. Antibiotic prophylaxis is provided to all women at delivery who have identifiable risk factors, while newborns without clinical signs of infection receive a single intramuscular dose of aqueous penicillin G within 1 hour of birth.

Antibiotic Use

Antibiotic use was calculated using 2 methods, length of therapy (LOT) and days of therapy (DOT). LOT refers to the number of calendar days that an infant received antibiotics, regardless of the number of antibiotics provided. DOT is an aggregate sum of the days of exposure accounting for each antibiotic, and is determined by multiplying the number of antibiotic doses by the dosing interval, then dividing by 24 hours. For example, 6 doses of ampicillin given every 8 hours and 2 doses of gentamicin given every 24 hours equal 2 LOT (2 DOT) and 4 DOT [(6 ampicillin doses × 8 hours/dose + 24 hours) + (2 gentamicin doses × 24 hours/dose + 24 hours) = 4]. Four doses of ampicillin given every 12 hours equal 2 LOT (2 DOT) and 2 DOT (4 ampicillin doses × 12 hours/dose + 24 hours = 2). Intramuscular penicillin for GBS prophylaxis counted for 0.5 DOT (1 dose × 12 hours/dose + 24 hours = 0.5) and was assigned a LOT of 1 day. Antibiotics with dosing intervals of >24 hours due to renal dysfunction or extreme prematurity had the intervening days included [ie, 2 doses of gentamicin given every 48 hours would equal 4 LOT (4 DOT) and 4 DOT (2 gentamicin doses × 48 hours/dose + 24 hours = 4)].

Statistical Analysis

Descriptive analyses, including mean and standard deviation or median and interquartile range as appropriate, were performed to describe the overall and condition-specific prevalence of antibiotic prescribing. Student t, Wilcoxon rank-sum and χ2 tests were used, where appropriate, to compare findings from the prospective and retrospective periods. All tests were 2-tailed, and a P value <0.05 was considered significant. The study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center.

RESULTS

During the 14-month study period, 1607 infants were admitted to the PMH NICU; 593 during the 5-month retrospective period and 1014 during the 9-month prospective period. Data were available on all infants, and there were no meaningful differences between the 2 periods (Table 1). The 1607 infants were administered 1420 antibiotic courses for a total of 9165 DOT [343.2 DOT/1000 patient-days (PD)] and a total LOT of 5215 days (195.3 LOT/1000 PD). All but 4 infants (99.8%) received at least 1 dose of an antibiotic.

Table 1. Demographic and Clinical Features of All Infants (N = 1607) Admitted to the NICU During the Prospective and Retrospective Study Periods

