Working to Decrease Sepsis for the Youngest Among Us: An Exploration of Early-Onset Neonatal Sepsis and a Quality Improvement Effort to Improve Timely Antibiotic Administration in the Neonatal Intensive Care Unit

by

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A paper presented to the faculty of The University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master of (Master of Science in) Public Health in the Department of Maternal and Child Health.

Chapel Hill, NC

April 7, 2016

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ABSTRACT

Objectives: To explore the burden of neonatal sepsis and evaluate a quality improvement (QI) project aimed at improving the timing of antibiotics to neonates with suspected sepsis at birth. The goal of the QI project was to identify and minimize barriers to antibiotic administration in an effort to improve overall morbidity and mortality rates.

Methods: A retrospective chart review was conducted over a 7-month period for infants born at UNC Women’s Hospital and admitted to North Carolina Children’s Critical Care Center (NCCC). For each infant, information was collected regarding time from birth to antibiotic order placement, time from order placement to administration of the first and second antibiotics, and time from birth to administration of both antibiotics.

Results: Results were analyzed before and after the June 2015 rollout of a hospital-wide Code Sepsis Initiative. The mean weekly average time from birth to order placement stayed the same throughout the project (51 minutes). Administration time for ampicillin improved (51 to 43 minutes), while the administration time for gentamicin remained the same (59 minutes). This resulted in a decreased difference in time between administration of gentamicin and ampicillin from 17 minutes to 11 minutes respectfully before and after Go-Live. Further, the total time from birth administration of both antibiotics decreased from 122 to 108 minutes overall.

Conclusions: A step-wise, interdisciplinary approach can work to analyze medication administration processes and decrease overall administration time.
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Background

Estimating the global burden of sepsis is difficult due to relatively crude estimates of the condition in developed countries and a virtual lack of data about rates in lesser developed countries (Jawad, Luksic, & Ranfnsson, 2012). Despite difficulty obtaining absolute figures, it is clear that the burden of sepsis is increasing worldwide. According to the Centers for Disease Control and Prevention (CDC), the total number of hospitalizations in the United States for which sepsis was listed as the primary diagnosis rose from 326,000 in 2000 to 816,000 in 2010 (National Center for Health Statistics, 2010). Overall hospitalizations did not increase during the same time period, indicating that sepsis accounted for a greater percentage of hospitalizations.

The World Health Organization (WHO) collects data about Global Burden of Disease (GBD), which indirectly suggest low-income countries are disproportionally affected by sepsis. Only 1 of the top 10 causes of death in high-income countries is categorized as an infectious disease: lower respiratory infections, which kill 31 people per 100,000 (World Health Organization, 2012). In contrast, for low-income countries, infectious diseases account for 5 of the top 10 causes of death: lower respiratory infections, HIV/AIDS, diarrheal diseases, malaria, and tuberculosis, which kill 275 people per 100,000 (World Health Organization, 2012). Because specific numbers on sepsis are not recorded, it is not possible to conclude the percentage of infectious disease deaths due to sepsis. However, given that infection is a necessary precursor to sepsis, the data suggest rates of sepsis are likely significantly higher in low-income countries.
Around the world, infants and children are at increased risk of contracting infectious diseases given their immature immune systems. The WHO estimated that 6.6 million children under the age of 5 died in 2012, with prematurity, pneumonia, birth asphyxia and birth trauma, and diarrheal illnesses being the most common causes of death (World Health Organization, 2012). Ninety-nine percent of these deaths were in low-and-middle-income countries, underscoring the disparity faced by children in lesser developed countries (World Health Organization, 2012). Of the total child deaths, 44% occurred during the neonatal period, which is comprised of the first 28 days after birth (World Health Organization, 2012). While addressing disparities and decreasing the global burden of sepsis is an important public health concern, this paper will explore the clinical challenges of identifying and treating early-onset neonatal sepsis and detail a quality improvement project undertaken by a Level IV neonatal intensive care unit aimed at improving care to this at-risk population.

