EVIDENCE BASED RECOMMENDATIONS FOR TREATING AND REDUCING THE INCIDENCE OF NOSOCOMIAL NEONATAL SEPSIS IN THE INTENSIVE CARE SETTING:

A BEST PRACTICE APPROACH

By

JANELLE LIANNA WESTBROOK

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Approved by:

Darice Taylor, MSN, RNC
College of Nursing

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ABSTRACT

The purpose of this thesis is to develop an educational sheet that could be kept on-hand in the Neonatal Intensive Care Unit (NICU) as a reference for a group of evidence-based recommendations designed to reduce the rates of neonatal sepsis. This handout includes information regarding primary and secondary interventions, as well as signs and symptoms of sepsis. The primary interventions include healthcare worker hygiene and evidence-based practice for caring for patients with central venous catheters. The secondary interventions include antibiotic treatment information.

CHAPTER 1

Statement of Purpose

The purpose of this thesis is to develop an educational reference sheet that could be kept at the bedside in the NICU. The reference sheet would contain information regarding healthcare worker hygiene, caring for patients with central venous catheters, and other tips on reducing sepsis rates. It would also include a list of signs and symptoms of neonatal bloodstream infection and recommendations for treating neonates diagnosed with a bloodstream infection.

Historical Background of Neonatal Sepsis

Although it is not possible to know exactly when the first case of neonatal sepsis occurred, it can be presumed that it has been occurring as long as there have been bacteria and susceptible neonates. The oldest case of infant sepsis that has been identified is from a mummy of an infant that lived between 1000 BCE and 700 BCE in ancient Egypt (Zink, Reischl, Wolf, & Nerlich, 2000). Using a method of DNA extraction and amplification, Zink et al. (2000) identified the presence of *Escheria coli* in the remains of the mummy. They theorize that the malnourished child developed a gastrointestinal infection which subsequently turned into a bloodstream infection that caused the death of the child (Zink, et al., 2000).

Our modern understanding of sepsis and bacteria has developed much more recently than the first case of neonatal sepsis. Nearly 200 years after Antony Van Leeuwenhoek wrote about his discovery of bacteria, Ignaz Semmelweis made the connection between hand washing, Puerperal Fever, and sepsis (Raju, 1999). In his 1861 publication, Semmelweis described his findings that mothers and neonates who died after birth in the hospital often had symptoms similar to those of individuals with the bloodstream infection Puerperal Fever (Raju, 1999). By instituting mandatory hand washing by obstetrical students between performing autopsies on mothers who had died in childbirth and performing vaginal exams on women in labor, the mortality rate dropped from approximately 18% to 1.7% (Raju, 1999). Although his theory was rejected during his lifetime, Semmelweis has since been proven correct.

The pathogens that most commonly cause sepsis have varied as time and scientific advances have progressed. *Streptococcus pyogenes* was a common culprit before the 1940's (Askin, 1995). In the 1950's, Staphylococcus aureus caused major outbreaks in nurseries across the country (Askin, 1995). By the late 1950's, bloodstream infections caused by gram-negative organisms such as *Escherichia coli* had become more common; in the 1970's, Group B Streptococcus was a significant cause of morbidity and mortality; and in the 1980's, *S. epidermidis*, *S. pneumoniae*, and *Hemophilus influenzae* emerged as important pathogens (Askin, 1995). Other agents, including *Chlamydia trachomatis*, *Mycoplasma hominis*, and *Ureaplasma urealyticum*, were identified through the technological advances made in the 1980's (Askin, 1995). The development of penicillin in the 1940's has significantly reduced the mortality associated with bloodstream infections (Askin, 1995).

Significance of the Problem

Sepsis occurs in about 1 to 10 neonates per 1000 births (Ward & Hisley, 2009). According to Watson et al. (2003), there is a 10-fold higher rate of sepsis in children less than 1 year of age than in older children and adolescents. In the high-risk neonatal population, such as small for gestational age (SGA), preterm (less than 27 weeks gestational age), or unwell newborns, the rate increases to 13 to 27 cases of sepsis per 1000 neonates (Ward & Hisley, 2009). Nearly 22% of very low birth weight (VLBW) infants, defined as less than 1500g, will develop sepsis in the weeks after their birth (Fanaroff et al., 2007). There are many causes of sepsis, some of which can be prevented. Early onset sepsis (EOS) occurs within the first 7 days of birth and usually is caused by organisms acquired intrapartum (Porter & Kaplan, 2011). Sepsis acquired after seven days of life is defined as late onset sepsis (LOS) (Porter & Kaplan, 2011). When caused by Group B Streptococcus, the fatality rate for sepsis in preterm neonates is approximately 23% for early onset sepsis and 9% for late onset sepsis; in term neonates, the fatality rate is about 4% for early onset sepsis ("Early-onset and late-onset neonatal group B streptococcal disease – United States, 1996-2004," 2005). This thesis will only examine late-onset sepsis. Unlike EOS, LOS is often caused by environmental factors rather than maternal or labor and delivery factors (Porter & Kaplan, 2011). LOS often results in meningitis, which is the swelling of the membranes that enclose the brain and spinal cord (Ward & Hisley, 2009). Nosocomial sepsis in neonates is most commonly caused by the bacteria Staphylococci epidermidis, *Pseudomonas, Klebsiella,* Serratia, or Proteus and is often related to the use of intravascular devices (Ward & Hisley, 2009; Porter & Kaplan, 2011).

Sepsis can have long term developmental effects on neonates who survive the infection (Schlapbach et al., 2011). Infants with proven sepsis are more likely to have neurodevelopmental impairment by 2 years of age, including cerebral palsy, than infants who do not become infected (Schlapbach et al., 2011). Sepsis can also lead to increased neonatal intensive care unit (NICU) costs, lengthened stay, and a predisposition to other morbidities (Johnson et al., 2013; Payne et al., 2004; Stoll et al., 2004).

Conclusion

Bloodstream infection is a prevalent complication within neonatal intensive care units. This problem has been occurring for centuries and, though there have been many improvements in preventing and treating it, sepsis continues to be a fatal problem. Late-onset sepsis is almost always a hospital-acquired infection, often caused by the healthcare workers who are trying to make their patient well. This thesis will create an educational reference sheet that can be kept within sight in the NICU setting in order to impart information to the healthcare workers on treating neonatal sepsis and reducing rates of hospital-acquired sepsis.

CHAPTER 2

Review of the Literature

Twenty-one articles obtained from the PubMed, CINAHL, and Cochrane databases that were published between 1991 and 2015 were reviewed for this thesis. This review includes two systematic reviews of randomized control trials (RCT), five RCTs, four quasi-experimental studies, six case control and cohort studies, one systematic review of descriptive studies, and three individual descriptive studies, divided into five major topics. These topics include risk factors associated with sepsis, current practices for preventing and treating sepsis, healthcare provider hygiene, staff education as an intervention, and pharmacologic and dietary interventions for preventing and treating sepsis.

Risk Factors Associated with Sepsis

Most of the neonate population does not develop a bloodstream infection while in the hospital. However, there are certain characteristics that place some neonates at a higher risk than their peers. This section discusses four evidence-based research studies that examine the risk factors that make a neonate more vulnerable to infection.

A recent study conducted by da Silva et al. (2014) examined the risk factors associated with bloodstream infections in several NICU patients. This study used a descriptive, quantitative design. The records for 14 neonates, admitted to Clemente Faria University Hospital of Montes Claros between January and June of 2010, were examined in this study. The 14 infants had been diagnosed with late-onset sepsis when they were less than 27 days old. Infants with severe abnormalities, complex congenital heart disease, and malformation of the gastrointestinal tract or central nervous system were excluded from this study.

Based on previous literature, da Silva et al. (2014) expected to find that low birth weight, prematurity, in-dwelling catheter use, surgery, and use of H_2 blockers were considered risk factors for late-onset sepsis. Their study confirmed their hypothesis. However, unlike the previous literature which found that sepsis was associated with vaginal birth, da Silva et al. (2014) found that 71% of the cases of sepsis followed Cesarean section births.

In a study conducted by Auriti, et al. (2010), it was found that hospital acquired infections in VLBW neonates were associated with multiple factors which differed in the non-VLBW neonatal population. This 28-month study of 1,692 neonates in six Italian NICUs used an observational prospective cohort design. During the study period, all neonates less than 30 days old who were admitted to one of the participating NICUs and stayed for at least two days were included in the study (Auriti, et al., 2010). These newborns were observed and monitored for infection until two days after discharge (Auriti, et al., 2010). Sepsis was considered confirmed in neonates with at least two clinical symptoms of sepsis, including fever, hypothermia, tachycardia or bradycardia, apnea, lethargy, problems with feeding, mottling, convulsions, or hypotonia (Auriti, et al., 2010). A diagnosis of sepsis was also based on the presence of at least two laboratory findings, including leukopenia, leukocytosis, a low platelet count, a C-reactive protein blood level of at least 1.5 mg/dL, a fibrinogen level of at least 150 mg/dL, metabolic acidosis, or a positive blood culture result (Auriti, et al., 2010). Sepsis was suspected in cases of neonates with at least two clinical or laboratory symptoms with a negative blood culture result (Auriti, et al., 2010).