<table>
<thead>
<tr>
<th></th>
<th>Retrospective Period (10/3/12–2/29/12)</th>
<th>Prospective Period (3/1/12–11/30/12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of infants</td>
<td>593</td>
<td>1014</td>
</tr>
<tr>
<td>Admissions/day, mean (SD)</td>
<td>4.0 (1.7)</td>
<td>3.7 (1.8)</td>
</tr>
<tr>
<td>Antibiotic DOT/1000 patient-days</td>
<td>348.2</td>
<td>340.3</td>
</tr>
<tr>
<td>Male (%)</td>
<td>338 (57%)</td>
<td>576 (57%)</td>
</tr>
<tr>
<td>Gestational age, median (IQR) (weeks)</td>
<td>38 (34.5–39.4)</td>
<td>37.4 (34.1–39.1)</td>
</tr>
<tr>
<td>Birth weight, median (IQR) (g)</td>
<td>2960 (2145–3457)</td>
<td>2793 (2070–3435)</td>
</tr>
<tr>
<td>Vaginal delivery, N (%)</td>
<td>289 (49%)</td>
<td>450 (44%)</td>
</tr>
<tr>
<td>Type of gestation, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singleton</td>
<td>528 (89%)</td>
<td>904 (89%)</td>
</tr>
<tr>
<td>Twin</td>
<td>61 (10%)</td>
<td>104 (10%)</td>
</tr>
<tr>
<td>Triplet</td>
<td>0 (0%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Quadruplet</td>
<td>4 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Maternal age, median (IQR) (years)</td>
<td>28 (23–33)</td>
<td>28 (23–34)</td>
</tr>
<tr>
<td>Maternal parity, median (IQR)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
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<tr>
<td>Respiratory distress N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age ≤34 weeks</td>
<td>159 (27%)</td>
<td>324 (32%)</td>
</tr>
<tr>
<td>Infant of a diabetic mother</td>
<td>41 (7%)</td>
<td>90 (9%)</td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>40 (7%)</td>
<td>63 (6%)</td>
</tr>
<tr>
<td>Perinatal depression</td>
<td>34 (6%)</td>
<td>51 (5%)</td>
</tr>
<tr>
<td>Birth weight &lt; 2100 g</td>
<td>28 (5%)</td>
<td>38 (4%)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>25 (4%)</td>
<td>26 (3%)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>11 (2%)</td>
<td>17 (2%)</td>
</tr>
<tr>
<td>Apnea</td>
<td>3 (1%)</td>
<td>13 (1%)</td>
</tr>
<tr>
<td>Temperature instability</td>
<td>6 (1%)</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Other</td>
<td>34 (6%)</td>
<td>57 (6%)</td>
</tr>
<tr>
<td>Preterm, N (%)</td>
<td>248 (42%)</td>
<td>483 (46%)</td>
</tr>
<tr>
<td>24–27 weeks</td>
<td>14 (2%)</td>
<td>32 (3%)</td>
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<tr>
<td>28–31 weeks</td>
<td>40 (7%)</td>
<td>84 (8%)</td>
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<tr>
<td>32–33 weeks</td>
<td>48 (8%)</td>
<td>96 (9%)</td>
</tr>
<tr>
<td>34–36 weeks</td>
<td>145 (24%)</td>
<td>244 (24%)</td>
</tr>
<tr>
<td>CRIB-II score, median (IQR)</td>
<td>5 (3–7)</td>
<td>5 (2–8)</td>
</tr>
</tbody>
</table>

*Mutually exclusive; preterm infants with respiratory distress classified as admitted due to prematurity.

1Infants of mothers with class B diabetes or greater observed for a minimum of 4 hours in NICU.

2For infants ≤32 weeks’ gestation only.

CRIB-II indicates Clinical Risk Index in Babies-II; IQR, interquartile range; SD, standard deviation.
percent (n = 1157) of infants received ≥1 (n = 691, 43% of cohort) or more (n = 466, 29%) courses of antibiotics. The remaining 450 (28%) infants received intramuscular penicillin prophylaxis only. The 4 infants (0.2%) who did not receive antibiotic therapy had critical heart disease and were transferred immediately after birth to the cardiac intensive care unit at Children’s Medical Center Dallas.

In all cases, the indication for antibiotic therapy was clear from review of the EMR. Before the beginning of the study period, the neonatology division had adopted problem-oriented clinical notes. Every infant had a problem list maintained in the EMR, and the diagnosis was detailed in his or her daily progress note. Of the 1420 antibiotic courses, 1116 (79%) were initiated within 72 hours of birth due to concern for early-onset sepsis. The remaining courses were initiated at ≥72 hours of age for suspected late-onset sepsis (21%) or for perioperative prophylaxis (0.2%). Gentamicin, ampicillin and oxacillin accounted for 93% of all antibiotic use (Fig. 1). Vancomycin and piperacillin–tazobactam accounted for 1% and 0.7%, respectively, of all antibiotic use. Meropenem (0.13%), cefotaxime (0.05%) and first-generation cephalosporin agents (0.04%) were the least-used antibiotics.