**Defining the Problem**

Neonatal sepsis is broadly defined as a systemic infection occurring in infants within the first 28 days of life (Edwards MS, 2004). It is often divided into early-onset sepsis (EOS) and late-onset sepsis (LOS) based upon infant age at the time infection begins. EOS is generally accepted as occurring within the first 3 days of life, while LOS typically occurs after day 3 of life. The distinction becomes clinically important when attempting to determine the cause of sepsis, as differing pathogens are more likely to cause infection in EOS and LOS. While the causative agent of EOS is typically
transmitted from the mother, LOS is more likely to be caused by a hospital-acquired pathogen.

Early-onset sepsis is most often caused by pathogens from the maternal environment with the infant being exposed either in utero or during passage through the birth canal. In term infants *Group B Streptococcus* (GBS) is the most common cause of EOS, while *Escherichia coli* (*E. coli*) is the most common cause of EOS in preterm infants (Stoll BJ H. N., 2011). Screening protocols for identification and treatment of *Group B Streptococcus* (GBS) have significantly decreased the incidence of GBS sepsis (van den Hoogen A, 2010). A 2000 study by Schrag et al reported a 65% decrease in the incidence of early-onset sepsis between 1993-1998 (Schrag SJ, 2000). In 1996, consensus guidelines were released by the American Academy of Pediatrics, the CDC, and the American College of Obstetricians and Gynecologists calling for treatment of GBS in high-risk pregnant women to reduce spread of the bacteria to newborns (AAP, 1997) (CDC, 1996) (ACOG, 1996). In the Schrag et al study, the steepest decline in GBS sepsis occurred shortly after this prophylactic treatment of mothers became routine practice. During this time, the percentage of EOS secondary to *E. coli* began to increase. One NICU reported that for the first time in 40 years *E. coli* comprised a larger percentage of EOS than did GBS (Bizzaro MJ, 2015). Treatment for *E. coli* sepsis includes administration of antibiotics (primarily ampicillin), however there are no screening methods for identifying and treating mothers at risk of passing *E. coli* to their newborns. The picture of EOS in neonates has changed. With screening and treatment of GBS in pregnant mothers, the bacteria causes fewer cases of EOS. Subsequently, *E. coli* now
accounts for a greater number of EOS cases. Despite sustained decreases in neonatal morbidity from treatment of maternal GBS, EOS continues to be a source of significant morbidity and mortality. Infants diagnosed with neonatal sepsis have an increased risk of death and significant complications including brain damage and neurodevelopmental delays when compared to neonates who do not become septic (Bakhuizen SE, 2014).

**Epidemiology**

Among all infants, the incidence of culture-confirmed EOS is approximately 0.77-0.98 cases per 1000 (Weston EJ, 2011) (Stoll BJ H. N., 2011). However certain groups of infants are at increased risk of developing EOS due to either maternal factors, infant factors, or a combination of both. The most common risk factors are listed below in Table 1.

**Table 1: Maternal and Infant Risk Factors for Neonatal Sepsis**

<table>
<thead>
<tr>
<th>Maternal Risk Factors</th>
<th>Infant Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chorioamnionitis</td>
<td>• Preterm birth</td>
</tr>
<tr>
<td>• Prolonged rupture of membranes &gt;18 hours</td>
<td>• Low birth weight</td>
</tr>
<tr>
<td>• Fever during labor (&gt;38C)</td>
<td>• Congenital anomalies</td>
</tr>
<tr>
<td>• Vaginal colonization with GBS</td>
<td>• Instrument-assisted delivery</td>
</tr>
<tr>
<td>• Procedures during pregnancy</td>
<td>• Apgar score ≤ 6 at 5 minutes</td>
</tr>
</tbody>
</table>

Prematurity and low birth weight are especially important risk factors that significantly increase the chance of developing sepsis in neonates. A neonate is considered premature if it is born prior to completion of 37 weeks gestation. Low birth weight is
defined as less than 2500 grams, regardless of gestational age. Important subcategories relevant to this discussion include very low birth weight (VLBW), which is less than 1500 grams, and extremely low birth weight (ELBW), less than 1000 grams. The incidence of EOS is higher in VLBW infants, with rates reported between 15-19 per 1000 (Stoll BJ H. N., 2005) (Stoll BJ G. T., 1996). Further, while EOS is associated with increased short-term and long-term sequel, these risks are magnified for smaller neonates. A study by the National Institute of Child Health and Human Development Neonatal Research Network showed that ELBW infants who were diagnosed with neonatal sepsis were more likely to suffer neurodevelopmental deficits than those ELBW infants who were not septic (Stoll BJ H. N.-C., 2004).

*Treatment*

The treatment of sepsis requires a complex set of evaluations and clinical decision making far beyond the scope of this paper. Treatment is tailored to individual patients; however, there are mainstays of sepsis management that have been proven to improve morbidity and mortality. The 3rd edition of “Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock” was released in 2012 (Dellinger RP, 2012). This was an update to the 2008 clinical practice guidelines and provides evidence-based information for the diagnosis and treatment of sepsis. Guidelines for management of newborn septic shock by the American College of Critical Care Medicine outline goals for the first hour of sepsis treatment (Brierley J, 2009). These goals are: maintain airway, oxygenation, and ventilation; restore and
maintain circulation, correct hypoglycemia and hypocalcemia, begin antibiotics, and begin prostaglandin until ductal-dependent lesion is ruled out (Brierley J, 2009).

Quality Improvement Project

Objective

The objective of the quality improvement (QI) project was to identify strategies to improve administration of antibiotics to neonates admitted to the neonatal intensive care unit (NICU) directly after birth. This NICU QI project was undertaken as part of larger hospital-wide “Code Sepsis” campaign by UNC Health Care to decrease raw mortality from sepsis 10% by June 2016 as compared to a baseline rate from 2013.

Methods

The quality improvement project took place at North Carolina’s Children’s Hospital’s Newborn Critical Care Center (NCCC), a 58-bed level IV neonatal intensive care unit. The NCCC cares for approximately 800 infants each year. Data were collected retrospectively from the electronic medical record for infants admitted to the NCCC between February 2015 and October 2015. Infants were included in the study if they were admitted to the NICU immediately after birth and were deemed to either be septic at birth or require a “rule-out sepsis” workup upon admission. Infants admitted to the NICU who did not meet these sepsis requirements at birth were not included. Likewise, infants who received antibiotics immediately after birth, but were not admitted to the NICU were not included our analysis. For each neonate, data collected included time and date of birth, time of initial antibiotic order, time of administration of the first antibiotic, and time of administration of the second antibiotic. In addition, the
admission note was reviewed to assess clinical decision making and to clarify discrepancies in data recording. From the information collected, five parameters were calculated for each patient: 1) time from birth to order placement, 2) time from order to administration of the ampicillin, 3) difference between administration of gentamicin and ampicillin, 4) time from order to administration of gentamicin, and 5) time from birth to administration of both antibiotics. QI Macros, an add-on feature of Microsoft Excel, was used to generate control charts to analyze the data.

Results

During the project period, 174 neonates were included over a total of 27 weeks. An interdisciplinary exploration of current antibiotic administration procedures at inception of the project revealed several target areas for improving efficiency. First, providers were not consistently placing the order for antibiotics immediately after birth. Once the order was placed, nurses were not prioritizing administering antibiotics over other medications or tasks. Finally, there was noted to be a delay in pharmacy distribution of antibiotics. Plans were devised to address these three bottlenecks.

Education was provided to nursing staff and providers regarding the importance of prioritizing antibiotic administration during the admission of neonates who were suspected of sepsis. This education occurred on March 13, 2015. The NCCC team also collaborated with pharmacy to improve workflow for the delivery of antibiotics. This new workflow called for a STAT antibiotic order and subsequent phone call to the pediatric pharmacy to alert them to the new STAT order.

Birth to Order Placement
The first parameter in the antibiotic administration pathway is placement of the order. The control chart (Figure 1) shows that with the exception of two weeks (8/23/15 and 8/30/15) the variation observed between the average weekly times in birth to order placement were within the upper and lower control limits, indicating process is stable overall. Starting with the week of 6/7/15, a process change is illustrated on the graph. This is the first week after the Children’s Hospital Go Live of the hospital-wide Code Sepsis initiative. The interval between the upper and lower control limits decreased after that time, however the mean weekly time remained the same (51 minutes) before and after the Go-Live event.

**Figure 1: Control Chart for Birth to Order Placement**

<table>
<thead>
<tr>
<th>Average Time to Antibiotic Order Placement</th>
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<tbody>
<tr>
<td><img src="control_chart.png" alt="" /></td>
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</table>

**Order Placement to Administration of Ampicillin**

Figure 2 shows the control chart for time to administration of ampicillin. With the exception of weeks 9/6/15 and 9/13/15, the process appears stable. The graph indicates a process change the week of 6/7/15, when the Children’s Hospital Go Live of
the hospital-wide Code Sepsis initiative was implemented. After this, there was a
decrease in the upper control limit for the process and a change in the average
administration time from 51 to 43 minutes.

**Figure 2: Control Chart for Time to Administration of Ampicillin**

Order Placement to Administration of Gentamicin

Average time from order to administration of gentamicin was 59 minutes prior
to initiation of the Code Sepsis initiative (6/7/15) and was unchanged after this date.
However, the confidence interval decreased, suggesting tighter control of the overall
process.
Difference between Time of Administration of Gentamicin and Ampicillin

The difference in administration time between gentamicin and ampicillin was calculated in an effort to explore if there was significant delay in administering gentamicin, which is routinely given after ampicillin. Results showed that prior to the Go-Live date of 6/7/15, there was an average of 17 minutes difference between administration of ampicillin and subsequent administration of gentamicin. This decreased to 11 minutes after 6/7/15.
When examining the overall process, there was a decrease in length of time for the entire process after the Go-Live of Code Sepsis (6/7/15) as compared with before the event. The average time from birth to administration of both antibiotics decreased from 122 minutes before 6/7/15 to 108 after.
Discussion

Overall, the results provide a mixed picture. The mean weekly average time from birth to order placement stayed the same throughout the project (51 minutes). Administration time for ampicillin improved (51 to 43 minutes), while the administration time for gentamicin remained the same (59 minutes). This resulted in a decreased difference in time between administration of gentamicin and ampicillin. Further, the total time from birth administration of both antibiotics decreased from 122 to 108 minutes overall.

At the onset of the study, an interdisciplinary team including physicians, nurses, pharmacists, and front desk staff were included in discussions regarding bottlenecks in medication administration. On March 13, 2015 providers and staff underwent relevant education to address identified needs in the medication administration pathway. Physician education reinforced the concept that antibiotics should be ordered STAT on admission when a neonate was considered at risk for sepsis. Nurse education underscored the importance of administering antibiotics prior to other medications or required duties. A new protocol for ordering antibiotics also involved calling pharmacy after placement of a STAT computer order for antibiotics to prompt acknowledgement of the medication order. Further, front desk staff were trained to recognize STAT medication orders arriving from pharmacy and ensure swift delivery of medications to the appropriate location.

Average time to administration of ampicillin decreased from 51 minutes to 43 minutes after the hospital-wide Go-Live of Code Sepsis. As part of the project
education, nurses were instructed to prioritize administration of antibiotics over other tasks. Further, ampicillin storage policy changed, and the medication started being stored in the NICU. This allowed nurses to override the medication order and administer the drug prior to pharmacy acknowledgement.

There was not a significant change in time to administration of gentamicin after the Go-Live event. To assess if pharmacy acknowledgement and release of medication orders served as a bottleneck, we assessed the change in the time differences between administration of gentamicin and ampicillin. Before the Go-Live date, there was an average difference of approximately 17 minutes between administration of the two medications, while afterwards this value decreased to 11 minutes. This indicates the new workflow, which included decreasing the time taken to obtain gentamicin from the pharmacy, helped to improve antibiotic administration time overall. It is unclear, however, why this was the case given the mean time to gentamicin administration remained the same. This may be attributed to a heightened sense among the nurses that both antibiotics need to be given promptly. Continued monitoring of the data and further dissecting the antibiotic administration pathway are necessary to help clarify these findings. Though there are no set guidelines for an acceptable amount of time between administration of the two antibiotics, a suggested target time was less than 10 minutes. Several weeks after the Go-Live event were able to achieve this target.

Perhaps the most important result overall was the decrease in time from birth to administration of both antibiotics. This represents the entirety of the individual processes previously discussed. There was improvement in the overall process from 122
minutes prior to the Go-Live to 108 minutes afterward. Again, because there were only
3 baseline data points, it is somewhat difficult to assess how representative these weeks
were of the actual baseline prior to education of providers and staff. In addition,
consensus regarding target time for administration of antibiotics from birth is unclear.
There is talk of the golden hour after diagnosis of sepsis, however neonates provide
unique challenges in creation of an electronic health record, obtaining access for
administration of antibiotics, and the potential for resuscitation and stabilization prior
to administration of medications. While the mean weekly average of 108 minutes does
not approach the 60 minutes in the golden hour, it does represent a significant
improvement over the 122 minute average prior to the Go-Live event.

Based on observed results during this QI project, changes in practice were
implemented. A provider pocket card was created for physicians detailing the proper
workflow when ordering a septic evaluation for an infant. The steps involved a STAT
order of antibiotics, followed by a call to the pediatric pharmacy to alert them of the
new stat order. Also included on the card were the antibiotics used in a neonatal sepsis
evaluation along with proper dosing guidelines. After several weeks of following these
steps, monitoring of the new process revealed there was no longer a need for a follow-
up phone call to pharmacy. STAT orders placed in the electronic medical record were
quickly acknowledged and acted upon by pharmacy. Efforts are underway with the
electronic medical record to further streamline the order placement process. Currently,
a sepsis evaluation order set is embedded in the NICU admission order set, which is a
lengthy series of admission orders. In the future there will ideally be an option for
providers to complete a more streamlined admission order set for newborns requiring a sepsis evaluation on admission. Important, but less time-sensitive admission orders can be completed in a follow-up separate order set.

Another outcome of this quality improvement project is the Small Baby Protocol. One of the bottlenecks identified in the antibiotic administration pathway occurred despite prompt placement of orders, pharmacy acknowledgement and delivery of medication. There were still delays in administration of medications because line placement conformation was delayed while awaiting x-ray technicians to perform imaging. This was addressed by implementing a text page to the x-ray technician with the placement of a STAT order for a chest x-ray to confirm line placement. This new step in the antibiotic administration pathway was a direct result of undertaking this quality improvement project.

A limitation of a retrospective quality improvement study such as this one is that it can be very difficult to decipher from the electronic medical record the actual course of events that lead to treatment or non-treatment. Particularly in the case of identifying newborns at risk for sepsis, there is a significant amount of clinical decision making left to the individual provider. There is the possibility that some newborns who should have been identified as at risk for sepsis were not labeled as such by the covering provider. Further, because this study took place in a teaching hospital, the plan documented by the fellow may differ from the initial plan documented by the attending in some cases.

Ideally, there would have been a longer period of baseline data prior to the education of providers and staff. Education was administered after only 3 weeks of data
were collected. More information prior to the education intervention may have made it easier to appreciate whether the educational efforts actually worked to improve antibiotic administration times. For this reason, the hospital-wide Go-Live of Code Sepsis served as a process change by which to reassess data. With the adoption of this initiative, there was a push from all stakeholders to decrease mortality from sepsis. While these data suggest a decrease in the amount of time elapsed between birth and administration of both antibiotics necessary for treatment of sepsis in neonates, continued monitoring and evaluation are needed to maintain and continue improvement in the process of antibiotic delivery.

**Conclusion**

Treating sepsis effectively requires more than quickly administering antibiotics. However, efficient administration of antibiotics is a key step in the process of rendering quality care to neonates at risk of sepsis. The results of this study indicate that a stepwise approach to evaluating the process by which antibiotics are administered can help identify areas for improvement.
References


