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Minimizing Antibiotic Exposure In Infants At Risk For Early Onset Sepsis.

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MINIMIZING ANTIBIOTIC EXPOSURE IN INFANTS AT RISK FOR EARLY
ONSET SEPSIS.

A Thesis Presented

by

Rachel Carrie Sooter, RN

to

The Faculty of the Graduate College

of

The University of Vermont

In Partial Fulfillment of the Requirements
for the Degree of Master of Science
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ABSTRACT

Current guidelines published by the Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics (AAP) recommend empiric antibiotics for all neonates born to mothers with a diagnosis of chorioamnionitis due to the risk of early onset sepsis (EOS). EOS is difficult to diagnose due to nonspecific symptoms and a lack of reliable tests, can progress quickly, and is potentially fatal or have neurodevelopmental consequences for survivors.

Antibiotics are frequently prescribed in the hospital and are lifesaving in the setting of a serious infection. Conversely, overuse of antibiotics has potential negative effects to individuals and the population as a whole. Antibiotic resistant infections are a consequence of antibiotic misuse, are costly and difficult to treat, and pose a risk to patients hospitalized.

To examine this problem at The University of Vermont Medical Center (UVMHC) a retrospective chart review was performed. Data on the maternal risk factors associated with EOS were collected in addition to clinical characteristics of their neonates and entered into a neonatal early onset sepsis (NEOS) calculator to determine the specific risk of infection to each infant. Treatment of the infant was compared to the NEOS calculator and CDC recommendations. Using posterior probability to determine a more specific risk profile better targets antibiotic therapy to ensure all infants that need treatment receive it, while reducing the number of infants treated empirically.

UVMHC currently treats 78% of infants according to CDC guidelines. Use of the NEOS calculator would reduce antibiotic treatment to 18% of term neonates born to mothers with a diagnosis of chorioamnionitis. Using a new tool to determine risk of EOS may safely reduce the number of infants receiving antibiotic treatment.

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I would like to dedicate this thesis to the memory of my mother, Joyce Roberts, and my father, Craig Sooter. Neither were able to see me complete this journey in person, but I know they are proud of me.

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CHAPTER 1: INTRODUCTION

1.1. Background and Significance

Early onset sepsis (EOS) is a systemic bacterial infection that affects neonates with onset in the first 72 hours following birth (Polin, 2012; Weston et al., 2011; Cotten, 2015). EOS is among the top 10 causes of neonatal and infant death. Of these cases, 10.9% are fatal, accounting for 390 deaths annually (Weston et al., 2011). Hearing loss, seizures, and neurodevelopmental abnormalities can affect survivors of EOS (Weston et al., 2011). EOS is associated with vertical transmission from the mother to the neonate during delivery from the normal flora of the birth canal or pathologic infection of the amniotic fluid and chorionic membranes, referred to as chorioamnionitis. The most common pathogens of EOS are Group B *streptococcus* (GBS) and *Escherichia coli* (*E. coli*) (Polin, 2012; Bizzarro et al., 2015).

Risk factors for EOS include preterm delivery, maternal GBS colonization, rupture of membranes (ROM) greater than 18 hours, maternal fever, maternal leukocytosis, maternal tachycardia, uterine tenderness, foul odor of amniotic fluid, or a formal diagnosis of chorioamnionitis. Chorioamnionitis alone is a major risk factor for EOS and is associated with a two to three fold increased risk to the term neonate (Mukhopadhyay & Puopolo, 2012). The Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics (AAP) both recommend that 100% of neonates born to a mother with a diagnosis of chorioamnionitis be treated empirically with broad spectrum antibiotics for 48 hours pending negative laboratory tests (Benitz et al., 2015; Verani et al., 2010; COFN, 2011).

Using the diagnosis of chorioamnionitis to determine neonatal management is problematic due to a variable definition that does not follow strict criteria in current practice (Benitz et al., 2015). Early studies that linked chorioamnionitis to EOS used strict diagnostic criteria for chorioamnionitis requiring one to two clinical findings in addition to intrapartum maternal fever (Benitz et al., 2015), such as maternal or fetal tachycardia, uterine tenderness, foul odor of the amniotic fluid, or maternal leukocytosis (Verani et al., 2010). Often, in clinical practice, maternal fever is used as a surrogate for the diagnosis of chorioamnionitis (Mukhopadhyay & Puopolo, 2012; Benitz et al., 2015; Malloy, 2014). The rate of culture proven EOS in infants born to mothers with clinical chorioamnionitis was found in several studies to be low; ranging from 0.47 to 1.24% (Jackson et al., 2004; Jackson, Rawiki, Sendelbach, Manning, & Engle, 2012; Kiser, Nawab, McKenna, & Aghai, 2014). Yet, current in treatment guidelines, maternal chorioamnionitis remains a key component of management decisions in term neonates.

Decisions regarding the need for treatment with systemic antibiotics are guided by algorithms published by the CDC (Verani et al., 2010) and have been adopted by the AAP (Polin, 2012; Brady & Polin, 2013). Algorithms are used to assist in timely treatment decisions because an immature immune system at the time of birth and no test that can reliably rule in or rule out EOS makes a definitive diagnosis of EOS difficult. The vague presenting signs and symptoms of EOS may delay treatment initiation and increase disease related mortality (Cotten & Smith, 2013). Subsequently, clinicians may have a low threshold for initiating treatment of suspected EOS based on maternal risk factors (Polin, 2012).

A 40% decline in neonatal EOS cases has been observed following the initiation of universal GBS screening and intrapartum antibiotic prophylaxis (IAP) for GBS positive women (Mukhopadhyay, Eichenwald, & Puopolo, 2013). Benitz et al. (2015) reported an 85% reduction of culture proven GBS sepsis from the early 1990s to 2010 through the adoption of obstetrical prevention strategies of IAP. Current treatment algorithms were developed prior to widespread GBS screening and IAP (Puopolo et al., 2011); a population with a much higher incidence of EOS than the current population. Thus, the algorithms are limited in their ability to precisely determine which neonates would benefit from empiric antibiotic treatment in present day. Despite the decreased incidence of EOS, empiric treatment based on risk factors remains the standard of care (Benitz et al., 2015) and result in antibiotic treatment of large numbers of uninfected newborns (Puopolo et al., 2011)

The use of outdated algorithms overestimates the risk of EOS and leads to overtreatment and unnecessary antibiotic use in neonates (Puopolo et al., 2011). The use of unnecessary antibiotics has been shown to have serious sequelae such as potential toxicities (Kiser, Nawab, McKenna, & Aghai, 2014, Cotten, 2015), development of antibiotic resistant organisms (Smith, M'ikanatha, & Read, 2015), and more recently concerns about the effects on the neonate's developing microbiome (Madan, Farzan, Hibberd, & Karagas, 2012). Further, antibiotics should be used with caution because the long term effects of antibiotics on neonate metabolism and immune programming are not fully understood (Ajslev, Andersen, Gamborg, Sørensen, & Jess, 2011). Kiser et al. (2014) found that infants receiving prolonged antibiotic therapy incur additional invasive

procedures such as lumbar puncture, central and peripheral lines, or umbilical catheterization that lead to longer hospital stays and higher costs. Additionally, there are psychological costs such as disruption of maternal bonding (Escobar et al., 2014).

Puopolo & Escobar et al. (2013) developed a neonatal early onset sepsis (NEOS) calculator that uses the relative contributions of EOS risk factors to develop an individualized infection probability that could decrease the number of neonates who receive empiric antibiotic treatment for EOS. By using recent prevalence data for EOS and the relative contribution of each risk factor, a more precise management strategy is achieved for individual neonates, which has the potential to reduce antibiotic exposure without compromising safety. Shakib et al. (2015) compared current AAP and CDC guidelines to NEOS calculator. Application of the NEOS calculator was estimated to reduce empiric antibiotic use by 65% of the study population (Shakib, Buchi, Smith, & Young, 2015). Further, Escobar et al. (2014) estimated that application of a model, which takes into account the relative risk factors of individual neonates, could reduce antibiotic exposure in 80,000 to 240,000 neonates in the US annually. Adoption of the NEOS calculator and a more precise risk stratification model to treat suspected EOS has the potential to decrease unnecessary antibiotic exposure, reduce health care costs, minimize antibiotic resistance, and lead to better health outcomes for neonates.