Antibiotic use for specific indications is shown in Figure 2. Ninety-four percent of all antibiotic use (323 DOT/1000 PD, 154 LOT/1000 PD) was initiated as empiric therapy for suspected infection. 5% (16.6 DOT/1000 PD, 33.2 LOT/1000 PD) was penicillin prophylaxis for GBS and 1% (3.5 DOT/1000, 4.6 LOT/1000 PD) was perioperative prophylaxis for 49 surgeries on 41 infants. For empiric antibiotic therapy, 5% were for suspected infections that eventually were confirmed by positive cultures (Fig. 3; Gram-negative bacteria, 8.5 DOT/1000 PD; Gram-positive bacteria, 8.7 DOT/1000 PD). All infants treated for coagulase-negative Staphylococcus sepsis had ≥2 positive blood cultures.

The remaining antibiotic use was in infants who had sterile cultures. “Ruled-out” sepsis—situations where cultures were sterile at 48 hours and antibiotics were discontinued—accounted for 63% of all antibiotic use (216.2 DOT/1000 PD, 94.1 LOT/1000 PD). Of these “ruled-out sepsis” courses, 32% were stopped within 48 hours, but 68% were extended beyond 48 hours despite physician documentation of intent to stop therapy. Prolonged (≥25 days) use despite sterile cultures accounted for 26% of all antibiotic use (89.4 DOT/1000, 46.8 LOT/1000 PD). The most frequent reasons for such prolonged therapy were pneumonia (16%) and “culture-negative” sepsis (8%) with length of treatment being ≥7 days in 64% and 69% of cases, respectively.

**DISCUSSION**

Prospective surveillance with intervention and feedback is a core strategy of effective antibiotic stewardship, but it has not been applied rigorously to antibiotic use in the NICU. Despite a growing body of literature on adverse effects associated with prolonged or unnecessary antibiotic therapy in the NICU, there has been little focus on how and how often these antibiotics are used. To our knowledge, this study represents the most comprehensive prospective evaluation of antibiotic use in the NICU. We identified several areas that should inform stewardship efforts and highlight clinical scenarios where further study is needed.

Only a small fraction of antibiotic use in the NICU was directed toward proven infection. Culture-proven sepsis, necrotizing enterocolitis, cellulitis and congenital infections combined to account for <7% of all antibiotic use. Pneumonia represented an additional 16% of all antibiotic use, although a portion of these infants may have had noninfectious conditions such as transient tachypnea of the newborn or respiratory distress syndrome rather than pneumonia. The largest amount of antibiotic therapy was empiric therapy for suspected sepsis (Fig. 2). Accurate identification of septic infants in the NICU remains a challenge, as neonates can present with nonspecific findings that overlap with noninfectious etiologies. Furthermore, at present, there is no combination of clinical findings or laboratory testing that has sufficient sensitivity to preclude the need for empiric therapy. Therefore, stewardship efforts must focus on timely discontinuation of antibiotic therapy once infection is no longer suspected. We observed a high rate of inadvertent continuation of antibiotic therapy beyond 48 hours despite clinicians documenting intent to stop therapy within 48 hours (68% of “ruled-out sepsis” courses). These extra doses accounted for an additional 40.1 DOT/1000 PD (22.3 LOT/1000 PD), or 12% of the total antibiotic use during the study period. A “hard stop,” or automatic discontinuation of empiric therapy at 48 hours by the computerized physician ordering system, may be an effective means of reducing inadvertent continuation of antibiotics, but will require close safety monitoring to prevent inadvertent discontinuation of needed therapy.

![FIGURE 1. Antibiotics used by DOT per 1000 PD.](https://www.pidj.com)
Pneumonia accounted for 16% of all antibiotic use during the study period, and it was the most common indication for prolonged therapy. There was significant variation in the treatment duration of infants diagnosed with pneumonia. The median duration of therapy was 7 days; approximately two thirds of infants received \( \geq 7 \) DOT, while one third received \( \leq 5 \) days. Engle et al\(^7\) performed a small, randomized trial for term infants in the newborn nursery diagnosed with pneumonia. Those who were asymptomatic by 48 hours were randomized to either 4 or 7 days of antibiotic therapy. No difference in short-term outcomes was found. Though small and not generalizable to the NICU, this study provides a basis for further research and validation. Although the diagnosis of neonatal pneumonia remains problematic and challenging, larger clinical trials evaluating the safe minimum duration of therapy for pneumonia could have a significant impact on antibiotic stewardship strategies.