In this study of 1,692 neonates, there were 255 episodes of nosocomial infection (Auriti, et al., 2010). Of those 255 episodes, 182 (71.4%) were cases of confirmed and suspected sepsis (Auriti, et al., 2010). Most of these were caused by *Staphylococcus* and *Klebsiella* bacterial species (Auriti, et al., 2010). It was found that VLBW neonatal in-hospital mortality was about 15.4%, compared to 3.0% for larger neonates (Auriti, et al., 2010). Mortality rates were also increased in infants with infection when compared to infants without infection (Auriti, et al., 2010). The most significant risk factors for acquiring a nosocomial infection for VLBW neonates were a gestational age of less than 28 weeks, an Apgar score of less than 4 at 5 minutes, the presence of congenital malformations, and receipt of continuous positive airway pressure (CPAP) (Auriti, et al., 2010). In non-VLBW neonates (those weighing greater that 1500g at birth), parenteral nutrition and the presence of congenital malformations were the most common risk factors for developing a nosocomial infection (Auriti, et al., 2010).

A prospective cohort study conducted in a 30-bed NICU in a Serbian hospital found that risk factors for developing a hospital acquired infection (HAI) included low birth weight, prolonged length of hospitalization, prolonged use of mechanical ventilation, and low Apgar score at five minutes after birth (Djordjevic, Markovic-Denic, Folic, Igrutinovic, & Jankovic, 2015). In the one year that this study took place, 381 neonates were observed and 74 infections were recorded in 71 neonates (Djordjevic et al., 2015). This study examined all types of HAIs and found that pneumonia was the most prevalent (64.9%), followed by urinary tract infection (20.3%), sepsis (9.5%), and omphalitis (5.4%) (Djordjevic et al., 2015). In 39.3% of the cases of sepsis, the causative agent was *Klebsiella-Enterobacter* (Djordjevic et al., 2015). The other agents identified were *Escherichia coli*, coagulase-negative staphylococci, and *candida albicans* (Djordjevic et al., 2015). The unit that this study was conducted in had hand hygiene-, glove-, and general hygiene-policies in effect at the time of the study, and did not perform vascular access through central lines (Djordjevic et al., 2015). Infants who had undergone surgery were not included in this study because they were treated at a different unit in the hospital (Djordjevic et al., 2015).

A retrospective study by Goutail-Flaud, Sfez, Berg, Laguenia, Couturier, Barbotin-Larrieu, and Saint-Maurice (1991) analyzed the records of 587 central venous catheters (CVC) that had been placed in newborns in the NICU of University Hospital St. Vincent de Paul in France in order to ascertain potential complications and their causes. They aimed to determine whether there was an optimal choice between surgical or percutaneous placement, between proximal or distal venous access, and between silicone or polyurethane catheters (Goutail-Flaud, 1991). They found that complications occurred in 28% of cases and included mechanical problems (76% of complications), septic complications (4%), and thrombotic complications (Goutail-Flaud, 1991). Overall, complications occurred more frequently in newborns with a body weight of less than 2500g (35%) than in those of a higher weight (26%) (Goutail-Flaud, 1991). The material of the catheter did not influence the rate of complications, nor did the technique of placement (Goutail-Flaud, 1991). However, it was found that septic complications occurred more often when the CVC was placed proximally (6.8%) than distally (3.6%) (Goutail-Flaud, 1991).

Current Practices

In order to attempt to reduce the rates of neonatal nosocomial sepsis, it must first be known what the current practices are in order to evaluate the need for adjustment. This section reviews three research articles that pertain to the treatment of suspected or diagnosed sepsis and to central catheter insertion technique.

A prospective trial conducted by Lutsar et al. (2014) examined the antibiotics that were chosen to treat individual cases of late onset neonatal sepsis in NICUs in Estonia, Lithuania, Greece, Italy, and Spain, and whether favorable outcomes were associated with any regimen. A favorable outcome was defined as the patient being alive with signs and symptoms of LOS resolved, no new need for antibiotic therapy, and eradication of the baseline pathogen (Lutsar et al., 2014). Eighteen NICUs provided a total of 113 patients with a diagnosis of sepsis for the study (Lutsar et al., 2014). Of these 113 cases, 69 were microbiologically proven; the others were diagnosed based on clinical signs (Lutsar et al., 2014). The majority of cases were caused by Coagulase-negative *Staphylococci* and Enterobacteriaceae, although other Gram positive and Gram negative organisms were identified in some cases (Lutsar et al., 2014). A total of 43 antibiotic regimens were used to treat the study participants (Lutsar et al., 2014). It was found that 50% of the participants were given meropenem or a third generation cephalosporin or ampicillin with or without an aminoglycoside or glycopeptides (Lutsar et al., 2014). Of the patients who had a culture performed, 61% received an appropriate antibiotic and 23% received an antibiotic to which the infection was not susceptible (Lutsar et al., 2014). Enterobacteriaceae were found to be susceptible to meropenem in 90% of cases and resistant to ampicillin in about 95% of cases (Lutsar et al., 2014). Coagulase-negative *Staphylococci* were susceptible to glycopeptides but resistant to the other antibiotics that were tested (Lutsar et al., 2014). The median duration of antibiotic therapy was 16 days (Lutsar et al., 2014). A favorable outcome was found in 47% of the 113 patients (Lutsar et al., 2014). The overall mortality rate was 8% with no difference between culture proven cases and those diagnosed based on symptoms (Lutsar et al., 2014).

This study found that antibiotic regimens differ by region and that some NICUs chose to use a different antibiotic than what experts recommend (Lutsar et al., 2014). The reasons for the selection of antibiotic were not given; however, it is possible that different regional customs and values may influence the views on acceptable risks (Lutsar et al., 2014). Local antibiotic resistance patterns may also have influenced the choice (Lutsar et al., 2014). Overall, this study suggests that there is a need for improved evidence-based guidelines for treatment of late onset sepsis (Lutsar et al., 2014).

A study by Korhonen (2010) proposed to evaluate the written protocols and clinical procedures used in 5 Finnish NICUs to determine if they met the standards of performance for aseptic technique in the use, insertion, and maintenance of central venous catheters (CVC) in neonates (Korhonen, 2010). This study used the data that was collected to revise protocols and to develop an education program in order to attempt to reduce the rates of catheter-related bloodstream infections (Korhonen, 2010).

This study used a mixed-method design which included observation and deductive content analysis (Korhonen, 2010). A total of seven written protocols from five NICUs were examined using deductive content analysis (Korhonen, 2010). There were five original protocols and two revised protocols (Korhonen, 2010). Observations of clinical practices included catheter insertions, tubing changes, and drug administration over a 2-month period (Korhonen, 2010). The observational data was quantified by basic descriptive statistics (Korhonen, 2010). Good performance for each practice was defined as accurately performing 100% of the items in the category (Korhonen, 2010).

This study found that all of the protocols listed the materials needed in a catheter insertion but that only two of the seven protocols discussed aseptic preparation of the instrument table (Korhonen, 2010). Revised protocols placed more emphasis on hand hygiene and the use of gloves and masks than old protocols (Korhonen, 2010). Catheter maintenance instructions were also more detailed in the revised protocols (Korhonen, 2010). During the observations, Korhonen (2010) found that none of the clinical practices had 100% aseptic performance. CVC drug administration had the highest compliance, ranging from 11% to 96% (Korhonen, 2010). Appropriate catheter insertion achievement ranged 0% to 69% and appropriate tubing changes varied between 7% and 64% (Korhonen, 2010). Overall, Korhonen (2010) found that clinical improvements are needed in order to reduce the risk of CVC-related sepsis.

A descriptive study conducted by Alkubati, Ahmed, Mohamed, Fayed, & Asfour (2015) sought to assess physicians' and nurses' knowledge of central venous catheter-related infection (CVCRI) as well as observe their practices (Alkubati et al., 2015). This study took place in the adult intensive care units of the Alexandria Main University Hospital in Egypt and included 40 physicians and 60 nurses (Alkubati et al., 2015). Although this study was performed in the adult population, the results are likely transferable because both the NICU and adult ICU staff deal with the same level of critically-ill patients. There were two parts to this study: first, a questionnaire tool with 18 multiple choice questions regarding the pathophysiology of CVC infection, diagnosis of infection, insertion site of catheter, CVC change frequency, skin antisepsis, dressing type, dressing change frequency, use of antibiotic and antiseptic ointments, and CVC care; second, healthcare workers' practices were observed while they cared for patients with CVCs and were compared to a checklist of items that should be completed (Alkubati et al., 2015). From the results of the questionnaire, it was found that physicians' and nurses' overall level of knowledge were not statistically different but that physicians scored significantly higher on the items relating to pathophysiology and skin antisepsis and nurses scored higher on the items regarding CVC care (Alkubati et al., 2015). The total percent of correct answers was 36.94% for physicians and 32.62% for nurses (Alkubati et al., 2015). The lowest scoring category for both groups was knowledge of the use of antibiotic and antiseptic ointments (Alkubati et al., 2015). From the observation portion of this study, it was found that most physicians (87.5%) performed hand hygiene but few nurses (22.5%) did (Alkubati et al., 2015). Physicians were also more likely to comply with sterile barrier precautions (caps 80%, masks 85%, gloves 90%, and sterile gloves 80%) than nurses (5%, 30%, 45%, and 15%, respectively) (Alkubati et al., 2015). Overall, this study shows that there is a low level of knowledge regarding CVCRI among healthcare workers and that more education and training is needed along with periodic assessments of that knowledge (Alkubati et al., 2015).

Healthcare Provider Hygiene

This thesis examines the spread of nosocomial sepsis. It is widely known that healthcare provider hygiene impacts the rates of infection being passed from one patient or object to a patient. This section reviews three evidence-based research articles that discuss the impact of hand hygiene.

The purpose of a study conducted by Helder, Brug, Looman, van Goudoever, and Konelisse (2010) was to examine the effectiveness of a hand hygiene education program on reducing the incidence of nosocomial bloodstream infections. A 27 bed NICU in a teaching hospital in the Netherlands was the setting for this study (Helder et al., 2010). Over 4 years, healthcare professionals who had physical contact with VLBW infants were followed before and after a hand hygiene education program (Helder et al., 2010). Their hand hygiene practices were compared between the two periods, as was the incidence of nosocomial sepsis in VLBW infants (Helder et al., 2010). There were a total of 1201 guided observations of hand hygiene.

Helder et al. (2010) found that hand hygiene compliance increased before patient contact from 68.8% to 86.9% and increased after patient contact from 68.9% to 84% after instituting the education program. Hand hygiene also increased before high-risk procedures (from 73.6% to 89.4%) and before low risk procedures (from 64.4% to 85.8) (Helder et al., 2010). The incidence of bloodstream infection in the VLBW NICU patients decreased from 44.5% before the education program to 36.1% after (Helder et al., 2010).

Another study, conducted over 10 years in the NICU of a teaching hospital in the Netherlands, aimed to find out if sequential hand hygiene promotion of hospital staff could reduce the amount of nosocomial bloodstream infections (NBSI) long term in the VLBW population (Helder, Brug, Looman, van Goudoever, Reis, & Kornelisse, 2014). Data regarding the incidence of NBSI from 2002-2005 was gathered retrospectively to distinguish a baseline before the interventions were implemented (Helder et al., 2014). The first phase of the intervention began in July 2005 and consisted of a 1-month hand hygiene education program (Helder et al., 2014). Phase 2 of the intervention included screen saver messages regarding hand hygiene, an infection prevention week, and promotion of clean glove use during tasks that might cause contact with infants' secretions (Helder et al., 2014). This phase was implemented from 2008 to 2011 (Helder et al., 2014).

Overall, 1,964 infants were included in this study (Helder et al., 2014). The percent of infants with more than one infection decreased from 47.6% to 21.2% and the number of NBSIs per 1000 patient days decreased from 16.8 to 8.9 (Helder et al., 2014). Analysis of the baseline data showed that the number of NBSIs per 1000 patient days had been increasing by 0.74 per quarter before the intervention but instantly decreased by 4.5 after the phase 1 intervention and then decreased by 1.27 per quarter while that intervention was being implemented (Helder et al., 2014). During phase 2, the number of NBSIs per 1000 patient days decreased by 2.1 immediately and then showed a neutral trend (Helder et al., 2014). The primary causative agents of NBSI were coagulase-negative staphylococcus and *Staphylococcus aureus* (Helder et al., 2014). This study shows that sequential hand hygiene promotion interventions can contribute to a sustained decrease in NSBIs in the NICU setting (Helder et al., 2014).

In addition to hand hygiene, Raad et al. (1994) found that using maximum sterile barrier precautions during CVC placement, consisting of a mask, cap, sterile gloves, gown, and large drape, was associated with a lower rate of catheter-related septicemia than the use of only sterile gloves and a small sterile drape. This randomized controlled trial consisted of 343 adult cancer patients who had a nontunneled CVC placed at the outpatient clinics of M.D. Anderson Cancer Center (Raad et al., 1994). Although this study focused on adults, the transfer of bacteria to a patient during CVC insertion could occur in the neonatal population as well. Catheter-related septicemia was defined as clinical manifestations of sepsis, including fever, chills, unexplained hypotension, or cardiac failure, with the only source of septicemia being from the catheter (Raad et al., 1994). Of the 167 patients in the control group, colonization of the catheters was detected in twelve patients, compared to only four patients out of the 176 maximum sterile barrier patients (Raad et al., 1994). In the control group, 67% of the infections occurred within the first two months of catheter insertion, whereas only 25% of the infections of the experimental group occurred that early on (Raad et al., 1994). The organisms that caused most of the septicemias in the control group included normal skin flora like coagulase-negative staphylococci, *Staphylococcus aureus*, *Micrococcus*, and *Corynebacterium*, unlike the experimental group septicemias which included *Enterobacter cloacae*, *Pseudomonas aeruginosa* and *Acinetobacter calcoaceticus* (Raad et al., 1994). This suggests that differences between the two groups can be attributed to the use of maximum sterile barrier precautions (Raad et al., 1994). In hospitals in which nurses do not insert CVCs in the neonatal population, the nurses can still remind the physician or surgeon doing the procedure to use maximum precautions or could perform a checklist to ensure that the precautions are being followed.

Staff Education as an Intervention

As part of this thesis attempts to use education as a primary prevention strategy, it is important to examine whether staff education actually works to reduce rates of sepsis in the NICU population. Two research studies and one literature review are included in this section which examines the effectiveness of various types of education programs on decreasing bloodstream infection, especially those studies focusing on CVCs.

A prospective cohort interventional study of neonates with a CVC, conducted by Sannoh, Clones, Munoz, Montecalvo, & Parvez (2010), used a multimodal approach to reduce the incidence of catheter-related bloodstream infections (CRBSIs). This intervention involved using a solution of 2% chlorhexidine in 70% isopropyl alcohol during CVC hub care, as well as an audiovisual education program for the healthcare professionals in the study (Sannoh et al., 2010). The incidence of CRBSIs was recorded pre-intervention and post-intervention and the rates were then compared (Sannoh et al., 2010). A total of 373 neonates were included in this study: 163 pre-intervention patients and 210 post intervention patients (Sannoh et al., 2010). The pre-intervention and post-intervention rates of CRBSIs were gathered from a database maintained by the Division of Newborn Medicine and the Department of Infection Control (Sannoh et al., 2010). Before the intervention, 24 nurses were observed performing CVC hub care; after the intervention, 26 nurses were observed (Sannoh et al., 2010). Performance was rated based on adherence to a 9-point catheter hub care checklist (Sannoh et al., 2010).

Overall, Sannoh et al. (2010) found that the CRBSI rate dropped from 15/1000 catheter days to 5/1000 catheter days for umbilical artery catheters and umbilical vein catheters (Sannoh et al., 2010). For peripherally inserted central catheters (PICC), the rate dropped from 23/1000 catheter days to 12/1000 catheter days (Sannoh et al., 2010). Sannoh et al. (2010) also found that the nurses' adherence to the CVC hub care protocol increased after the educational program (Sannoh et al., 2010). However, because this was a multimodal intervention, it is difficult to determine which approach was the most useful (Sannoh et al., 2010).

Another prospective study, conducted by Rosenthal, Guzman, Pezzetto, and Crnich (2003), examined the efficacy of using an education program and performance feedback on rates of intravascular device (IVD) associated bloodstream infections (BSI). The study took place in the adult cardiac and medical-surgical intensive care units (ICUs) of two private Argentinean hospitals (Rosenthal et al., 2003). There were three phases to this research trial; Phase 1 involved active surveillance of the hospital care workers (HCWs) while they performed tasks related to caring for intravascular devices such as CVCs and PICCs, Phase 2 involved implementing an education program regarding infection control based on the Centers for Disease Control and Prevention and Hospital Infection Control Practices Advisory Committee's guidelines, and Phase 3 was performance feedback, given at a monthly infection control meeting with bar charts recording the rates of compliance with handwashing, gauze placement and assessment, and IV set labeling (Rosenthal et al., 2003).

Overall, it was found that an education program followed by performance feedback decreased the rates of IVD-associated BSI (Rosenthal et al., 2003). During Phase 1, there were approximately 45.94 BSIs per 1000 IVD days, whereas there were only 11.10 BSIs per 1000 IVD days during phases 2 and 3 (Rosenthal et al., 2003). Although this study focused on adults rather than neonates, the results are likely transferable to the NICU because CVCs and PICCs are used in both populations. Staff education and performance feedback are valuable tools in reducing BSI rates.

A literature review conducted by C. Semelsberger (2009) attempted to determine the efficacy of educational programs in reducing the rates of catheter-related bloodstream infections (CRBSI) in neonates in Level II/Level III NICUs. Of the ten studies included, none were conducted in NICUs but rather adult ICUs (Semelsberger, 2009). However, much of the findings are applicable in both settings (Semelsberger, 2009). Six of the studies included pretest-posttest design with data on CRBSI rate collected before and after the educational intervention (Semelsberger, 2009). The interventions included lectures, study modules completed individually, and staff in-service and/or training (Semelsberger, 2009). Four of the six studies showed statistically significant reductions in CRBSI rates (Semelsberger, 2009). The remaining four studies included in the literature review implemented an educational program without a pretest or posttest (Semelsberger, 2009). These studies consisted of web-based training with and without a lecture series and also showed a significant reduction in CRBSIs (Semelsberger, 2009). One of these studies compared the reduction in CRBSIs between an ICU that underwent an educational program versus another ICU that had an educational program in addition to other interventions (Semelsberger, 2009). The other interventions included the creation of a cart containing all necessary central catheter insertion supplies in order to keep materials close by, daily review of the necessity of the central catheter for each patient, use of a checklist for catheter insertion, and a procedure to empower nurses to stop a catheter insertion if they observed it being performed incorrectly (Semelsberger, 2009). This study found that the CRBSI rate reduced 72% ($p = 0.56$) in the ICU with the educational program alone, and with the additional interventions, there was a 100% decrease ($p = <0.001$) (Semelsberger, 2009). This literature review concluded that an educational program could be helpful in reducing the rates of CRBSI in the NICU setting, especially in conjunction with other interventions (Semelsberger, 2009).

Pharmacologic and Dietary Interventions

Certain pharmacological therapies and dietary interventions can be useful in preventing sepsis, especially for neonates who are at an increased risk of susceptibility. Other pharmacological interventions are useful in treating sepsis once it has been diagnosed or is suspected. This section reviews six studies and two systematic reviews which discuss the prevention and treatment of neonatal sepsis.

A randomized control trial conducted by Manzoni et al. (2010) examined the effects of giving VLBW neonates a treatment of bovine lactoferrin (bLF) with or without a probiotic (*Lactobacillus GG*). Bovine lactoferrin is a whey protein in mammalian milk that has important biological and immunological properties (Manzoni et al., 2010). A total of 11 centers across Italy participated in this study (Manzoni et al., 2010).

In this study, which used a randomized, double-blind, placebo-controlled, multicenter design, qualifying neonates were assigned to one of three groups: bLF alone, bLF with *Lactobacillus GG*, or placebo (Manzoni et al., 2010). The bLF, *Lactobacillus GG,* and placebo were administered daily for 30 days in neonates with a birth weight of 1000-1500 g and for 45 days for neonates that weighed below 1000 g at birth (Manzoni et al., 2010). The hospitals' usual protocols for nutrition and feeding were followed as well (Manzoni et al., 2010).

Manzoni et al. (2010) found that bLF alone and with *Lactobacillus GG* was effective in reducing the incidence of late-onset bloodstream infections in neonates (Manzoni et al., 2010). In the treatment groups, the rates of sepsis were 5% and 6%, respectively, compared to 18% in the placebo group (Manzoni et al., 2010). There were no adverse reactions to the bLF (Manzoni et al., 2010).

Another study found that probiotics did not affect the rates of culture-proven late-onset sepsis in neonates (Jacobs et al., 2013). This randomized controlled trial of 1099 newborns in eight Australian and two New Zealand hospitals compared the rates of sepsis in newborns given a placebo to the rates of newborns given a probiotic pill containing the organisms *Bifidobacterium infantis*, *Streptococcus thermophilus*, and *Bifidobacterium lactis* (Jacobs et al., 2013). The neonates in this double-blind study were born at less than 32 weeks gestation and weighed less than 1500g (Jacobs et al., 2013). The probiotic was not found to be helpful or harmful in the case of sepsis, although there was some reduction in the number of cases of necrotizing enterocolitis in the experimental group (Jacobs et al., 2013). Overall, 23.5% of the probiotic group had definite or clinical sepsis compared to 26.5% of the placebo group (*P* value = 0.26) (Jacobs et al., 2013).

A prospective cohort study was conducted by Patel et al. (2013) to assess the incidence of neonatal bloodstream infections and their associated costs in the NICU, as well as the effects of increasing human milk consumption on those factors. A total of 175 neonates were included in the data (Patel et al., 2013).

The dose of human milk that each neonate consumed was recorded as the daily average mL/kg of body weight for 28 days (Patel et al., 2013). Based on this data, the neonates were grouped into three categories: low- (<25 mL/kg), moderate- (25-49.99 mL/kg), and high consumption (50+ mL/kg) (Patel et al., 2013). The data regarding the NICU costs was gathered using the medical center's system-wide accounting system, which provided the direct cost of care for each patient, excluding physicians' costs (Patel et al., 2013).

Patel et al. (2013) found that sepsis occurred in 13% of the study participants overall. For each 10 mL/kg per day of human milk, there was a 19% reduction in the odds of developing a bloodstream infection after adjusting for other risk factors (Patel et al., 2013). For the neonates that were in the low consumption group, the NICU costs were $31,514 higher than those who were in the high consumption group and $20,384 higher than those who were in the moderate consumption group (Patel et al., 2013). Patel et al. (2013) also found that a diagnosis of sepsis was associated with a 31% increase in NICU costs (Patel et al., 2013).

A randomized controlled trial by Ramasamy, Biswal, Bethou, and Mathai (2014) aimed to determine whether it was more effective to use broad spectrum antibiotics (Cefotaxime plus Gentamicin) or antibiotics targeted against pathogens associated with late onset sepsis (Cloxacillin plus Amikacin) to treat suspected or nonculturable sepsis. This study took place in India and included 90 neonates age 3-28 days (Ramasamy et al., 2014). The two groups were similar in their rates of complications, duration of hospitalization, rehospitalization, treatment failure, mortality, and cost, but the broad spectrum antibiotic group had higher rates of sequelae at one month (25% versus 5.5% in the narrow spectrum group) (Ramasamy et al., 2014).

A study conducted in the rural Sylhet district of Bangladesh attempted to determine whether the use of a 4.0% chlorhexidine cleanse was helpful in reducing the colonization of the umbilical cord by organisms that could cause omphalitis and bloodstream infection (Mullany et al., 2012). Overall, Mullany et al. (2012) found that cleansing the umbilical cord within 24 hours after birth and then once per day for the next 6 days resulted in a lower bacterial colonization count than no intervention, with multiple cleanses being more effective than just one cleanse.

This study included 1928 infants born between September 2008 and October 2009 (Mullany et al., 2012). The infants were assigned to one of three groups: single cleanse, multiple cleanses, or no intervention (Mullany et al., 2012). The cleanses were performed by a village health worker using aqueous 4.0% chlorhexidine applied with a cotton ball (Mullany et al., 2012). On day 1, day 3, and day 6 of life, culture swabs were taken of the umbilical cord by a community health worker in order to determine the type and amount of organisms present (Mullany et al., 2012). It was found that 77.5% of the swab specimens were positive for at least one organism, 38.3% of specimens positive for two organisms, and 18.1% for three (Mullany et al., 2012). The intervention groups were less likely to have a positive swab on the first visit (Mullany et al., 2012). The multiple cleanse group had 55.3% positive swabs on the final visit, which was 43% lower than the control group (Mullany et al., 2012). Although the single cleanse group had an initial reduction compared to the no-cleanse group, that reduction decreased on subsequent visits until the proportion of final swabs for the single cleanse group showed only an 8% reduction in colonization rates (Mullany et al., 2012). The most common organisms that were cultured were gram-negative, with *Escherichia coli* (29%), *Klebsiella pneumonia* (27.3%), and *Pseudomonas* (25.5%) species being the most common (Mullany et al., 2012). Gram-positive organisms comprised 34.2% of the organisms cultured and included *Staphylococcus* and *Streptococcus* species (Mullany et al., 2012). By decreasing the amount of organisms colonizing the umbilical cord after birth, it is hypothesized that the amount of bacteria that enters the bloodstream through the patent vessels of the cord will also be reduced and that the rates of sepsis and mortality will therefore decrease (Mullany et al., 2012).

Unlike the Mullany et al. (2012) study which examined the effects of cord cleansing in rural regions of developing countries, a systematic review conducted by Zupan, Garner, and Omari (2004) reviewed studies that mostly took place in high-resource countries. Based on the data from 21 randomized and quasi-randomized trials, Zupan, Garner, and Omari (2004) determined that there was no evidence to support applying topical sprays, creams, or powders (as opposed to keeping the umbilical stump clean and dry) in order to reduce the rates of systemic infection and mortality in countries with abundant medical resources.

Ten of the 21 studies compared dry cord care/placebo with antiseptic application (Zupan, Garner, & Omari, 2004). The antiseptics studied included alcohol, triple dye, silver sulfadiazine, zinc powder, chlorhexidine, salicylic sugar powder, green clay powder, katoxin powder, and fuschine (Zupan, Garner, & Omari, 2004). There were no significant differences in rates of serious infection between the placebo and experimental groups, although there was a trend of later cord separation in the groups that used alcohol, triple dye, and fuschine antiseptics, and shorter separation in the groups that used powder antiseptics (Zupan, Garner, & Omari, 2004). Two studies compared the efficacy of antiseptics versus antibiotics in reducing infection (Zupan, Garner, & Omari, 2004). No infections were reported in either study, but it was found that antibiotics tended to reduce the colonization of *Staphylococcus aureus* more than the antiseptics and that there was a generally shorter time for cord separation when antiseptics were used than antibiotics (Zupan, Garner, & Omari, 2004). There were seven studies that compared antiseptics to each other (Zupan, Garner, & Omari, 2004). It was found that triple dye resulted in fewer cord infections than alcohol; there was no difference in the rate of infection when comparing povidone-iodine with alcohol; more infections were seen in povidone-iodine than triple dye; and more infections were seen when chlorhexidine was used than when hydrophobic gauze was used (Zupan, Garner, & Omari, 2004).

A review conducted by C. Tom-Revzon (2004) details the specific antibiotics that should be administered to treat bloodstream infection caused by each of the major pathogenic organisms. Based on data from the literature reviewed, Tom-Revzon (2004) suggests treating late-onset sepsis caused by Group B Streptococcus (GBS) with penicillin or rifampin, or amoxicillin if penicillin cannot be used. The evidence suggests that *Escherichia coli* infection be treated with ampicillin, gentamicin, or a third generation cephalosporin, and that *Listeria monocytogenes* is most effectively treated with ampicillin with or without gentamicin or vancomycin or a third generation cephalosporin (Tom-Revzon, 2004). The gram-positive organism *Staphylococcus epidermidis* should be treated with vancomycin and an aminoglycoside or cephotaxime, while *Staphylococcus aureus* is best treated with an antistaphylococcal penicillin like methicillin, nafcillin, or oxacillin (Tom-Revzon, 2004). In order to treat sepsis caused by the organism *Pseudomonas aeruginosa*, an antipseudomonal penicillin, such as ticarcillin, or a third generation cephalosporin is most effective (Tom-Revzon, 2004). For treating *Clostridium difficile*, metronidazole and vancomycin are recommended (Tom-Revzon, 2004). In general, the antibiotics recommended for suspected LOS should be able to treat GBS, *E. coli*, and *L. monocytogenes* (Tom-Revzon, 2004). A β-lactam such as ampicillin or penicillin G with an aminoglycoside like gentamicin or tobramycin is recommened (Tom-Revzon, 2004).

In addition to administering the correct antimicrobial that corresponds to the specific pathogen causing sepsis, the timing of administration is also important. A retrospective observational study conducted in the Pediatric Intensive Care Unit (PICU) by Weiss et al. (2014) demonstrated that delayed administration of antibiotics by three hours or more resulted in increased mortality and organ dysfunction.

One hundred and thirty patients with confirmed severe sepsis or septic shock were included in this study (Weiss et al., 2014). All patients were treated with antibiotics and in 78% of cases, the initial antimicrobial chosen was the appropriate one (Weiss et al., 2014). On average, it took 140 minutes from sepsis recognition to initial antimicrobial administration and

177 minutes to first appropriate antimicrobial administration (Weiss et al., 2014). There was no difference in mortality rate between those who received the appropriate antibiotic initially versus those who changed antibiotics after a culture was performed (Weiss et al., 2014). Although there was an increase in mortality rate for each hour delay from sepsis recognition to antibiotic administration, this difference was not significant until three hours (Weiss et al., 2014). Patients who received antibiotics within three hours after sepsis recognition had less organ dysfunction (20 organ failure-free days) than those who received antimicrobials after three hours (16 organ failure-free days) (Weiss et al., 2014).

Conclusion

Based on the studies and data found for this literature review, it can be seen that low birth weight, prematurity, central venous catheter use, and surgery are all risk factors that are associated with developing a bloodstream infection as a neonate in a NICU. It can also be seen that current protocols and practices need improvement in order to prevent catheter-associated bloodstream infection and to ensure that the proper antibiotic is administered to the infected neonate. Changes that can be made include instituting a hand hygiene education program for the healthcare workers in the NICU to improve hand hygiene compliance and creating central venous catheter hub care protocols. There is also some promising research that suggests using bovine lactoferrin as a supplement to the usual nutrition given to a neonate can reduce sepsis rates. However, more research needs to be done to know for sure if this intervention is usable. Increasing the amount of human milk consumed by an infant could also reduce the incidence of sepsis in VLBW infants. In low resource communities, 4.0% chlorhexidine cord cleanses can prevent the development of omphalitis which can be a precursor to sepsis, but this intervention is unlikely to be useful in high resource communities.

CHAPTER 3

Best Practice Recommendations

The purpose of this thesis is to design an educational reference sheet that can be kept within sight in the NICU in order to be used as a guide for healthcare workers when caring for neonates who might be at risk for developing a bloodstream infection or who have already developed one. This chapter will integrate the information gathered from the literature reviewed into a set of best practice recommendations which will be displayed on the reference sheet.

The recommendations in this thesis can be categorized into two types: primary and secondary prevention. Primary preventions are interventions which are performed before a neonate has been diagnosed with a bloodstream infection in order to prevent the infection from occurring. Secondary prevention slows the progression of the infection after it starts in order to prevent sequelae, such as organ damage or death. In other words, secondary prevention is the treatment of bloodstream infection.

The primary prevention recommendations in this thesis include hand hygiene education for healthcare workers, catheter care education and recommendations, and promotion of increased breast milk consumption.

From the research reviewed in the previous chapter, it can be seen that hand hygiene education programs can improve the rates of hand washing before and after patient contact which reduces the transmission of infection (Helder et al., 2010). Various types of education programs were reviewed and multiple methods were found to be effective, including using an audiovisual format for the program, having sequential education programs to reinforce the desired behavior over time, and using performance feedback on a regular basis to evaluate compliance over periods of time (Sannoh et al., 2010; Helder et al., 2014; Rosenthal et al., 2003). Individual institutions should use the format that they believe fits in best with their policies or which may have the most effect at their location. Hygiene education is also important for the healthcare workers that treat patients with CVCs as the catheters may act as a direct portal for pathogens to enter the bloodstream. Education and hands-on training has proven effective at reducing the rates of catheter-related bloodstream infection (Alkubati et al., 2015).

In addition to knowing how to properly care for the patient with a CVC, healthcare workers must be able to determine if the CVC is necessary in the individual. Routine placement should be avoided and the device should be removed as soon as it is no longer necessary (Semelsberger, 2009). Distal placement of a peripherally inserted central catheter (PICC) should be chosen over a proximal placement as distal placement is less often associated with bloodstream infection (Goutail-Flaud et al., 1991). During the insertion of a CVC, a designated room should be used instead of the bedside as it has been shown to decrease the risk of contamination of the procedure (Goutail-Flaud et al., 1991). Maximal sterile barrier precautions, including the use of a mask, cap, sterile gloves, gown, and large drape, should be observed during the procedure (Goutail-Flaud et al., 1991). Using 2% chlorhexidine skin prep in the area of insertion and having a designated team of healthcare workers insert the CVC have also been shown to reduce infection (Goutail-Flaud et al., 1991). Other recommendations pertaining to CVC insertion include keeping instruction on aseptic preparation of the instrument table in the hospital protocols, maintaining a CVC supply cart that is present at each placement, keeping CVC insertion recommendations on hand during the procedure, and empowering nurses to stop an insertion of a CVC if they observe it being performed incorrectly (Korhonen, 2010; Semelsberger, 2009). When caring for a patient with a CVC, 2% chlorhexidine in 70% isopropyl alcohol should be used for hub care (Sannoh et al., 2010).

Some dietary interventions have proven to be useful in reducing the rates of sepsis in neonates. For this reason, it is recommended that neonates consume as much human milk as possible, which can be accomplished by the healthcare workers educating the parents of the neonates on the benefits of increased milk consumption (Patel et al., 2013). Lactoferrin, a whey protein, shows some evidence of reducing rates of sepsis when given as a supplementation to regular feedings, but there isn’t enough research on this topic to recommend it as regular practice (Manzoni et al., 2010). Research on probiotics has shown that they are not effective in reducing bloodstream infection and they therefore are not recommended (Jacobs, et al., 2013).

The secondary prevention recommendations in this thesis include methods of recognizing sepsis and using antibiotics to treat it. Some subpopulations of neonates are more at risk for developing infection and should therefore be monitored more closely. These neonates include low birth weight individuals and those who were born prematurely, as well as those who have undergone surgery or who have a CVC or proximally placed PICC (Goutail-Flaud et al., 1991; da Silva et al., 2014; Auriti et al., 2010; Djordjevic et al., 2015). When sepsis is suspected in a neonate, a bacterial culture should be performed in order to determine the causative agent (Lutsar, et al., 2014). Antibiotics should be administered immediately. If they are administered within three hours of suspicion of infection, there is less risk of organ dysfunction (Weiss, 2014). Depending on the results of the blood culture, the prescribed antibiotic may need to be changed to one which is more effective against the specific pathogen (Tom-Revzon, 2004). Although nurses are not directly responsible for prescribing antibiotics, they can serve as an addition check to ensure that the antibiotic being administered is effective and can advocate for their patient if the antibiotic is not targeted to the cultured organism. Table 1 summarizes best practice recommendations for preventing and treating neonatal sepsis.

Table 1

Best Practice Recommendations for Preventing and Treating Neonatal Sepsis

Primary Interventions			
Hygiene Education			
Topic	Recommendation	References	Strength of Recommendation*
Healthcare Workers Must Be Educated On Hand Hygiene To Help Prevent The Spread Of Infection	- Hand hygiene education programs should be implemented in NICUs. - Sequential promotions, performance feedback, and/or an audiovisual format may decrease the incidence of sepsis in the NICU.	Helder, O. K., Brug, J., Looman, C. W., van Goudoever, J. B., & Kornelisse, R. F. (2010). The impact of an education program on hand hygiene compliance and nosocomial infection incidence in an urban neonatal intensive care unit: An intervention study with before and after comparison. *International Journal of Nursing Studies*, *47*(10), 1245-1252. Sannoh, S., Clones, B., Munoz, J., Montecalvo, M., & Parvez, B. (2010). A multimodal approach to central venous catheter hub care can decrease catheter-related bloodstream infection. *American Journal of Infection Control*, *38*(6), 424-429. Rosenthal, V.D., Guzman, S., Pezzetto, S.M., & Crnich, C.J. (2003). Effect of an infection control program using education and performance feedback on rates of intravascular device-associated bloodstream infections in intensive care units in Argentina. *American Journal of Infection Control 31*(7), 405-409.	A

		Helder, O.K., Brug, J., van Goudoever, J.B., Looman, C., Reis, I.K.M., & Kornelisse, R.F. (2014). Sequential hand hygiene promotion contributes to a reduced nosocomial bloodstream infection rate among very low-birth weight infants: An interrupted time series over a 10-year period. *American Journal of Infection Control 42*, 718-722.	
Healthcare Workers Must Know How To Properly Care For Central Venous Catheters (CVC) In Order To Prevent Catheter-Related Bloodstream Infection (CRBSI)	- Implement education and training on the proper procedures to use when cleaning a CVC and caring for a patient with a CVC.	Alkubati, S.A., Ahmed, N.T., Mohamed, O.N.E., Fayed, A.M., & Asfour, H.I. (2015). Healthcare workers' knowledge and practices regarding the prevention of central venous catheter-related infection. *American Journal of Infection Control 43*, 26-30.	B

Central Venous Catheter Care			
Topic	Recommendation	References	Strength of Recommendation
Evaluating The Necessity Of Using A CVC	-As a CVC carries the risk of sepsis if not cared for properly, routine CVC placement should be avoided. -A CVC should be removed when it is no longer needed. - A distal site should be chosen over a proximal site when inserting a peripherally inserted central catheter (PICC). -Nurses should collaborate with the physician if their patient no longer seems to need a CVC.	Semelsberger, C.F. (2009). Educational interventions to reduce the rate of central catheter-related bloodstream infections in the NICU. *Neonatal Network 28*(6), 391-395. Goutail-Flaud, M.F., Sfez, M., Berg, A., Laguenia, G., Couturier, C., Barbotin-Larrieu, F., & Saint-Maurice, C. (1991). Central venous catheter-related complications in newborns and infants. *Journal of Pediatric Surgery 26*(6), 645-650.	B

Precautions Taken During CVC Insertion	- Training a specific team of healthcare workers on CVC insertion may decrease the rates of infection. - Using a special room for CVC insertion rather than the bedside may lead to a cleaner procedure. - Maximal sterile barrier precautions should be observed during the insertion procedure. This includes the use of a mask, cap, sterile gloves, gown, and large drape. - Apply 2% chlorhexidine skin prep to the area of insertion and the surrounding skin.	Goutail-Flaud, M.F., Sfez, M., Berg, A., Laguenia, G., Couturier, C., Barbotin-Larrieu, F., & Saint-Maurice, C. (1991). Central venous catheter-related complications in newborns and infants. *Journal of Pediatric Surgery 26*(6), 645-650. Raad, I.I., Hohn, D.C., Gilbreath, B.J., Suleiman, N., Hill, L.A., Bruso, P.A. ... (1994). Prevention of central venous catheter-related infections by using maximal sterile barrier precautions during insertion. *Infection Control and Hospital Epidemiology 15*(4), 231-238.	A

Other Tools To Help Prevent Incorrectly Performed CVC Insertions	- Include instructions on aseptic preparation of the instrument table in hospital protocols for CVC insertion. - Maintain a CVC supply cart and bring it to each CVC placement. This allows healthcare workers to quickly access new supplies if something becomes contaminated rather than have to stop the procedure. - Keep a list of CVC practice recommendations on hand during insertions for reference. - Empower nurses to stop an insertion if they observe it being performed incorrectly.	Korhonen, A. (2010). A multicentred clinical improvement project among preterm population evaluation of current practices. *The Journal of Perinatal & Neonatal Nursing, 24*(4), 341-347. Semelsberger, C.F. (2009). Educational interventions to reduce the rate of central catheter-related bloodstream infections in the NICU. *Neonatal Network 28*(6), 391-395.	B
Caring For The Patient with A CVC	- 2% chlorhexidine in 70% isopropyl alcohol should be used for hub care.	Sannoh, S., Clones, B., Munoz, J., Montecalvo, M., & Parvez, B. (2010). A multimodal approach to central venous catheter hub care can decrease catheter-related bloodstream infection. *American Journal of Infection Control, 38*(6), 424-429.	B

Dietary prevention of bloodstream infection			
Topic	Recommendation	References	Strength of Recommendation
Diet And Supplementation May Affect Susceptibility To Infection	- Increase human milk consumption by the neonate by encouraging mothers to breastfeed or bring in breast milk to the NICU.	Patel, A. L., Johnson, T. J., Engstrom, J. L., Fogg, L. F., Jegier, B. J., Bigger, H. R., & Meier, P. P. (2013). Impact of early human milk on sepsis and health-care costs in very low birth weight infants. *Journal of Perinatology : Official Journal of the California Perinatal Association, 33*(7), 514-519.	B

Secondary Interventions			
Recognizing and Evaluating Sepsis			
Topic	Recommendation	References	Strength of Recommendation
Some Populations Have An Increased Risk Of Developing Sepsis	-High risk populations should be observed for signs and symptoms of infection. -Low birth weight neonates and those born prematurely have higher rates of bloodstream infection. - The use of CVCs and surgery create an opening for bacteria to enter the bloodstream. -A proximally placed PICC is more likely than a distally placed PICC to lead to infection.	Auriti, C., Ronchetti, M.P., Pezzotti, P., Marrocco, G., Quondamcarlo, A., Seganti, G., … (2010). Determinants of nosocomial infection in 6 neonatal intensive care units. *Infection Control and Hospital Epidemiology 31*(9), 926-933. da Silva, P., Soares, A., Gonçalves, R., Mota, E., Torres, M., & Lima, C. (2014). Late neonatal sepsis: An analysis of risk factors of an intensive care unit. [Sepse neonatal tardia: análise dos fatores de risco de uma unidade de terapia Intensiva] *Journal of Nursing UPFE, 8*(7), 2964-2974. Djordjevic, Z.M., Markovic-Denic, L., Folic, M.M., Igrutinovic, Z., & Jankovic, S.M. (2015). Healthcare-acquried infections in neonatal intensive care units: Risk factors and etiology. *American Journal of Infection Control 43*, 86-88. Goutail-Flaud, M.F., Sfez, M., Berg, A., Laguenia, G., Couturier, C., Barbotin-Larrieu, F., & Saint-Maurice, C. (1991). Central venous catheter-related complications in newborns and infants. *Journal of Pediatric Surgery 26*(6), 645-650.	A

Pharmacologic treatment of bloodstream infection			
Topic	Recommendation	References	Strength of Recommendation
Many Pathogens Can Cause Neonatal Sepsis	-Neonates with suspected sepsis should have a blood culture taken to determine the pathogen causing the infection in order to determine the most effective antibiotic to use.	Lutsar, I., Chazallon, C., Carducci, F.I.C., Trafojer, U., Abdelkader, B., Cabre, V.M. …(2014). Current management of late onset neonatal bacterial sepsis in five European countries. *European Journal of Pediatrics 173*, 997-1004.	B
Timing the Administration of Treatment	- Administer antibiotics within three hours of recognition of sepsis. -Organ dysfunction may result if treatment is delayed.	Weiss, S.L., Fitzgerald, J.C., Balamuth, F., Alpern, E.R., Lavelle, J., Chilutti, M. … (2014). Delayed antimicrobial therapy increases mortality and organ dysfunction duration in pediatric sepsis. *Critical Care Medicine 42*, 2409-2417.	A

Some Antibiotics Are More Effective Against Specific Pathogens Than Others	-Use penicillin, rifampin, or amoxicillin to treat sepsis caused by Group B Streptococcus. -Use ampicillin, gentamicin, or a 3rd generation cephalosporin to treat an infection caused by E. coli. -Use ampicillin with or without gentamicin or vancomycin or a 3rd generation cephalosporin to treat L. monocytogenes. -Use vancomycin with an aminoglycoside or cefotaxime to treat sepsis caused by S. epidermidis. - Use an antistaphylococcal penicillin (methicillin, nafcillin, oxacillin) to treat sepsis caused by S. aureus; use vancomycin if MRSA is suspected. -Use an antipseudomonal penicillin (ticarcillin) or a 3rd generation cephalosporin with an aminoglycoside to treat an infection by P. aeruginosa. -Use metronidazole and vancomycin to treat a C. difficile bloodstream infection. -When a culture is inconclusive or unable to be performed, a broad spectrum antibiotic like a β-lactam (ampicillin, penicillin G) should be used with an aminoglycoside (gentamicin, tobramicin).	Tom-Revzon, C. (2004). Strategic use of antibiotics in the neonatal intensive care unit. *Journal of Perinatal and Neonatal Nursing 18*(3). 241-258.	A

Note: Strength of recommendations is based on the Strength of Recommendation Taxonomy (SORT) (Ebell et al., 2004) (Appendices B & C).

CHAPTER 4

Implementation and Evaluation

This chapter will include information on designing an educational reference sheet and implementing it in the NICU setting, as well as how the effectiveness of the recommendations and reference sheet would be evaluated. The reference sheet is an educational tool that nurses and other healthcare staff can utilize as they work with neonates who are at risk for developing sepsis or who have already been diagnosed with a bloodstream infection. Education has been shown to be effective in reducing rates of infection so this 8.5x11" reference sheet would serve to enforce the education that nurses have already received on caring for their patients. It would also serve as a guide if a nurse has a specific inquiry regarding sepsis. The ultimate goal of this reference sheet is to reduce the rates of bloodstream infection and subsequent mortality of neonates.

In order to implement this reference sheet, research on creating effective health education tools will be utilized. In addition, Kotter's Change Phases model will be used. This eight step process for creating change in the clinical setting includes establishing urgency, creating a coalition, developing a vision and strategy, communicating the vision, empowering broad-based action, generating short-term wins, consolidating improvements and producing more change, and anchoring the change (Brown & Schmidt, 2012). The success or "anchoring" of the recommendations will be used as an evaluation. Finally, the strengths and limitations of this thesis will be discussed, as well as additional recommendations for future research.

Implementation

Creating an Effective Reference Sheet

The purpose of this thesis is to develop an evidence-based educational reference sheet that can be utilized by the nursing and other healthcare staff in the NICU. The reference sheet will include information about sepsis and caring for patients who are at risk for developing sepsis or who have already been diagnosed with sepsis. This information is based on the literature and evidence-based recommendations summarized in Chapter 3. In order to develop an effective reference sheet, several factors must be assessed (U.S. Department of Health and Human Services. Center for Disease Control and Prevention [CDC], 2009). First, the audience and their key characteristics, such as literacy skills, behaviors, and current knowledge about the topic, must be determined (CDC, 2009). In this case, the audience is the nursing staff. The staff has some years of college education, has at least background knowledge of sepsis, and has cared for patients with sepsis or CVCs in the past. The level of education and literacy for nurses is higher than the general public so more complicated language can be used when discussing sepsis; however, individuals with higher health literacy skills still “want health information that is understandable, meaningful to them, and easy to use,” so overly complicated language should be avoided when possible (CDC, 2009, p.3). In addition, the key messages of the reference sheet should be determined, and the most important information should be communicated first (CDC, 2009). The reference sheet should include what actions the audience should take and why those actions are important (CDC, 2009). To be most effective, an active voice using positive language should be utilized (CDC, 2009).

The design of a reference sheet should stand out and grab attention (Pennisi, Gunawan, Major, & Winder, 2011). This can be done by using catchy phrases and color (Pennisi et al., 2011). Readability is also important, so a font with serifs and a font size between 12 and 14 points are recommended (CDC, 2009). Other design factors to consider are leaving white space to decrease clutter, organizing the messages so they are easy to recall, utilizing columns that are 40 to 50 characters in length, and including text boxes with the most important information (CDC, 2009).

Change Phases Model

The Change Phases model will be used to theoretically implement the evidence-based recommendations in this thesis into the NICU setting. This theory was developed by John Kotter in 1996 and is described as a top-down transformation process, meaning that each step builds upon the successes of the prior steps (Brown & Schmidt, 2012). The Change Phases model includes eight steps: establishing urgency, creating a coalition, developing a vision and strategy, communicating the vision, empowering broad-based action, generating short-term wins, consolidating improvements and producing more change, and anchoring the change (Brown & Schmidt, 2012).

The first step, establishing urgency, requires creating a sense that change is needed within the unit. Data can be very powerful in this step, so collecting data about the rate of bloodstream infection in a specific NICU could create the necessary sense of urgency. Data regarding the mortality rates of infected neonates or the cost incurred due to the higher acuity of these patients could also be useful. The act of collecting the data and presenting it to others also creates a sense of urgency.

The second step in Kotter’s model is to create a coalition (Brown & Schmidt, 2012). A coalition is a group of individuals who “share similar thoughts and a vision for change” (Brown & Schmidt, 2012, p.408). Often times, communicating the sense of urgency results in the creation of a coalition because the colleagues who are interested in the issue decide to be the force that creates change. A group of NICU nurses, physicians, and other healthcare workers could collaborate to form a coalition.

Once a coalition is formed, the third step of Kotter's model can begin. The goal in this step is to develop a vision and strategy for change (Brown & Schmidt, 2012). In this case, implementing the evidence-based recommendations in this thesis would be the strategy used to attain the vision of decreased sepsis and mortality rates among neonates in the NICU.

Once the vision and strategy have been determined, the coalition would work towards completing the fourth step of the Change Phases model, communicating the vision (Brown & Schmidt, 2012). Communication of the vision could happen at a staff meeting so that all staff are aware of the vision. Clear communication is important to avoid misunderstandings and misconceptions regarding the change. Misunderstandings and misconceptions can lead to unnecessary resistance to the change (Brown & Schmidt, 2012). However, good communication can potentially gain support for the proposed change.

The fifth step of Kotter's model is the first that includes any change in action or practice (Brown & Schmidt, 2012). This step, empowering broad based action, requires the continued support of the coalition to ensure that the unit follows the new policy that has been developed (Brown & Schmidt, 2012). Members from all departments, including nurses, physicians, pharmacists, and ancillary staff, have responsibility and accountability for following the policy (Brown & Schmidt, 2012). The larger the variety of staff that are empowered to follow the policy, the greater its chance for success. Displaying the reference sheet in prominent areas, creating access to it where educational materials are kept, and providing copies for individual nurses to carry with them encourages nurses and other healthcare providers to follow the recommendations that are included on the reference sheet. Empowering nurses to speak up if they see a procedure being performed incorrectly that could potentially increase a neonate’s risk of contracting sepsis is another way to ensure action. Creating a culture with a sense that it is important to perform every procedure correctly every time can also prompt nurses to follow the evidence-based recommendations.

The next step in the Change Phases model is to generate short-term wins (Brown & Schmidt, 2012). This involves recognizing small successes along the way to the grand vision. Recognizing the small successes reinforces the change and creates a positive environment for the change to occur (Brown & Schmidt, 2012). For example, if a nurse routinely performs CVC dressing changes using the recommended materials described in the reference sheet and encourages other to do so as well, the nurse should be told how much her support is appreciated. This will encourage her to continue utilizing the recommendations and encourage others to do the same, and many short-term wins will be created.

The seventh step in Kotter’s Change Phases model is to consolidate the improvements (Brown & Schmidt, 2012). Each time there is a short-term win, the change is reinforced. Eventually, the short-term wins consolidate so that all members of the healthcare team are following the recommendations and perpetuating adherence. By this, success is achieved (Brown & Schmidt, 2012).