1.2. Advanced Practice Nurse Competencies

The following discussion addresses how this thesis fulfills the 2013 advanced practice nurse (APN) competencies (Thomas, 2012). The core competencies of scientific

foundation and practice inquiry are specifically addressed. The scientific foundation competency involves critically analyzing data and using evidence to improve practice. The aim of this thesis is to translate research, observation, and knowledge into practice by applying new practice approaches to a vulnerable population. Observation of a clinical problem paired with physiologic understanding generated the base of the research question. Extensive research allowed for exploration of the current knowledge about the topic and narrowing of the particular question of interest. The practice inquiry competency involves the APN being a leader in the translation of new knowledge into practice. This thesis will apply clinical investigative skills using a systematic chart review to add to the body of knowledge leading to improved health outcomes. Additionally, this research will be presented to hospital staff and submitted for publication that will improve collaboration between disciplines, improve patient outcomes, and advance the role of the APN.

1.3. Purpose

The aim of this study is to determine if the application of a NEOS calculator (Kaiser Permanente, 2015) to generate treatment recommendations would reduce antibiotic exposure of term neonates born to mothers with a diagnosis of chorioamnionitis at an academic medical center in the northeastern United States. A secondary aim is to retrospectively evaluate provider adherence to previously published guidelines for the treatment of neonates born to mothers with chorioamnionitis published by the CDC and adopted by the AAP.

1.4. Hypotheses

The *a priori* hypothesis was that the application of the NEOS calculator would reduce the number of term neonates born to mothers with a diagnosis of chorioamnionitis that receive empiric antibiotics. We hypothesized that there were neonates not managed according to current CDC guidelines in the study population.

1.5. Significance

This study examined a more sophisticated and current EOS management tool to determine if it could reduce empiric antibiotic use while maintaining patient safety and achieve improved patient outcomes. Study results will inform future practice regarding the treatment of EOS and may result in a reduction of empiric antibiotic use in neonates born to mothers with a diagnosis of chorioamnionitis. Further, the findings of this study provide baseline data of antibiotic administration using current treatment guidelines that were in place for the year 2014 at an academic medical center in the northeastern United States. Areas of antibiotic administration that might be improved upon in the neonatal population are reviewed.

The use of antibiotics in the neonatal intensive care unit (NICU) is an area under consideration for quality improvement initiatives through the Vermont Oxford Network (Soll & Edwards, 2015). Study findings will serve as pilot data for a larger, multicenter quality initiative examining the empiric use of antibiotics for suspected EOS treatment.

Through presentation of the research findings clinicians may consider current practice in the context of the most current research and improve antibiotic stewardship.

CHAPTER 2: LITERATURE REVIEW

The following chapter will describe the current literature surrounding antibiotic use in the NICU and opportunities for improvement. EOS is a difficult diagnosis to make clinically or with laboratory tests, so treatment guidelines based on risk factors are used in practice. However, the guidelines were developed prior to the widespread use of IAP that have significantly lowered the rates of EOS compared to when the guidelines were developed. The risk factor that leads to the most broad empiric antibiotic use is the maternal diagnosis of chorioamnionitis. Chorioamnionitis has variable diagnostic criteria that confer a variable amount of risk to neonates. Antibiotic use is not benign with potential long term health consequences to individuals and overuse is a cause of antibiotic resistance. Finally, a new model that uses continuous rather than dichotomized data and the relative contributions of each risk factor is presented and its ability to stratify risk to target empiric therapy to decrease antibiotic use is described.

2.1. Antibiotic Use in the NICU

The most prescribed medication class in American NICUs are antibiotics (Cantey, Wozniak, & Sánchez, 2015; Grohskopf et al., 2005). In a survey of 29 NICUs 43% of patients were receiving antibiotics (Grohskopf et al., 2005). Cantey et al. (2015) found that 72% of neonates in a level three NICU in Texas had one or more courses of antibiotics with an average of 5.7 antibiotic treatment days per neonate. In the study by Cantey et al. (2015) less than 7% of antibiotic use was directed toward proven infection. Antibiotics are frequently used and often unavoidable in the NICU. Neonates have subtle

clinical presentations of infection, are at high risk of infection, and potentially severe outcomes due to infection (Cotten, 2016; Magsarili, Girotto, Bennett, & Nicolau, 2015).

Antibiotic use rates and prescribing patterns vary considerably between NICUs. In a study of 44 French NICUs there was an average of nine different dosing regimens for each of the 41 antibiotics examined (Leroux et al., 2015). During 2013, California NICUs with similar rates of proven infection, mortality, and surgical volume had a 40-fold variation in antibiotic prescribing practice (from 2.4% to 97.1% of patient days) (Schulman et al., 2015). Schulman et al. (2015) concluded that the variation between prescribing practices differed only in how practitioners respond to clinical situations of suspected infection. The discrepancy in antibiotic use rates, without a difference in neonatal outcome supports antibiotic overuse (Schulman et al., 2015) and represents an opportunity for antibiotic stewardship.

The majority of antibiotic use in the NICU is for suspected infection. Only 5% of antibiotic use was for culture proven infection (Cotten, 2016), while 94% was empiric use for suspected infection (Cantey et al., 2015). In a prospective surveillance study of antibiotic use the majority (63%) of all antibiotics during the study period were initiated for suspected EOS that was subsequently ruled out by a sterile blood culture at 48 hours (Cantey et al., 2015). Despite documentation to discontinue antibiotics when the blood culture was negative and infection was no longer clinically suspected antibiotics were inadvertently continued 68% of the time accounting for 12% of total antibiotic use during the study period (Cantey et al., 2015).

Although empiric antibiotics are a component of early initiation of treatment for neonates with culture proven infection, it is not clear how many asymptomatic neonates with negative blood cultures are exposed to unnecessary antibiotics through this practice (Braun, Bromberger, Ho, & Getahun, 2015). Conversely, the potential ramification of decreasing the number neonates who receive empiric antibiotic therapy is the failure to achieve early treatment for true infections (Benitz et al., 2015). The risk of untreated infection needs to be balanced against the potential adverse effects of antibiotic treatment in neonates with sterile blood cultures (Tripathi, Cotten, & Smith, 2012).

2.2. Early Onset Sepsis

2.2.1. Definition and diagnosis. EOS is a systemic bacterial infection that affects neonates in the first 72 hours following birth (Cotten, 2015; Polin & COFN, 2012; Weston et al., 2011). The presentation of EOS varies widely, from clear clinical illness to subtle and nonspecific signs. Any change from a neonate's usual pattern of activity, breathing, or feeding could potentially be an indication of EOS, or could be attributable to the normal transition to extra-uterine life. A definitive diagnosis of EOS is the isolation of a pathogen from the blood stream. However, a blood culture cannot be relied upon for diagnosis because culture confirmed cases represent a small fraction of the EOS burden, and only 5% of all clinically suspected cases are culture confirmed (Weston et al., 2011). A blood culture is an unreliable diagnostic because of high false negative rates resulting from either inadequate blood volume or IAP suppressing bacterial growth in the sample (Escobar et al., 2000). Conversely, a portion of clinical EOS diagnoses include

syndromes that are noninfectious, such as complications of birth and metabolic instability contributing to the difficulty of the EOS diagnosis (Weston et al., 2011).

Clinical signs are the most reliable diagnostic for EOS (92% sensitive and 53% specific) (Escobar et al., 2000). The majority of infants who develop EOS are symptomatic in the first 12 hours of life (Duvoisin, Fischer, Maucort-Boulch, & Giannoni, 2014). A neonate that is asymptomatic during the first 12 hours of life was found to be significantly protective for EOS (mothers with IAP, OR: 0.36 (95% CI 0.14-0.96); mothers without IAP OR: 0.26 (95% CI 0.11-0.63)) (Escobar et al., 2000). The proven infection rate for clinically asymptomatic neonates was 0.9% while the critically ill proven infection rate was 10.0% (Escobar et al., 2000).

Physical exam findings have been shown to be a safe and effective way to reduce the use of antibiotics in neonates suspected to have EOS. In a historically controlled study, Duvoisin et al. (2014) examined an EOS practice change with the aim of reducing the number of diagnostic tests. Their study population was neonates with a gestational age greater than or equal to 35 weeks, risk factors for EOS (inadequate IAP, ROM greater than 18 hours, maternal fever, or less than 37 weeks gestation), and intravenous antibiotic treatment in the first week of life. The authors examined a practice change that neonates were examined every eight hours by providers and vital signs every 4 hours for the first 24 hours of life and every 8 hours for the second 24 hours. This was compared to a standard of care consisting of complete blood count (CBC) with manual differential count and C- reactive protein (CRP) performed in all infants born to mothers with one risk factor and vital signs measured in the same manner. The number of

neonates treated for suspected EOS decreased from 2.1% to 1.7% ($p = 0.09$) after implementing the new protocol and the use of CRP and CBCs were reduced by 91% and 30%, respectively (Duvoisin et al., 2014). The authors found that detection of illness and initiation of antibiotics was effective using direct observation for clinical EOS symptoms. Foregoing traditional blood tests resulted in no differences in duration of hospital stay or proportions of infants needing respiratory or cardiovascular support. Following the author's practice change the first dose of antibiotics was administered 6.2 hours earlier than in the standard of care. The findings suggest that eliminating routine blood tests and enhancing physical exam appears to be safe, results in earlier initiation of treatment, and decreases the number of neonates receiving antibiotics, while eliminating many costly and painful laboratory tests.