“Culture-negative” sepsis was the second most common indication for prolonged therapy. Similar to pneumonia, approximately two thirds of infants received \( \geq 7 \) DOT, while one third received 5 days. Suspected sepsis remains a challenge in the NICU. The clinical signs that result in the initiation of a sepsis evaluation may be due to problems associated with prematurity rather than infection, and distinguishing the 2 often is difficult.\(^{32,38,39}\) Infants who do not have another explanation for their illness may receive prolonged therapy for suspected sepsis, particularly when cultures are not obtained or are obtained after antibiotic therapy has been initiated. Debate continues on the optimal amount of blood for culture, and whether the lack of a sufficient quantity may preclude identification of a bacterial cause. The sensitivity of blood cultures is not 100%, although it approaches 100% at adequate volumes (\( \geq 1 \) mL).\(^{40}\) Furthermore, infants born to mothers who have received intrapartum antibiotic prophylaxis may be viewed as having falsely negative blood cultures.
Antibiotics in the NICU

Antibiotic stewardship efforts often focus on broad-spectrum antibiotic use. Preauthorization is a key aspect of stewardship and is intended to steer clinicians toward narrow-spectrum antibiotic therapy. However, over 92% of antibiotic use in our study was narrower spectrum therapy (amoxicillin, oxacillin, gentamicin and penicillin) that is not monitored or restricted routinely by antibiotic stewardship programs. Less is known about the potential adverse effects of such narrower spectrum therapy. Although these agents may be viewed as safe by many providers, they may alter the infant’s microbiome and are associated with an increased risk of necrotizing enterocolitis or death in very preterm infants. Further study is needed to determine the short-term and long-term impact that these agents may have on vulnerable neonates.

Our study has several limitations. The optimal metric for antibiotic use in the NICU has not been defined and requires further study. It is not known which metric best represents the degree of antibiotic exposure and thus the impact on the infant’s microbiome. For these reasons, we chose to report both DOT and LOT, although most pediatric antibiotic stewardship efforts use DOT as the main benchmark. In addition, there was a risk for observer effect in the prospective portion of the study, as the neonatologists and fellows were aware of the surveillance. However, there was no significant change in the frequency of antibiotic use between the retrospective period and prospective period, suggesting that any observer effect was minimal. EMR review was performed by 1 study member (J.B.C.), so interrater reliability of the reasons for antibiotic use could not be examined. Finally, our study may not be generalizable to other NICUs, especially those in children’s hospitals where most or all infants are outborn or admitted from the community. Surveillance can guide institution-specific interventions.

In conclusion, prolonged or excessive antibiotic therapy has been associated with a variety of adverse outcomes. Stewardship efforts to minimize unnecessary therapy are needed urgently, but must be informed by appropriate prospective surveillance of antibiotic use. “Ruled-out” sepsis evaluations, pneumonia and “culture-negative” sepsis courses are high-yield targets for antibiotic stewardship interventions; culture-proven infections account for a small fraction of antibiotic use. Focusing on timely discontinuation of therapy once infection is ruled out is as well as evaluating the safe, minimum duration of therapy for common clinical scenarios will help to reduce antibiotic use in the NICU and avoid the adverse outcomes associated with their use. While routine prospective surveillance is time-consuming and may not be practical for all centers, prospective audit with feedback and interventions is a keystone of good antibiotic stewardship and should be a focus in the NICU.

ACKNOWLEDGMENTS

The authors thank John Gard, PharmD, Melody Bush, RPh, Sara Murreeba, PharmD and Sheeba Tharayil, PharmD, of the PMH NICU pharmacy for their help with the study. Dr. Cantey had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES


