Antibiotic Timing in Neonates With Suspected Hospital-Acquired Infections

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ABSTRACT
There exists general agreement within neonatology that antibiotics should be administered promptly to neonates with possible bacterial sepsis and meningitis. We initiated a series of quality improvement cycles designed to reduce delays in the initiation of antibiotic therapy to less than 2 hours when hospital-acquired infection (HAI) was suspected. All infants in this study were in neonatal intensive care (level II or III) who were started on antibiotics for a suspected HAI (defined as an infection that occurred 72 hours after admission to the NICU) were audited. Through a series of quality improvement cycles, we analyzed sources of delays in the initiation of antibiotic therapy from the time the order was written through administration. In subsequent cycles, we intervened to reduce delays through education, standardize the evaluation process, and develop an online ordering system that streamlined the workflow patterns in the nurseries and pharmacy. Using a prospective cohort design, we compared antibiotic delivery times after each process improvement cycle. Antibiotic delivery time was reduced from a median of 137.5 minutes to 75 minutes and variation of practice was reduced in terms of standard deviation and range ($P < .001$). The use of computerized physician order entry significantly improved the writing of STAT orders ($P < .0001$). A systematic analysis of workflow patterns and efficiencies, coupled with improvement cycles targeting delays and development of a computerized physician order entry system, allowed us to improve antibiotic delivery time in neonates with suspected HAI in an intensive care nursery system.

Key Words: antibiotics, computerized physician order entry, hospital-acquired infection, infant, neonate, nosocomial sepsis, sepsis, timing, timeliness, very low birth weight

Neonatal infections, especially hospital-acquired infections (HAIs), are a major healthcare concern secondary to high morbidity and mortality in addition to extended length of stay and hospital cost.$^{1,2}$ Neonatal intensive care units (NICUs) have developed extensive preventive strategies to eliminate infection, although rates continue to be as high as 33% in very-low-birth-weight (VLBW) infants ($<1500$ g; range, 17%–24%).$^{3,6}$ Immature, immunocompromised, VLBW infants often have interventions and invasive procedures during their NICU stay, increasing infection rates to 5 times that of hospitalized older children.$^{7,8}$ Premature and ill neonates are susceptible to infection, often presenting with nonspecific, subtle signs that delay the identification and early treatment of their illness. Host defense is compromised with decreased cellular and humoral immunity as well as barrier function. Cellular immunity is diminished
because the neutrophils have a decreased ability to marginate and move into the tissue. Once they get to the area of inflammation and infection, they have a deficient killing capacity. This is even more pronounced in critically ill neonates because they quickly deplete their neutrophil stores, which is compounded by a diminished response of the bone marrow to keep production up. In addition to this, VLBW infants have decreased levels of immunoglobulins. Although they can generate a response to infection, it is decreased. Barrier function is present in neonates but the skin and mucous membranes are fragile and invasive procedures add additional risks. When sepsis is suspected, it can be argued that that treatment must be immediate due to both the immunosuppression and subtle signs. Antibiotics should be started as soon as diagnostic tests are performed.

Once a decision is made to treat an infant for a possible HAI, antibiotics are routinely started as definitive treatment for infections, and it would seem that early antibiotic administration would be better than late treatment. Data regarding improved outcomes with prompt antibiotic administration in neonates are limited, but neonatologists agree that antibiotics should be administered promptly to neonates with possible bacterial sepsis and meningitis. However, the “process of care” that is undertaken to assess, diagnose, or treat an infant with a possible HAI may delay initiation of effective treatment. For example, HAI evaluation usually involves obtaining blood and urine cultures as well as lumbar puncture (L/P). Also, antibiotic administration requires vascular access. These processes can be delayed because of lack of skill by the provider in obtaining a culture, decreased ability to obtain vascular access when perfusion is poor, or the inability to perform an L/P because of the instability of the critically ill neonate. Even under the best circumstances, the workup can take 30 to 45 minutes. In our nurseries, we decided to do a quality improvement initiative for prevention of late-onset sepsis. One part of the assessment was a review of the in-hospital process of sepsis workups for HAIs and antibiotic initiation. Although we did not think we had a problem, this process had not been internally evaluated and we felt this review might reveal opportunities to improve clinical outcomes. Through this process and review of literature, we felt that our antibiotic time could and should be improved.

To our knowledge, Weiner and colleagues are the first to describe parenteral antibiotic timing for infants with early-onset sepsis; identifying barriers to prompt administration; and assessing the effectiveness of subsequent interventions for minimizing barriers to care. The goal of their study was to administer antibiotics within 1 hour of physician orders and within 2 hours of birth, meeting 80% compliance. Antibiotic delivery under these parameters was significantly improved: antibiotics were initiated within 0.9 hours of the order, even if cultures had not yet been obtained, and intramuscular antibiotic administration was used when intravascular access was unavailable. Finally, empiric therapy (ampicillin and gentamicin) was stocked in the NICU.

Antibiotic therapy is the cornerstone of treatment for infections; the influence of delay in antibiotic administration has not been well studied in patients with sepsis. Currently, the only guidelines for management of severe sepsis and septic shock are for pediatric and adult patients. These 2008 international guidelines recommend that blood cultures be drawn before antibiotic initiation and that antibiotics be administered within 1 hour of diagnosis of septic shock or severe sepsis without shock. Although the guidelines note that little direct evidence supports these recommendations, they underscore that patients with sepsis are at high risk of disease progression and antibiotic timing appears to be clearly linked with poor survival, almost 8% to 9% for each hour delayed. These studies are on pediatric and adult populations and do not take into account the immaturity, immunosuppression, and high risk of infection in the VLBW infant. Understanding neonates often present with subtle signs of infection with limited capacity to fight infections has led neonatal providers to start antibiotics before waiting on culture results. The difficulty in determining whether nonspecific signs are an indication of infection often delays the decision to order cultures or other tests means that antibiotic timing may be even more critical in the neonatal population.

After reviewing antibiotic timing for HAIs in our NICU, we found that antibiotic dosing could be as late as 5 to 6 hours after the decision to perform a sepsis evaluation. After reviewing the literature in pediatric and adult patients, understanding the increased morbidity and mortality of neonates who are infected, and reviewing the one study in neonates, we decided that in critical care, a 2-hour window for antibiotic timing should be the standard of care. To investigate what we considered to be a delay in treatment, we conducted a prospective quality improvement study to analyze antibiotic timing in infants evaluated for HAIs. We identified barriers to antibiotic administration and designed interventions to ensure timeliness of antibiotic administration. An initial antibiotic audit tool was developed and a prospective audit completed. This step provided initial data regarding antibiotic timing as well as the potential barriers to antibiotic administration within the 2-hour time frame. The second phase of study included development of a computerized physician order entry (CPOE) system.
Next, a prospective audit tool was developed to measure time intervals including order writing, signing off orders by nursing, transmission to pharmacy, processing and delivery of antibiotics, and administration of the antibiotics (noting time each antibiotic was given). Also, the number of orders written STAT was measured. A baseline audit was completed and the care process was reviewed to examine steps taken from the time a decision was made to perform the sepsis evaluation, until the time of antibiotic administration.

In phase II of the study, a CPOE system was developed. This multidisciplinary approach involved professionals from pharmacy, neonatology, nursing, and information technology. We identified the current workflow involved in preparing orders, transmitting orders to pharmacy, and dispensing medications to the nurseries. We also considered a larger university-wide electronic medical record that is to be implemented in the nurseries in approximately 1 to 2 years, and ensured that our record would be compatible with any future system or workflow. To accomplish this, we created interactive Web-based forms and used electronic means to transfer information to pharmacy (fax to fax server). Throughout the process of development, attention was focused on improved safety through automated calculations, optional pop-up windows with prescribing information, and obligatory warning pop-ups and improved efficiency for both individuals and the system. The system also emphasized ease of use to prevent users from reverting to written order forms rather than the new computerized order entry system.

**Statistical Analysis**

Analysis of variance was used to analyze the difference between the preintervention time period and phases I...
and II of the process improvements for antibiotic timing. The Student t test was used for pairwise comparisons of antibiotic timing among the 3 time periods (baseline, phase I, and phase II); and χ² tests compared proportions of antibiotic orders within 1 and 2 hours of ordering and proportions of STAT orders by the intervention phase. P values were Bonferroni-corrected for multiple comparisons. All statistical tests were performed using SAS statistical software, version 9 (SAS Institute, Inc, Cary, NC). This study was exempt by the Medical University of South Carolina’s institutional review board.

RESULTS

During the 5 years, 551 antibiotic orders were audited for duration from the time the order was written until the time the antibiotic was administered, timeliness (within 1 and 2 hours of order), and whether or not it was ordered STAT.

After collection and analysis of baseline data, barriers to timely administration were identified. In phase I of the intervention, changes in practice were implemented on the basis of the identification of these barriers. Staff education was provided and guidelines were developed to improve antibiotic timing.

Phase I: Obstacles Identified for Timely Administration of Antibiotics

Obstacles to timely administration of antibiotics were categorized as workflow, organizational communication, and work process. Prioritization was recognized as a significant workflow obstacle. Because most evaluations for sepsis were expected to be negative, there was often no sense of urgency among physicians, practitioners, and nurses. For example, a sepsis evaluation was perceived as inconvenient and disruptive to the workflow of rounds, resulting in delays obtaining necessary cultures and writing orders. In some instances, orders were written well before the cultures were drawn, resulting in delivery of antibiotics to the unit but delays in administration. Communication issues were compounded when nurses did not know to look for the antibiotics because they had not been made aware that a decision had been made that the infant under their care was to be examined for sepsis. To address this, all providers were informed that any infant suspected to have an HAI required an immediate workup. This meant that the provider would immediately discuss the plan with the nurse so they could start the process. The orders would be written while the nurses obtained the blood cultures and ensured intravenous access and then the urine and L/P were completed.

Another obstacle was organizational communication. Providers perceived that the pharmacy would regard any intensive care unit antibiotic order as STAT (delivery to unit within 30 minutes of order receipt) as opposed to routine (2-hour goal), which was not the case. To address this in phase I, physicians and neonatal nurse practitioners were to write all antibiotic orders as STAT orders to ensure antibiotics arrived in the NICU within 30 minutes of order receipt. In phase II, this was included in the electronic order form. Timely order writing included decreasing antibiotic administration to within 2 hours for infants suspected of having an HAI. The complete sepsis evaluation was to be completed within 30 minutes of the order.

Another process delay was order transmission to the pharmacy. Initially, providers would write the antibiotic order placing the flagged chart at the bedside. Because nurses were assisting with the sepsis evaluation, faxing of orders to pharmacy could be delayed 20 to 40 minutes. Thus, even STAT orders for antibiotics were delayed arriving in the NICU 50 minutes to more than 1 hour after being written. The new online order system delivered these orders directly to the pharmacy without a time delay.

A fourth problem, delay in antibiotic administration, occurred at 2 points in the process. First, antibiotics were held until the sepsis evaluation was completed. Often nurses would obtain 2 required blood cultures but would then wait on the providers to perform the L/P and urine tap, delaying antibiotics for 1 to 2 hours. To address this, nurses and physicians were instructed to administer the antibiotics within 30 minutes of the medical order even if the workup for infection was not completed, indirectly placing time constraints on the evaluation phase. Next, a pattern emerged for the nursing staff to give the first antibiotic on time, but to schedule the second antibiotic 2 hours later, compromising antibiotic administration, sometimes by 4 to 6 hours. To address this, protocols were developed to permit nurses to give the first 2 antibiotics upon arrival in the NICU and then to administer subsequent doses 1 hour apart.

Phase II: Effect of Online CPOE System

Despite new guidelines and interdisciplinary education to improve practice, compliance remained problematic. An online order system was developed to ensure correct antibiotic dosing calculation, automatic STAT orders, and electronic transmission directly to the pharmacy avoiding any time delay. Order sets encompassing the sepsis evaluation were designed in an effort to make this process more efficient.

There was a significant difference in antibiotic timing when comparing preintervention with phase II online intervention (P < .001). There was also a significant difference in antibiotic timing when comparing phase I (education and guidelines) with phase II online intervention (P < .001). When comparing all antibiotic timing (before intervention and education)
with phase II online intervention, there was a significant difference in overall antibiotic timing with the CPOE system \( (P < .001) \) (Table 2). Most of the orders (88%) were written STAT after the implementation of a CPOE, and there was a significant improvement in STAT orders before and after the online intervention \( (P < .0001) \).

### Antibiotic Timing Before and After Interventions

There was a statistically significant difference in antibiotic timing when comparing baseline with phase I: after education and guideline development with mean time (± standard deviation) from ordering to administration of an antibiotic \( (P < .001) \) (Table 2). Also, time from antibiotic order to administration after initiation of phase II decreased significantly \( (P < .001) \). Thus, marked improvements occurred in antibiotic delivery within 2 hours after each change was made—the proportion of antibiotics delivered within 2 hours nearly doubled from preintervention to phase I \( (P < .001) \) (Table 3). For antibiotic delivery within the 1-hour window, significant improvements were also noted \( (P < .001) \). Moreover, STAT antibiotic orders significantly improved over time \( (P < .001) \) (Table 4). Problems remained with the pharmacy receiving the antibiotic orders in a timely manner after they were written, with a mean time of 25 minutes (range, 0–70 minutes).

### DISCUSSION

Neonatology texts advise that antimicrobial therapy be initiated “immediately” after completion of appropriate diagnostic evaluation.\(^9\) We found no published data describing nursery practices or guidelines regarding the time required to complete neonatal diagnostic evaluation for infection or administer antibiotics, but several studies suggest that prompt antibiotic therapy can improve patient outcomes.\(^9,12,14\)

The Joint Commission established antibiotic administration within 4 hours of hospital arrival as a core measure of quality care for patients with pneumonia; however, in 2007, this was changed to 6 hours.\(^15\) Although definitive data in neonates are lacking, the administration of early antibiotics makes good clinical sense with the killing of the invading organism and the reduction in the likelihood of progression to infection.

### TABLE 2. Median, Mean, Standard Deviation, and Range in Minutes for Antibiotic Timing at Preintervention Phase, Phase I, and Phase II\(^a\)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Median</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before intervention (n = 186)</td>
<td>137.5</td>
<td>150</td>
<td>85.1</td>
<td>0–480</td>
</tr>
<tr>
<td>Phase I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education and guidelines (n = 235)</td>
<td>100</td>
<td>113</td>
<td>70.4</td>
<td>10–380</td>
</tr>
<tr>
<td>Phase II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Online intervention (n = 130)</td>
<td>75</td>
<td>74</td>
<td>43.4</td>
<td>0–190</td>
</tr>
</tbody>
</table>

\(^a\)Analysis of variance, \( P < .001 \).

### TABLE 3. Timeliness of Antibiotic Treatments at Preintervention Phase, Phase I, and Phase II\(^a\)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Within 2 h</th>
<th>Within 1 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before intervention (n = 186)</td>
<td>83</td>
<td>25</td>
</tr>
<tr>
<td>Count</td>
<td>45%</td>
<td>13%</td>
</tr>
<tr>
<td>Percent</td>
<td>66%</td>
<td>26%</td>
</tr>
<tr>
<td>Phase I: Education and guidelines (n = 235)</td>
<td>155</td>
<td>61</td>
</tr>
<tr>
<td>Count</td>
<td>66%</td>
<td>26%</td>
</tr>
<tr>
<td>Phase II: Online intervention (n = 130)</td>
<td>110</td>
<td>60</td>
</tr>
<tr>
<td>Count</td>
<td>85%</td>
<td>46%</td>
</tr>
</tbody>
</table>

\(^a\)Administration within 1 to 2 hours.

\(^b\)\( \chi^2 \) tests.

### TABLE 4. Antibiotic Orders Written for STAT\(^a\)

<table>
<thead>
<tr>
<th>Phase</th>
<th>% Written STAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before intervention (n = 186)</td>
<td>94</td>
</tr>
<tr>
<td>Count</td>
<td>51%</td>
</tr>
<tr>
<td>Phase I: Education and guidelines (n = 235)</td>
<td>169</td>
</tr>
<tr>
<td>Count</td>
<td>72%</td>
</tr>
<tr>
<td>Phase II: Online intervention (n = 130)</td>
<td>114</td>
</tr>
<tr>
<td>Count</td>
<td>88%</td>
</tr>
</tbody>
</table>

\(^a\)Chi-square \( (\chi^2) \) test: \( P < .001 \) (Bonferroni-adjusted).
multisystem organ failure. Delay in treatment allows the infection to continue with an increasing bacterial load. A larger bacterial load might exaggerate the antibiotic-induced cytokine release, resulting in a more dramatic response to bacterial death that can lead to complications and death.

The Institute of Medicine suggests that 1 of 6 broad aims to improve delivery of healthcare is that it be “timely,” which is defined as reducing waits and/or harmful delays for those who receive or give care. To achieve this goal, the process of care must be analyzed and where feasible, new technology implemented to improve this process must be implemented. A delay in treatment in VLBW infants will increase both morbidity and mortality. Therefore, the “timely” administration is essential to prevent a harmful delay. The use of an online antibiotic ordering system streamlined orders to the pharmacy, thus ensuring more rapid delivery to the NICU, so that antibiotics could be started quickly. The pop-up boxes that were embedded in the online system guided the providers and facilitated appropriate antibiotic choices for the patient.

The issues of workflow play a central role in contributing to the improper timing of antibiotics for suspected HAIs. There were time lags between the decision to perform a sepsis workup, completion of the provider evaluation/workup and orders, and antibiotic administration. As hospitals embrace electronic data systems, we must realize that transmission of orders is only one component of efficiency. Attention to workflow remains a priority.

Often ignored but equally relevant is that infants present differently with symptoms of disease than that of children and adults, leading to delays in the initial workup as providers evaluate symptoms as they emerge. Presentation of disease can confound the association of antibiotic timing and survival because the infant’s response to infection may delay a rapid diagnosis and decision to treat. Data from adults demonstrate that appropriate antibiotic timing is a determinant of survival and outcome. The first antibiotic dose should be administered before the infant shows signs of fulminant sepsis or septic shock with associated activation of inflammatory pathways and cytokines.

Timely and appropriate dosing of antibiotics has been shown to decrease mortality rate and reduce the inflammatory response. Adult studies of antibiotic timing in meningitis, pneumonia, and septic shock indicate that early treatment was associated with survival and decreased length of stay. Large studies in adult patients hospitalized with community-acquired pneumonia depict strong associations between the time to first antibiotic dose and length of stay and mortality. Other studies of antibiotic timing in adults with bacterial meningitis have correlated antimicrobial therapy to patient outcomes. Early antibiotic therapy for patients with septic shock should be guideline-driven and considered standard of care as patients with septic shock clearly improve when early antibiotics were part of their treatment strategy. Even modest improvements in timeliness of antibiotic administration are thought to benefit patients.

Because neonates differ from adults in disease presentation, studies of antibiotic choice and timing are needed in this population. Previous emergency department studies of antibiotic timing in suspected pediatric meningitis revealed that antibiotic timing delays were attributed to the diagnostic evaluations needed. The average time for antibiotic administration due to these delays was 2 to 3 hours. Interestingly, no studies in neonates indicate that antibiotic therapy timing is an outcome determinant. Weiner and colleagues found that infants with early-onset sepsis received antimicrobial therapy by an average of 1.4 hours (range, 1.05-1.65 hours), within 2-hour window.

A potential disadvantage of changing antibiotic timing could result if the rapid initiation of antibiotics resulted in administration before completion of the evaluation (especially the lumbar and bladder punctures for culture). In these situations, it is necessary to use clinical judgment in making a decision regarding duration of treatment. At this time, we do not have evidence that suggests that antibiotic therapy duration is prolonged because of uncertainty arising from antibiotic pretreatment. It is essential that we look at the timeliness of care to critically ill newborns. Barriers to rapid care need to be addressed and appropriate interventions taken. In the busy world of healthcare, sometimes we do not acknowledge that daily workload on delay in treatment. Initiation of antimicrobial therapy to infants with potential infection is sometime delayed for hours. Guideline establishment and a CPOE can assist with timely antibiotic administration and additional improvements should include ongoing compliance monitoring with a CPOE system and ensuring that the interdisciplinary team makes the sepsis evaluation a priority over the daily routine.

**CONCLUSIONS**

Our analysis suggests that antibiotic delay is a common but preventable problem in medicine, especially neonatal-perinatal medicine where prompt antibiotic administration for suspected sepsis is critical. Although definitive data to indicate improved outcomes with earlier antibiotic administration are few, efficient antibiotic delivery should be the standard of care in the NICU. Our analysis of obstacles and interventions shows that significant improvements in processes supporting medical interventions are possible through quality analysis and improvement techniques. Our findings may not directly apply to all institutions, but the process is universal,
and integrated teams are instrumental in identifying and solving such errors.

Of note, we accomplished this process even as a CPOE becomes standard nationwide. Our methods were sufficiently flexible to permit future orders in this format, and notes could be converted into a system-compatible format currently initiated within our institution. Thus, this project will be one of several such improvement cycles as a CPOE is implemented, focusing on the user, reducing workload, developing supporting forms that reduce duplication of information entry, and other optimizations.

References