Cantoni et al., (2013) also compared physical exam alone to physical exam with laboratory tests in a prospective, sequential, population based study of term infants in north-eastern Italy. The parameters of the standardized physical exam included skin appearance (pink, pale, mottled, or cyanotic), respiratory rate (above or below 60 per minute), and respiratory retractions (yes or no) measured every one to six hours in the first 48 hours of life. Laboratory tests with standardized physical exam did not offer any advantage over standardized physical exam alone (Cantoni, Ronfani, Da Rioli, & Demarini, 2013). In this study antibiotic initiation decreased from 1.2% to 0.5% ($p < 0.001$), and there was a 91% relative reduction in the use of blood cultures (Cantoni et al., 2013). During the study periods there was no difference in need for respiratory support or length of hospital stay. Presence of clinical signs was the most frequently documented

reason for starting antibiotics followed by presence of risk factors and then abnormal CBC or CRP (Cantoni et al., 2013).

2.2.2. Incidence of EOS. Current incidence of EOS is between 0.5 and 1.2 per thousand live births (Escobar et al., 2014). Weston et al. (2011) used state vital records of live birth data to calculate the EOS rate to be 0.77 per thousand live births in 2005, which remained stable at 0.76 per thousand live births in 2008. Weston et al. (2011) demonstrated a disparate disease burden based on race and prematurity. Black preterm neonates had the highest incidence (5.14 per thousand live births) and a fatality rate of 24.4% of cases (Weston et al., 2011). The group with the lowest incidence of EOS was non-black term neonates, 0.40 per thousand live births and fatality rate of 1.6% (Weston et al., 2011). Preterm neonates accounted for 47.3% of all EOS cases and 92.3% of deaths from EOS (Weston et al., 2011). The estimated national burden of culture positive cases was 3320 cases annually (Weston et al., 2011).

Incidence of EOS has declined more than 80% from 1990 to 2008 corresponding to universal screening and treatment for GBS that was first introduced in 1996 and updated in 2002 and 2010 (Cotten, 2015; Weston et al., 2011). Escobar et al. (2000) found that neonates born to mothers treated with IAP were less likely to be symptomatic, need assisted ventilation, or have bacterial infection. Nearly half (48%) of women had at least one dose of antibiotics during labor (Braun et al., 2015). The current treatment guidelines for EOS were developed IAP use was widespread (Cantey & Patel, 2014) therefore neglecting the protective properties of that practice change.

Despite the decreased incidence of EOS empiric treatment of neonates remains high. Although the frequency of neonatal bacterial infection ranges from 0.001 to 0.005%, the percentage of neonates treated with systemic antibiotics is between 4.4 and 10.5% (Escobar et al., 2000). The short term economic burden of caring for neonates with EOS is estimated to be \$700 million in the United States annually (Wynn et al., 2014).

2.2.3. Risk factors for EOS. Perinatal risk factors for EOS are neither sensitive nor specific. Identified risk factors for EOS include preterm delivery, maternal GBS colonization, premature ROM greater than 18 hours, maternal signs of infection: fever greater than 100.4°F (38°C), maternal leukocytosis (total blood leukocyte count greater than 15,000 cells/ μ L), maternal tachycardia (greater than 100 beats per minute), uterine tenderness, foul odor of amniotic fluid, or a diagnosis of chorioamnionitis (Polin & COFN, 2012). Each of the individual risk factors (ROM greater than 24 hours, maternal fever greater than or equal to 38°C, and chorioamnionitis) was found to have poor predictive value for EOS (Flidel-Rimon, Galstyan, Juster-Reicher, Rozin, & Shinwell, 2012). Puopolo et al. (2011) found that EOS risk decreased with gestational ages between 34 and 40 weeks, but after 40 weeks gestation EOS risk increased again. Additionally, EOS risk increased with increasing time of ROM. Risk of EOS had a nearly linear relationship for maternal temperatures between 99.5°F and 100.4°F, with a rapid escalation in risk of EOS in neonates born to mothers with a temperature greater than 100.4°F (Puopolo et al., 2011). The diagnosis of chorioamnionitis is the only risk factor that leads to the treatment of well appearing, term neonates, an otherwise low EOS risk segment of the population.

2.3. Chorioamnionitis

Chorioamnionitis is a complication of labor. The diagnosis implies inflammation or infection of the fetal membranes (Higgins et al., 2016). The term chorioamnionitis encompasses a heterogeneous group of infectious and inflammatory conditions with varying degrees of severity and duration (Higgins et al., 2016). Higgins et al. (2016) argue that the term chorioamnionitis inaccurately implies the presence of infection, is outdated, and overused.

Braun et al. (2015) found that the rate of culture proven EOS was four per thousand live births exposed to chorioamnionitis versus 0.61 per thousand live births in all neonates. Exposure to chorioamnionitis increases the neonatal mortality rate from 0.81 to 1.40 per thousand live births (Malloy, 2014). Exposure to chorioamnionitis had a positive predictive value of 7%, the highest of all maternal risk factors for EOS (Flidel-Rimon et al., 2012). In the 1980s culture proven neonatal EOS for neonates born to mothers with chorioamnionitis was reported to be 80 to 200 per thousand live births (Braun et al., 2015). Through the use of IAP the rate of culture proven EOS has been reduced to between 12 and 30 per thousand live births (Braun et al., 2015). The risk of infection after chorioamnionitis exposure is much higher in preterm neonates (NNT 6 to 21) than neonates with gestational ages equal to or greater than 35 weeks (NNT 80 to 210) (Benitz et al., 2015).

Diagnostic criteria for chorioamnionitis varies widely in practice (Higgins et al., 2016). Strict diagnostic criteria for chorioamnionitis requires one to two additional findings including intrapartum maternal fever (Benitz et al., 2015). Additional criteria for

the diagnosis of chorioamnionitis include maternal or fetal tachycardia, uterine tenderness, foul odor of the amniotic fluid, or maternal leukocytosis (Verani et al., 2010).

The amount of risk conferred to a neonate born to a mother with a diagnosis of chorioamnionitis depends on the criteria utilized at the time of diagnosis. The term chorioamnionitis is imprecise and does not convey the severity of maternal or fetal illness (Higgins et al., 2016). Escobar et al. (2000) used three levels of chorioamnionitis severity to stratify neonatal risk of EOS. Neonatal infection rates increased with more rigorous documentation of chorioamnionitis, infection rate for neonates born to mothers with possible chorioamnionitis was 2.4%, probable chorioamnionitis 2.5%, and definite chorioamnionitis 8.1% (Escobar et al., 2000). Flidel-Rimon et al. (2012) used strict diagnostic criteria of chorioamnionitis plus one additional criteria more than fever to find a positive predictive value for EOS of 7% when exposed to chorioamnionitis. Conversely, using the less rigorous ICD-9 diagnosis criteria, the positive predictive value was only 0.4% (95% CI 0.13 to 0.94) in a study of neonates with greater than or equal to 35 weeks gestation in Southern California (Braun et al., 2015). In a systematic review of 12 studies, the more strict diagnosis criteria of fever plus one additional finding conferred twice the risk of EOS to neonates compared to the diagnosis made on fever alone (OR 4.0, OR 1.9) (Avila et al., 2015).

The antibiotic initiation rate for neonates born to mothers with a diagnosis of chorioamnionitis ranged between 7 to 76% (Braun et al., 2015). The authors hypothesized that these rates reflect a variation of attitudes toward EOS infection risk incurred from a chorioamnionitis diagnosis. The number needed to treat to prevent one

culture proven EOS infection for neonates born to mothers with a formal diagnosis of chorioamnionitis was 249, for fever alone the number need to treat to prevent one case of culture proven EOS infection was 1,707 (Braun et al., 2015). In Malloy's (2014) analysis of birth certificates in 2008, it was estimated it would take treatment of 1785 exposed neonates to chorioamnionitis to prevent one death. The cost of providing care to prevent one death was \$10,424,400 in a level two NICU for administration of IV antibiotics (Malloy, 2014). These figures lead Malloy (2014) to suggest refinement of the guidelines regarding asymptomatic term infants exposed to maternal chorioamnionitis would appear to need some refinement.

The CDC guidelines for neonatal management use maternal fever as a surrogate for a diagnosis of chorioamnionitis (Verani et al., 2010). In clinical practice the diagnosis of chorioamnionitis is made based on maternal fever, either defined as greater than 99.5°F (37.5°C) or 100.4°F (38°C) (Benitz et al., 2015; Malloy, 2014; Mukhopadhyay & Puopolo, 2012).

The use of fever as a marker for chorioamnionitis and subsequent empiric antibiotic treatment for suspected EOS in neonates is flawed. Higgins et al. (2016) posits that maternal fever is not synonymous with chorioamnionitis as not all fevers are infectious in origin. Fever can be caused by ambient temperature, epidural use, dehydration, prostaglandins or other pyrogenic medications. Braun et al. (2015) found that 60% of women with intrapartum fever did not meet an operational definition of chorioamnionitis based on formal diagnostic criteria. Additionally, not all infectious fevers put the neonate at risk as does chorioamnionitis. Maternal fevers may result from

pyelonephritis, gastroenteritis or upper respiratory infection without increasing risk of EOS in the neonate (Higgins et al., 2016).

The common practice of epidural pain control during labor appears to increase risk of maternal fever and may be contributing to the overuse of empiric antibiotics in neonates (Greenwell et al., 2012). As many as 70% of women receive epidural anesthesia during labor (Mukhopadhyay, Eichenwald, & Puopolo, 2013). Greenwell et al. (2012) estimated that more than 90% of fevers during labor are related to epidural use. Intrapartum temperature greater than 100.4°F is more frequent (19.2%) in women who receive epidural analgesia during labor compared to women who do not receive an epidural (2.4%) (Greenwell et al., 2012). Thus, using fever as a marker for chorioamnionitis in women with epidurals may contribute to the overtreatment of EOS in neonates.

Current algorithms for the prevention and treatment of EOS recommend that all neonates born to mothers with a diagnosis of chorioamnionitis be treated empirically with broad spectrum antibiotics for 48 hours until infection can be ruled out. Cantey and Patel (2014) estimated that upwards of 150,000 neonates in the United States receive empiric antibiotics annually based on the diagnosis of maternal chorioamnionitis. There is a low threshold for the clinical diagnosis of chorioamnionitis and subsequent neonatal treatment decisions are not considered in the maternal diagnostic process (Higgins et al., 2016). Reevaluation of the current guidelines centered on the diagnosis of chorioamnionitis is warranted because of its limited predictive ability and imprecise diagnostic criteria (Benitz et al., 2015).

2.4. Treatment Guidelines for EOS

Clinical signs of EOS are nonspecific, and are similar to the symptoms of any inflammatory process and are difficult to differentiate from noninfectious causes such as the normal transition to postnatal life. Because there is no specific finding or test that reliably identifies those with an EOS infection, treatment is broadly recommended to ensure all infected neonates are treated. Such practices lead to treating a significant number of uninfected infants (Taylor & Opel, 2012). New EOS incidence data, more precise data on relative risk of each risk factor, and emerging information about the long term health effects of antibiotics are reasons to reevaluate current treatment approaches (Benitz et al., 2015).

The most recent revision of the CDC guidelines was published in 2010 and recommends that all neonates symptomatic of EOS should have antimicrobial therapy (Verani et al., 2010). Well appearing neonates born to women with a diagnosis of chorioamnionitis are recommended to have empiric antimicrobial therapy (Verani et al., 2010). The 2010 guidelines do not clearly define chorioamnionitis (Puopolo, 2012). The lack of a consistent definition for chorioamnionitis limits the ability of the guidelines to precisely determine which neonates should receive empiric treatment.

Mukhopadhyay et al. (2014) demonstrated that clarification to the definition of inadequate IAP for GBS reduced use of empiric treatment for suspected EOS, without increasing NICU admissions, signs of infection prior to discharge, or incidence of EOS. This retrospective cohort study compared applied the original 2002 and revised 2010 CDC guidelines to a population of neonates with gestational ages greater than or equal to

36 weeks, had a sepsis evaluation in the first 48 hours of life, and were clinically asymptomatic or well-appearing (n = 7226 or 14.7% of all births at the study center). When applying the CDC 2010 guidelines to this sample, there would have been a reduction of empiric antibiotic exposure from 7.24% to 5.21% of all neonates. The decrease in neonates evaluated for EOS because of inadequate IAP (from 25.4% to less than 1%) increased the proportion of well-appearing neonates evaluated for maternal fever (from 70.4% to 93.3%) making exposure to fever the most frequent reason for empiric antibiotic treatment in well appearing neonates. As a more precise definition of inadequate IAP was able to reduce antibiotic exposure, clarification of the risk of EOS conferred to neonates by chorioamnionitis exposure may also be able to safely reduce empiric antibiotic therapy.

The AAP adopted treatment guidelines for suspected or proven EOS in 2012. Polin and the COFN identified three challenges for clinicians; identifying neonates with a high likelihood of EOS and promptly starting antimicrobial therapy; distinguishing high-risk neonates or neonates with clinical signs that should not be treated; and discontinuing antibiotics when sepsis has been ruled out (Polin & COFN, 2012). In this guideline all symptomatic neonates are to be treated. The only asymptomatic neonates with gestational ages greater than 37 weeks that are recommended to receive broad spectrum empiric antibiotic therapy are those born to a mother with a diagnosis of chorioamnionitis (Polin & COFN, 2012). All other neonates greater than 37 weeks gestation with any other risk factor are observed clinically and with laboratory tests before treatment is initiated. All

empiric antibiotic treatment should be discontinued at 48 hours if the blood culture is negative, lab data are normal, and the neonate remains well (Polin & COFN, 2012).

The AAP guideline has also been criticized for not offering a standard definition of chorioamnionitis. As written chorioamnionitis is interchangeable with intrapartum maternal fever, effectively making neonatal treatment decisions based on an imprecise risk profile of maternal fever (Puopolo, 2012). Puopolo (2012) argues that combining all preterm neonates into one group of less than 37 weeks gestation is too broad given the different risks based on gestational age and birth weight. Puopolo (2012) contends that the AAP guidelines take each risk factor for EOS in isolation and fail to consider the relative contribution of each (Puopolo, 2012).

2.5. Consequences of Antibiotic Overuse

When used appropriately antibiotics are life-saving. In the past 75 years antibiotic use has become a crucial component of global health (Laxminarayan et al., 2016; Meropol & Edwards, 2015). Antibiotic use is not benign and has consequences on an individual and population level. (Magsarili et al., 2015; Mukhopadhyay et al., 2013). Antibiotic use contributes to the development of antibiotic resistant pathogens, super-infections, and research demonstrates links between antibiotic exposure and changes to the gut microbiome influencing obesity, asthma, and allergy (Meropol & Edwards, 2015). Antibiotic stewardship positively impacts quality of care, patient safety, clinical outcomes, and resource utilization through monitoring and reducing unnecessary

antibiotic using multi-disciplinary solutions (Goldman & Jackson, 2015; Patel & Saiman, 2010; Yang et al., 2016).

Antibiotic resistance is an emerging and major public health problem that is a direct result of antibiotic overuse and selective pressure (Cotten, 2016; Laxminarayan et al., 2013). Rates of antibiotic resistance are outpacing the discovery and development of new antimicrobials (Magsarili et al., 2015). In a meta-analysis of 243 studies there was a positive association between the rate of antibiotic consumption and the development of antibiotic resistance (Bell, Schellevis, Stobberingh, Goossens, & Pringle, 2014).

Although there is no single solution to antibiotic resistance, one strategy is to remove or reduce the selective pressure of antimicrobial exposure (Holmes et al., 2016). Antibiotic stewardship slows antibiotic resistance through judicious use which decreases selective pressure (Patel & Saiman, 2010). Antibiotic resistance prevention strategies such as antibiotic stewardship are simple, inexpensive, and effective (Cailes, Vergnano, Kortsalioudaki, Heath, & Sharland, 2015).

The NICU has been identified as a site for development and transmission of antibiotic resistant bacteria because of the frequency of empiric antibiotic therapy (Cailes et al., 2015). Additionally, neonates are particularly susceptible to the consequences of resistant infections. Laxminarayan et al. (2016) estimate 214,500 global neonatal deaths annually attributable to resistant pathogens.

The gut microbiome serves several essential roles: competition against the proliferation of pathogens in the gut; metabolic functions of digestion, energy extraction, breakdown of toxins, vitamin synthesis, and ion absorption; stimulating the

differentiation of the epithelial cells of the intestine; and developing immune host tolerance of food antigens (Cotten, 2016; Meropol & Edwards, 2015; Yang et al., 2016). A diverse microbiome has been found to be health protective while low diversity is associated with irritable bowel syndrome, necrotizing enterocolitis, and obesity (Yang et al., 2016).

The human microbiome has a important window of colonization from birth through approximately the first three years of life (Yallapragada, Nash, & Robinson, 2015). The most rapid stage of colonization is in the perinatal period (Meropol & Edwards, 2015; Yallapragada et al., 2015). The composition of the microbiome is influenced by mode of delivery (vaginal or surgical), antibiotic use, and method of feeding (breast fed or bottle fed) (Yang et al., 2016). Vaginal delivery allows for vertical transfer from mother to neonate. Neonates born vaginally have a microbiota that mirror the composition of their mother's. Neonates born via cesarean-section have less diversity in their microbiome and transfer is horizontal from the mother's skin and the environment of the neonate (Meropol & Edwards, 2015; Yang et al., 2016). Antibiotic exposure decreases the diversity of microbiota and delays colonization of commensal flora (Bailey et al., 2014; Li, Wang, & Donovan, 2014; Yang et al., 2016). Formula feeding results in a more diverse microbiome, however it appears to be of an unfavorable makeup with higher tendency for atopy (Yang et al., 2016).

The timing of antibiotic exposure matters. Microbiota of neonates and children are particularly vulnerable to disruption while the adult's microbiome is more stable (Saari, Virta, Sankilampi, Dunkel, & Saxen, 2015; Trasande et al., 2013). Major

taxonomic shifts happen as breast feed neonates are weaned (Meropol & Edwards, 2015), while less dramatic changes are seen in formula fed neonates at weaning (Yang et al., 2016). The major shifts in diet, growth, and the establishment of the microbiome that occur in the first 24 months of life may make individuals more susceptible to the effects of antibiotics during this critical developmental window (Bailey et al., 2014). Yang et al. (2016) identified future research priorities of investigating the critical window of birth through the first years of life, variables that influence colonization patterns, and the makeup of a healthy microbiome.

Obesity. Obesity is a multifactorial condition, and identification of modifiable risk factors is a key to reducing obesity rates (Magsarili et al., 2015). Alterations in the microbiome have been attributed to alterations in metabolism (Yallapragada et al., 2015). Sub-therapeutic doses of antibiotics are used as growth promoters in animal farming (Saari et al., 2015). The microbiome contributes to the energy extracted from the diet so a shift in the composition of the microbiome may lead to altered microbial gene expression and more efficient energy harvest (Saari et al., 2015). In studies of mice it has been found that the timing of antibiotic administration is critical, there is a synergistic effect between antibiotics and diet, and the obese metabolic phenotype can be transferred to germ free mice via the microbiome (Cox et al., 2014).

A study of children in Philadelphia between 2001 and 2009, found that 69% were exposed to antibiotics before 24 months of age (Bailey et al., 2014). When the cohort was analyzed based on age at first antibiotic exposure, there was a greater effect on obesity for earlier exposure, which was significant for broad-spectrum antibiotics

(Bailey et al., 2014). A study of more than 11,000 children in the United Kingdom found that antibiotic exposure in the first six months of life was associated with increased body mass index at 38 months (overweight OR 1.22 at 38 months, $p = 0.029$; Trasande et al., 2013). Trasande et al. concluded that early exposure to antibiotics may have a substantial effect on population health, even if the individual effects are modest. In a cohort of healthy Finnish children, antibiotic exposure was linked to a higher BMI (Saari et al., 2015). There was a significant association between earlier antibiotic exposure (less than six months old) and repeated courses of antibiotics. Bailey et al. (2014) suggested that antibiotic treatment in the first 24 months of life might be a modifiable risk factor for obesity, and treatment guidelines should limit antibiotic recommendations to situations that have clearly demonstrated benefit and efficacy.

Allergy. The microbiome in the gastrointestinal tract functions to help mature the immune system and achieve homeostasis through communication between intestinal epithelium cells and the microbiome (Li, Wang, & Donovan, 2014). Li et al. (2014) hypothesized that an imbalance between immune tolerance and active immune response contributed to allergies and inflammatory bowel disease. The increase in allergic diseases, particularly in industrialized countries, suggests a cause rooted in a western lifestyle. Limited microbial exposure or antibiotic disruption to the microbiome early in life appears to cause dysfunctional development of the immune system. A healthy microbiome promotes balance between immune tolerance and response to help prevent an abnormal immune reaction to benign substances.

Asthma. The dysfunctional immune response and increase in allergies may have a role in the increase of childhood asthma globally. In a nationwide cohort study of American children, antibiotics in the first year of life were associated with transient wheezing (beginning and resolving before age three; OR 2.0; 95% CI 1.9 to 2.2; $p < 0.001$), and persistent asthma (starting before age three and persisting through age four to seven; OR 1.6; 95% CI, 1.5 to 1.7; $p < 0.001$) with a clear dose response (Ong et al., 2014). Five or more courses of antibiotics doubled the odds of persistent asthma (OR 1.9; 95% CI 1.5 to 2.6; $p < 0.001$). Late onset asthma (onset after age three) tends not to be related to allergic causes. In this study late onset asthma was not associated with early antibiotic use, suggesting the association between asthma and antibiotic use is mediated by intestinal microbial disruption and inappropriate immune response. The association of asthma and antibiotics seem to be especially true in children without a family history of asthma (Cotten, 2016).

Antibiotic administration can have effects beyond the direct physiological impacts to the individual and population. Breast feeding is recognized as the optimal feeding method in the first year of life. Mukhopadhyay, Lieberman, Puopolo, Riley, & Johnson (2015) demonstrated a possible unintended consequence of antibiotic initiation. An observational study of mothers intending to breastfeed, whose infants were well appearing at birth, found that breast feeding was delayed and supplementation with formula was increased when neonates were separated from their mothers for EOS evaluation. The authors concluded that the effects of EOS evaluation and treatment could be minimized by attempting breast feeding initiation before separation, or using better

criteria to identify neonates with sufficient risk to warrant evaluation and treatment. This study demonstrates the need to re-examine practices that have been previously considered benign, and recognizes the need to revise potentially disruptive practices.

2.6. Proposed Model to Minimize Antibiotic Exposure in Neonates at Risk for EOS

The NEOS calculator was developed based on initial data from a nested case control study by Puopolo et al. (2011) that used multivariate analyses and split validation to divide a population of infants born at greater than or equal to 34 weeks gestation into high and low risk cohorts based on their maternal intrapartum risk factors. Case subjects had a culture confirmed bacterial infection less than 72 hours of age. Controls were matched through random selection according to birth year and hospital. The incidence of EOS in the entire study population was 0.58 per thousand live births. Through posterior probability calculations it was determined that 6% of the population was high risk (4.2 per thousand live births) and 94% of the population was low risk (0.34 per thousand live births) (Puopolo et al., 2011). Gestational age accounted for 17% of the predictive ability of the NEOS calculator (Puopolo et al., 2011). Highest maternal temperature accounted for 58% of the predictive ability of the model (Puopolo et al., 2011). Highest maternal intrapartum temperature offers the advantage of being an objective measure instead of the subjective and variable diagnosis of chorioamnionitis (Puopolo, 2012).

Escobar et al. (2014) proposed a quantitative risk stratification model of EOS risk for newborns greater than or equal to 34 weeks gestational age based on risk factors. In this model neonates are allocated into three risk categories based on objective data

obtained during delivery; low, medium, and high risk. By evaluating and treating these groups based on a more specific probability of EOS, they propose that clinicians would be better able to guide care and provide treatment to those meeting criteria while avoiding treatment for those that do not require it. In this study the majority (85%) of births met low risk criteria. Low risk infants are recommended to receive routine observation based on the EOS incidence estimated at 0.11 per thousand live births (NNT of 9370). Equivocal presentation accounts for 11% of births. Neonates with an equivocal presentation have an EOS rate of 1.31 per thousand live births and a NNT of 823. These neonates are recommended to be followed closely and have a low threshold for treatment should they become symptomatic or as indicated by abnormal laboratory results. The final group, neonates with clinical illness, account for only 4% of births. These neonates have an EOS rate of 5.57 per thousand live births and NNT of only 180 (Escobar et al., 2014). With these neonates the authors recommend to begin immediate empiric antibiotics pending a negative blood culture. By stratifying risk groups, clinicians are better able to interpret data and determine clinical course of evaluation and treatment for EOS.

Importantly, when applying the NEOS calculator, neonates are evaluated and treated based upon continuous measures and duration of symptoms in contrast to previous models which dichotomize data into symptomatic or asymptomatic, risk factors present or absent (Escobar et al., 2014; Puopolo et al., 2011). Escobar's model is limited in that it only identifies neonates that require evaluation and treatment for EOS, it does not determine what that evaluation and treatment should consist of. Applied nationally, this

model could potentially reduce empiric antibiotic treatment by 80,000 to 240,000 neonates annually (Escobar et al., 2014).

Shakib et al. (2015) applied the NEOS calculator to a population of well appearing neonates born to mothers with chorioamnionitis and gestational age greater than or equal to 34 weeks. There was only one culture proven case of EOS (0.14%) and was recommended to have empiric treatment indicating that the NEOS calculator would not have missed any cases. In this sample use of the NEOS calculator would reduce the portion of neonates receiving empiric antibiotic treatment to only 5% of the population compared to the 62% that were actually treated (Shakib et al., 2015). The authors concluded that use of the NEOS calculator would substantially reduce the number of well-appearing neonates subjected to laboratory testing and empiric antibiotic exposure based on the risk factor of maternal chorioamnionitis.

CHAPTER 3: MANUSCRIPT

Background

Early onset sepsis (EOS) is a systemic bacterial infection that affects neonates with onset in the first 72 hours following birth (Cotten, 2015; Polin & Committee on Fetus and Newborn (COFN), 2012; Weston et al., 2011). Risk factors for EOS include preterm delivery, maternal Group B *Streptococcus* (GBS) colonization, rupture of membranes (ROM) greater than 18 hours, maternal fever, or diagnosis of chorioamnionitis. There is no single test that can reliably rule in or rule out EOS. A definitive diagnosis of EOS is made with a positive blood culture, however blood culture can be unreliable related to high false negative rates from either inadequate volume for testing or intrapartum antibiotic prophylaxis (IAP) use (Escobar et al., 2000). Subsequently, clinicians have a greater index of suspicion for the diagnosis and a low threshold for initiating treatment of suspected EOS in neonates with broad-spectrum antibiotics based on maternal risk factors alone (Polin & COFN, 2012).

Chorioamnionitis is a major risk factor for EOS, associated with a two to three fold increased risk of EOS in term neonates (Mukhopadhyay & Puopolo, 2012). Clinical chorioamnionitis is diagnosed based on maternal signs during labor while histologic chorioamnionitis is diagnosed through microscopic evaluation of the placenta after delivery. Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics (AAP) both recommend that all neonates born to a mother with a diagnosis of chorioamnionitis be treated empirically with broad-spectrum antibiotics for 48 to 72 hours pending laboratory tests (Benitz et al., 2015; COFN, 2011; Verani et al., 2010).

The current CDC and AAP treatment algorithms are based on risk factor thresholds established prior to the widespread use of GBS testing and IAP (Puopolo et al., 2011). Universal GBS screening and IAP have resulted in a 40% (Benitz et al., 2015; Mukhopadhyay, Eichenwald, & Puopolo, 2013) to 85% reduction in incidence of EOS.

Antibiotics have potential adverse sequelae such as toxicities (Cotten, 2015; Kiser et al., 2014), development of antibiotic resistant organisms (Smith et al., 2015), and concerns about the effects on the neonate's developing microbiome (Madan, Farzan, Hibberd, & Karagas, 2012). The long term effects of antibiotics on the physiology of the neonate's metabolism and immune programming are not fully understood leaving much unknown (Ajslev, Andersen, Gamborg, Sørensen, & Jess, 2011). Further, Kiser et al. (2014) found that infants receiving prolonged antibiotic therapy incur additional invasive procedures such as lumbar puncture, central and peripheral lines, or umbilical catheterization that lead to longer hospital stays and higher costs. Additionally, there are psychological costs such as disruption of maternal bonding (Escobar et al., 2014) and delayed initiation of breastfeeding (Mukhopadhyay, Lieberman, Puopolo, Riley, & Johnson, 2015).

In an effort to improve management of neonates who receive empiric antibiotic treatment for EOS, Puopolo and Escobar (2013) developed a Neonatal Early Onset Sepsis (NEOS) calculator that uses the relative contributions of EOS risk factors to compute an individualized risk profile. The NEOS calculator achieves a more precise management strategy for individual neonates by using current epidemiologic data to assess population risk and weighing the relative contribution of continuous data related to risk rather than

dichotomized data. Implementation might reduce unnecessary antibiotic exposure without compromising safety. Shakib, Buchi, Smith, and Young (2015) compared antibiotic use between current guidelines and NEOS calculator. They found a reduction of empiric antibiotic use of 80% between current practice and the recommendations of the NEOS calculator. Further, Escobar et al. (2014) estimated that application of a model that takes into account the relative risk factors of individual neonates could reduce antibiotic exposure by 80,000 to 240,000 neonates in the United States annually. Adoption of the NEOS calculator and risk stratification model to more precisely target empiric treatment for suspected EOS has the potential to decrease unnecessary antibiotic exposure, reduce health care costs, minimize antibiotic resistance, and lead to better health outcomes for neonates.

Using the maternal diagnosis of clinical chorioamnionitis to determine neonatal management can be problematic due to non-standard diagnosis criteria in current practice (Benitz et al., 2015). In clinical practice, maternal fever alone is often used as a surrogate for the diagnosis of chorioamnionitis (Benitz et al., 2015; Malloy, 2014; Mukhopadhyay & Puopolo, 2012). Further, the rate of culture proven EOS in infants born to mothers with clinical chorioamnionitis has been shown to be low; from 0.47% to 1.24% (Jackson et al., 2004, 2012; Kiser et al., 2014). The inconsistent diagnostic criteria for chorioamnionitis and recent studies that indicate a low rate of culture proven EOS in term neonates support the need to reexamine current guidelines for the treatment of EOS in neonates (Benitz et al., 2015; Brady & Polin, 2013; Polin & COFN, 2012).

The purpose of this study was to analyze current practice and apply the NEOS calculator to a population of term neonates born to mothers with a diagnosis of chorioamnionitis at an academic medical center in the northeastern United States. Our hypothesis was that application of the NEOS calculator (Kaiser Permanente, 2015) would reduce the number of neonates that receive empiric antibiotic based on the risk factor of maternal chorioamnionitis as compared to CDC guidelines, and current practice.

Methods

Research Design

A retrospective chart review was conducted to examine risk factors and treatment of EOS in mothers with chorioamnionitis and their neonates at an academic medical center in the northeastern United States. Puopolo et al. (2011) and Escobar et al.'s (2014) NEOS calculator was applied to this data set to examine how an alternative model would perform compared to current guidelines published by the CDC, the AAP, and compared to current practice within the institution.

Inclusion criteria consisted of deliveries at the University of Vermont Medical Center between January 1, 2014 and December 31, 2014 with a maternal diagnosis of intrapartum or post partum chorioamnionitis and neonates with an estimated gestational age greater than or equal to 37 weeks. Exclusion criteria were neonates with congenital anomalies as defined by the Vermont Oxford Network (2013) and multiple gestation.

Definitions

Chorioamnionitis was defined as a diagnosis documented in the maternal or neonatal medical record. Post partum chorioamnionitis was defined as chorioamnionitis diagnosed less than 12 hours following delivery. Broad-spectrum antibiotics were defined as more than one antibiotic agent. Ampicillin or gentamicin alone were also considered broad-spectrum when given to a GBS negative woman. Penicillin or ampicillin alone administered to a GBS positive woman was considered to be a GBS specific antibiotic.

The following definitions are consistent with those used by the NEOS calculator (Escobar et al., 2014). Neonatal clinical illness was defined as a five minute Apgar score of less than five, neonatal encephalopathy, use of vasoactive drugs, clinical seizure, continuous positive airway pressure, high flow nasal cannula, mechanical ventilation outside of the delivery room, or need for supplemental oxygen to maintain saturation greater than 90% for more than two hours.

Equivocal presentation was defined as an single vital sign category documented as abnormal greater than four hours apart, or two vital sign categories each documented as abnormal two hours apart in the first 12 hours of life.

Abnormal vital signs were defined as heart rate greater than or equal to 160 beats per minute, respiratory rate greater than or equal to 60 per minute, temperature instability (greater than 100.4°F or less than 97.5°F), or respiratory distress (grunting, flaring, retractions).

Well appearing neonates were defined as not meeting the criteria for clinical illness or equivocal presentation in the first 12 hours of life. In cases that were not clearly in one clinical category, the neonate was classified into the more severe illness category.

In this study ruled out EOS was defined as neonates who received less than 72 hours (nine doses) of ampicillin under the assumption that the neonate had a reassuring clinical presentation and normal labs at the time antibiotics were discontinued.

Study Procedures

Primary sampling was done by the Medical Center's Institute for Quality. A search was conducted of the electronic health records (EHR) for ICD-9 codes (762.7, 658.40, 658.41, and 658.43) representing both maternal and neonatal diagnoses associated with chorioamnionitis. An additional search was conducted through the OB Net database of maternal discharge summaries using diagnosis or treatment of chorioamnionitis. Mothers and neonates were paired to the corresponding EHR depending on which health record was identified first. The second EHR was reviewed to ensure the dyad met inclusion criteria.

The following data was abstracted from the EHR: estimated gestational age, GBS status (positive, negative, or unknown), highest maternal intrapartum temperature, antibiotic treatment of the mother and neonate (type and length of treatment), Apgar scores at one and five minutes of life, and laboratory testing with results (including complete blood count (CBC), C-reactive protein (CRP), and blood culture (BC)) from the maternal and neonatal charts. Abstracted data was randomly spot verified during manual review of charts by the principal investigator (PI).

Manual chart review was conducted by the PI to collect data from the EHR that were identified by OB Net alone, inclusion and exclusion criteria of all dyads, missing data in the primary data set, duration of membrane rupture before delivery, and clinical presentation of the neonate. ROM was calculated the nearest tenth of an hour based on clinical notes of when ROM occurred relative to delivery time. Antibiotic administration to the mother was categorized according to Puopolo and Escobar's NEOS calculator (Escobar et al., 2014). Clinical presentation was determined using progress notes and documented vital signs in the first 12 hours of life using the criteria described by Escobar et al. (2014). Dyads that did not meet well defined inclusion criteria or clinical presentation underwent a second review by an experienced neonatologist to determine inclusion.

Data were entered into the online NEOS calculator using the CDC national incidence of EOS (0.5/1000 live births) (Kaiser Permanente, 2015). Each neonate's risk of EOS per thousand live births and the treatment recommendations based on clinical presentation were recorded. Institutional review board approval was obtained prior to any study procedures.

Data Analysis

Current practice was compared to Puopolo and Escobar's NEOS calculator recommendations using binomial distribution and paired *t*-tests. McNemar's chi-square test was used to determine significant differences between treatment rates in practice, following strict interpretation of the CDC and AAP algorithms, and following

recommendations from the NEOS calculator. Data was analyzed with IBM SPSS Statistics 23 software, alpha was set *a priori* at the 0.05 level, two-sided.

Results

In 2014, there were 2,255 deliveries at the University of Vermont Medical Center. The overall rate of chorioamnionitis for all gestational ages was 4%. The two sampling methods identified 78 dyads. Six dyads were added to the sample from the OB Net query alone. Of the 11 dyads identified by the Institute for Quality alone, 88% were diagnosed with chorioamnionitis post partum and were included in the final sample. The final sample consisted of 95 paired mother-neonate health records with the diagnosis of chorioamnionitis.

Characteristics of the population entered in the NEOS calculator are included in Table 1. The GBS status of all mothers was known; 22.1% (n = 21) were GBS positive while 77.9% (n = 74) were GBS negative. The majority of women (52.6%, n = 50) did not have IAP or IAP was less than two hours prior to birth. Broad-spectrum antibiotics were given during labor greater than or equal to four hours prior to birth in 20% (n = 19) of deliveries, 8.4% (n = 8) received broad-spectrum antibiotics two to 3.9 hours prior to birth, and 19% (n = 18) had GBS specific antibiotics greater than or equal to two hours prior to birth. Mean length of stay for neonates was 4.1 days (*SD* = 3.7). Blood cultures were obtained in 83.1% (n = 79) of neonates. A single positive result grew staphylococcus at 28 hours and was determined to be contamination.

There were 18 (19%) neonates born to mothers diagnosed with chorioamnionitis who would be treated with antibiotics due to signs of neonatal sepsis (equivocal presentation or clinical illness) according to CDC and AAP guidelines. The remaining 77 (81%) neonates would be treated with antibiotics for chorioamnionitis exposure alone if strictly following the recommendations of the CDC and AAP (Figure 1). Puopolo and Escobar's NEOS calculator recommended empiric antibiotic treatment for 17 neonates (0.18, 95% CI 0.12 to 0.29). 74 of 95 neonates were treated in current practice (0.78, 95% CI 0.69 to 0.85).

Table 2 compares current practice to recommendations of Puopolo and Escobar's NEOS calculator. A total of 34 (35.8%) neonates were managed congruently with the NEOS calculator recommendations; 19 (20.0%) had no empiric treatment and 15 (15.8%) had empiric treatment. There were 59 (62.1%) neonates that the calculator would not recommend empiric treatment who received a total of 568 doses of ampicillin (mean 9.6 doses per neonate, 189 treatment days). They received a total of 194 doses of gentamicin (mean 3.3 doses per neonate, 194 treatment days). There were two (2.2%) neonates that the calculator recommended to treat based on risk factors that were not actually treated.

A safety analysis was done by comparing ampicillin administration stratified by NEOS calculator recommendation (Figure 3). Of the 78 neonates that the calculator recommends no treatment, 62 (79.5%) had less than nine doses of ampicillin and 16 (20.5%) had greater than nine doses of ampicillin. Of the 17 neonates that the calculator recommends empiric antibiotic treatment 9 (52.9%) had fewer than nine doses of ampicillin (including two neonates that did not receive any antibiotic treatment, contrary

to the recommendations of the calculator) and eight (47.1%) had more than nine doses of ampicillin.

Discussion

Our findings suggest that implementation of Puopolo and Escobar's NEOS calculator would result in a 60% reduction in the number of neonates unnecessarily treated with broad-spectrum antibiotics for suspected EOS due to maternal chorioamnionitis. Considering only well appearing neonates, the NEOS calculator recommendations would reduce empiric antibiotic use by 74% over current practice, and 99% over current CDC and AAP guidelines. The human microbiome plays an important role in metabolic and immune functions, as well as endocrine and neural pathways (Yang et al., 2016). Antibiotic use early in life can disrupt colonization decrease diversity of the neonatal microbiome. Research linking antibiotic use to obesity, asthma, and allergies is cause to rethink the threshold for initiating empiric antibiotics in neonates. Between the three major influences on the microbiome (delivery mode, antibiotic exposure, and mode of feeding) (Yang et al., 2016), antibiotic use is the modifiable risk factor most within clinicians' control. Term neonates exposed to the diagnosis of clinical chorioamnionitis may no longer meet the increased risk threshold to treat with empiric antibiotics when examined with Puopolo and Escobar's NEOS calculator.

In a similar study, 65% of well appearing neonates were managed in practice according to CDC and AAP guidelines and the application of Puopolo and Escobar's infection probability calculator would reduce antibiotic treatment to only 12% of

neonates (Shakib et al., 2015). In the study by Shakib et al. (2015) gestational ages greater than or equal to 34 weeks were included. The higher gestational age range in our study may demonstrate the reduced risk of sepsis with increasing gestational age. Additionally, in our study GBS status of all mothers was known whereas Shakib et al. (2015) reported that 62% had unknown GBS status. GBS status and treatment with IAP are protective factors for EOS.

This study examined a population with documented chorioamnionitis that, according to the CDC and AAP treatment algorithms, is at high enough risk to warrant empiric treatment for EOS. The diagnosis of chorioamnionitis is problematic as clinicians do not consistently follow strict diagnostic criteria in clinical practice and the diagnosis of chorioamnionitis does not convey the degree of risk to mother or neonate (Higgins et al., 2016). In practice, intrapartum fever is used as a surrogate for the diagnosis of chorioamnionitis (Higgins et al., 2016). Many of the studies that linked increased risk of EOS to chorioamnionitis used strict diagnostic criteria for chorioamnionitis (Benitz, 2015). We did not examine diagnostic criteria resulting in chorioamnionitis. It is possible that the current algorithms for secondary prevention of EOS are appropriate when the diagnosis of chorioamnionitis is made using strict diagnostic criteria. Until chorioamnionitis is better defined and diagnosed, Puopolo and Escobar's infection probability calculator eliminates one subjective criteria that may lead to antibiotic overtreatment in neonates by using maximum intrapartum temperature as a continuous variable to stratify risk.

Current practice favors overtreatment helping to ensure no cases of EOS are missed due to the potential morbidity and mortality of untreated sepsis. To examine the safety of Puopolo and Escobar's NEOS calculator actual doses of ampicillin were compared to calculator recommendations. The neonates that the calculator would not recommend empiric antibiotic treatment for, but received more than nine doses of ampicillin, are an area of safety concern as missed cases have harmful sequelae if antibiotics are not initiated promptly. If these neonates were treated based on evolving clinical presentation instead of empiric treatment for risk factors, antibiotic stewardship is improved, but there is a possibility of delayed treatment. Clear empiric antibiotic savings come from the neonates that the NEOS calculator would not treat and had less than or equal to nine doses of ampicillin. A quarter of these neonates were not treated at all, which could be case studies for potential outcomes of the NEOS calculator if used in practice. If the neonates who were ruled out for EOS were managed with the NEOS calculator recommendation not to be treated, 42 fewer children would be at risk for the adverse effects of antibiotics and 273 fewer doses of ampicillin would be administered. Reviewing cases that antibiotics were continued for a full course would offer more insight into the clinical reasons antibiotics were continued and examine if there are potential savings by discontinuing empiric treatment appropriately. The neonates that the NEOS calculator recommends to treat had risk factors that warranted empiric antibiotics, but the neonate was well enough at 48 to 72 hours to discontinue treatment. In this group the risk is high enough to justify empiric antibiotic use. The neonates that the NEOS calculator recommends to treat and had greater than nine doses of ampicillin are

conclusively ill. Despite negative blood cultures the risk factors and presentation of the neonate indicated treatment according to the NEOS calculator and in practice treatment was continued. The use of Puopolo and Escobar's infection probability calculator appears to offer antibiotic exposure reduction without compromising safety for neonates.

This study is limited by its homogenous population. Black neonates are disproportionately affected by EOS and have amongst the highest incidence and fatality rates (Weston, 2011). Our study population was predominantly non-black and all term, which has amongst the lowest incidence and fatality rates (Weston, 2011). Although we examined a population least impacted by EOS, perhaps this is a population best targeted for antibiotic reduction. We did not follow neonates after initial discharge. It is not known if there were hospital readmissions for infection or if neonates suffered any adverse outcomes related to antibiotic treatment.

Conclusion

The potential adverse effects of antibiotics demonstrate the need to raise the threshold for initiating treatment. Until there are reliable tests to improve the detection of EOS, algorithms must be relied on to assist management decisions. Puopolo and Escobar's NEOS calculator appears to offer advantages over current models without compromising safety in term neonates. Term neonates (greater than or equal to 37 weeks) are at decreased risk for EOS compared to preterm neonates (Benitz et al., 2015), and therefore appears to be a population that can afford to be observed without empiric antibiotic treatment.

Table 1: Population characteristics. Population characteristics entered into the NEOS calculator.

	Minimum	Maximum	Mean
Estimated Gestational Age	37 weeks	42 weeks 1 day	40 weeks 2 days
Maximum Intrapartum Temperature	97.0°F	102.7°F	100.7°F
Rupture of Membranes	0 hours	77 hours	15.6 hours
Group B <i>Streptococcus</i> Status	Positive: 22.1% (21) Negative: 77.9% (74)		
Intrapartum Antibiotics	Broad spectrum antibiotics > 4 hrs prior to birth: 20% (20) Broad spectrum antibiotics 2-3.9 hrs prior to birth: 8.4% (8) GBS specific antibiotics > 2 hrs prior to birth: 19% (18) No antibiotics or any antibiotics < 2 hrs prior to birth: 52.6% (50)		

		CDC/AAP	Infection Probability Calculator	Actual Treatment	Interpretation
Signs of neonatal sepsis?	Yes	Treat: n = 18	Treat: n = 16	> 9 amp: n = 8	Illness- treatment needed
				< 9 amp: n = 7	Justifiable empiric antibiotics, but sepsis is ruled out
				No antibiotics: n = 1	Sepsis not suspected enough for treatment
				> 9 amp: n = 0	Potential sepsis cases missed by the calculator
No			Do not treat: n = 2	< 9 amp: n = 1	Justifiable empiric antibiotics, but sepsis is ruled out
				No antibiotics: n = 1	Sepsis not suspected enough for treatment
Maternal chorioamnionitis?	Yes	Treat: n = 77	Treat: n = 1	> 9 amp: n = 0	Illness- treatment needed
				< 9 amp: n = 0	Justifiable empiric antibiotics, but sepsis ruled out
				No antibiotics: n = 1	Sepsis not suspected enough for treatment
				> 9 amp: n = 16	Potential sepsis cases missed by the calculator
			Do not treat: n = 76	< 9 amp: n = 42	Sepsis ruled out, potential empiric antibiotics savings
				No antibiotics: n = 18	Sepsis not suspected enough for treatment

Figure 1. Comparison of how each treatment scheme would manage the population.

Table 2. NEOS calculator recommendations.

NEOS calculator recommendations for antibiotics	Actual treatment with antibiotics		
	No treatment	Empiric antibiotic treatment	Total
No treatment	19*	59**	78
Empiric antibiotic	2***	15*	17
Total	21	74	95

Note: Puopolo and Escobar's infection probability calculator would recommend no empiric antibiotic treatment for 78 (82.22%) neonates. 74 (77.89%) neonates were treated with empiric antibiotics.

*34 (35.79%) neonates were managed congruently with the NEOS calculator recommendations; 19 (20%) no empiric treatment; 15 (15.79%) to treat empirically.

** 59 (62.11%) neonates that the calculator would not recommend to treat received a total of 568 doses of ampicillin (mean 9.63 doses per neonate) representing 189.33 treatment days. They received a total of 194 doses of gentamicin (mean 3.29 doses per neonate) representing 194 treatment days.

***There were two (2.22%) neonates that the calculator recommended to treat based on risk factors that were not actually treated.

Table 3. Safety analysis.

Calculator recommendation	Actual ampicillin administration		Total:
	< 9 doses of ampicillin	> 9 doses of ampicillin	
No antibiotic treatment	62 (65.26%)*	16 (16.84%)**	78
Empiric antibiotic treatment	9 (9.47%)***	8 (8.42%)****	17
Total:	71	24	95

Note: Nine doses of ampicillin indicates a cut point of 72 hours of treatment. According to CDC and AAP guidelines a well appearing, term neonate, with a negative blood culture should not be treated longer than 48 to 72 hours.

*Clear empiric antibiotic savings: NEOS calculator would not treat and had less than or equal to nine doses of ampicillin. Of these 62 neonates, 19 were not treated with any ampicillin. The remaining 43 in this group had sepsis ruled out in 48 to 72 hours and ampicillin was discontinued. These neonates received 273 doses of ampicillin.

**Safety concern or potential missed cases: 16 neonates that the calculator would not recommend empiric antibiotic treatment, but received more than nine doses of ampicillin. These neonates could represent an area of with harmful sequelae if antibiotics are not initiated promptly.

***Justifiable empiric antibiotics: Antibiotics were initiated, but the neonate was well enough at 48 to 72 hours to discontinue treatment (52.9%, n = 9).

****Conclusively ill: Empiric treatment recommended by the NEOS calculator based on risk factors and had greater than nine doses of ampicillin based on concerning lab results or clinical presentation of the neonate 47.1% (n = 8).

Clinical Presentation	Sepsis risk at birth estimated from maternal risk factors		
	Low (< 0.65) n = 41	Medium ($0.65 - 1.54$) n = 42	High (≥ 1.54) n = 12
Well Appearing n = 77	Continued Observation n = 39 <i>61.54% were treated</i>	Observe and Evaluate n = 29 <i>89.66% were treated</i>	Treat Empirically n = 9 <i>88.89% were treated</i>
Equivocal Presentation n = 9	Observe and Evaluate n = 2 <i>50% were treated</i>	Treat Empirically n = 5 <i>80% were treated</i>	Treat Empirically n = 2 <i>100% were treated</i>
Clinical Illness n = 9	Treat Empirically n = 0 <i>N/A</i>	Treat Empirically n = 8 <i>100% were treated</i>	Treat Empirically n = 1 <i>100% were treated</i>

Figure 2. Proposed and actual population management.

Note. When the sepsis risk score generated by Puopolo and Escobar's infection probably calculator is used to determine treatment recommendations for the population are as follows: continued observation for 41.05% (n = 39) of the population, observe and evaluate 32.63% (n = 31), and empiric antibiotic treatment for 26.63% (n = 25). Actual treatment of each subpopulation is indicated in italics.

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