The final step in Kotter’s model, anchoring the change, follows the consolidation of improvements. When all healthcare team members are following the recommendations, the new way of doing things becomes permanent or “anchored” (Brown & Schmidt, 2012). This step is important because if the new recommendations don’t become anchored, the effort to create the change will have been wasted. However, if the change does become anchored, the vision of reducing sepsis and mortality rates can be achieved.

Summary

The design of the sepsis prevention and treatment reference sheet is based on research about implementing health education materials. Creating an effective reference sheet ensures that the most important information is imparted its readers so that prior knowledge can be reinforced or modified to the most current practices. The theoretical implementation of the reference sheet and the evidence-based recommendations in this thesis are based on Kotter's Change Phases model of creating change in the clinical setting. The Change Phases model is a method of imparting the necessity of change, designing a cohesive plan regarding what needs to change and what the ultimate goal of the change is, and actually creating and encouraging the change to occur and become permanent.

Evaluation

Evaluating the implementation of the evidence-based recommendations is the last section that will be discussed in this chapter. The final stage of Kotter's Change Phases model, anchoring the change, and data regarding sepsis and mortality rates will be used in this theoretical evaluation.

Kotter's eighth Change Phases model step is the anchoring of the change. This step is completed when all healthcare team members follow the recommendations and the new changes have become a permanent part of practice. The success of the implementation could be measured by the adherence to the practice recommendations by the healthcare team members in the NICU a year after the changes were first implemented. Nurses' actions while caring for neonates at risk for developing sepsis could be observed. A checklist for procedures, such as CVC dressing changes, could be used by the observer to determine if the nurse is following each recommendation, including having the correct materials and using sterile technique. This could be conducted for a few nurses to gain an idea of whether the nurses are following the recommendations. If they are, the change has been anchored successfully.

In addition, the efficacy of the recommendations in a specific NICU can be evaluated by comparing data on the rates of sepsis and subsequent mortality from before the changes to the same data collected a year after the changes. The rate would be expected to decrease if the changes were implemented correctly and were being followed.

In order to evaluate the implementation of the reference sheet, a questionnaire could be administered to the nurses on the unit two, six, and twelve months after the reference sheet has been posted around the unit. The questionnaire would include inquiries regarding the nurse's use of the reference sheet in the past week, whether they think the recommendations are meaningful and helpful, and if they follow the recommendations. There could also be a section where the nurses could write in recommendations for any changes that could be made to make the reference sheet more effective, such as including specific information or excluding something that is already on the sheet. The results of this questionnaire would indicate the nurses' compliance with the recommendations over time and give feedback on the efficacy of using reference sheets to impart information regarding caring for patients with sepsis.

Strengths and Limitations and Recommendations for Future Research

The strengths of this thesis include that it contained a thorough review of the literature regarding preventing neonatal sepsis, treating neonatal sepsis, and caring for the patient who is at risk for developing sepsis or who has already been diagnosed with a bloodstream infection. The review of the literature also indicated that current practices need improvement and that education can be used as an intervention to decrease sepsis rates. A wide variety of studies was examined, including those at the highest level of evidence. The demographics of these studies varied as well, which supports implementing the evidence-based recommendations in a wide variety of locations and sizes of NICUs. The reference sheet includes these recommendations and is an easy method of imparting information to a wide variety of nurses and healthcare team members.

A limitation of this thesis is that it does not include recommendations on what practices should not be performed. For example, data from the literature review suggests that umbilical cord cleanses and probiotics are not effective in preventing sepsis in neonates, but this thesis does not include any recommendation to avoid those. In addition, data on rates of sepsis varies depending on the source, so it is not possible to give an exact number regarding the cases of late onset sepsis or to determine the rates of neonatal sepsis in a specific hospital. Also, the implementation and evaluation of the recommendations presented in this thesis are theoretical so it is not possible to determine what potential problems may arise or changes that would be needed to implement the recommendations.

Recommendations for future research include conducting studies that examine rates of neonatal sepsis in specific locations, as well as more research on what recommendations are already in place to prevent neonatal sepsis and the efficacy of these recommendations. Additionally, research regarding imparting health information to healthcare professionals instead of to the general public would be useful in designing reference sheets.

Summary

The purpose of this thesis was to develop an educational reference sheet that included information on caring for neonatal patients at risk for sepsis or who have been diagnosed with sepsis. Current research indicated that sepsis increases a neonate’s risk of mortality and comorbidity, and that there is a need for improvement in the current practices of caring for these patients. An extensive literature review determined specific recommendations for nursing practice that could improve the outcomes of neonatal patients, including additional education for nurses. The evaluation process would determine the magnitude of effect of the recommendations, as well as nurses' opinions on the efficacy of using a reference sheet when caring for neonates with bloodstream infection. Overall, the implementation of the evidence-based recommendations and the reference sheet would create a culture of performing procedures correctly every time, and looking for the correct procedure when one is unsure of how it is performed. The goal of these recommendations is to create the best outcomes possible for neonates who have had a rough start to life.

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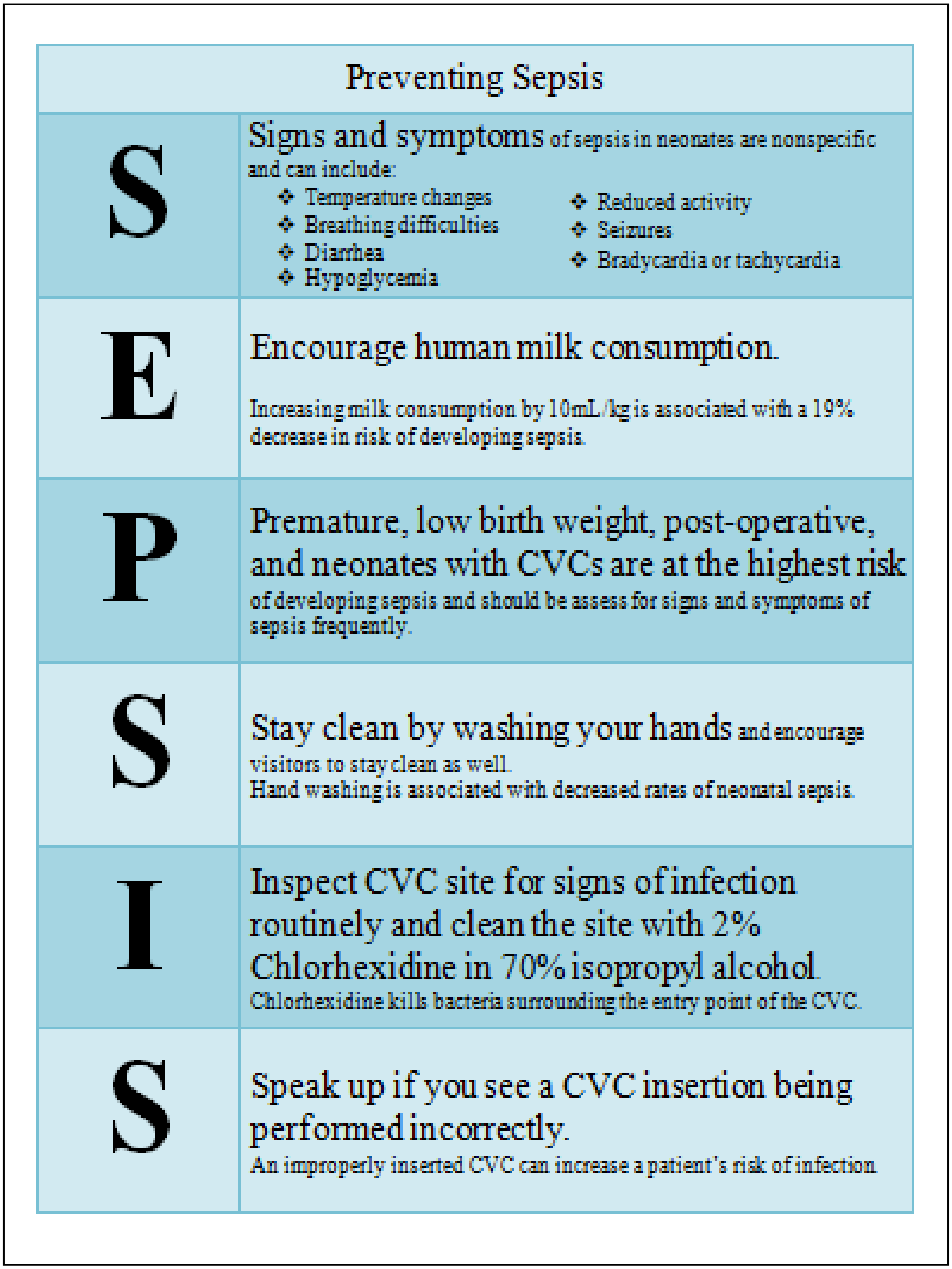
Appendix A

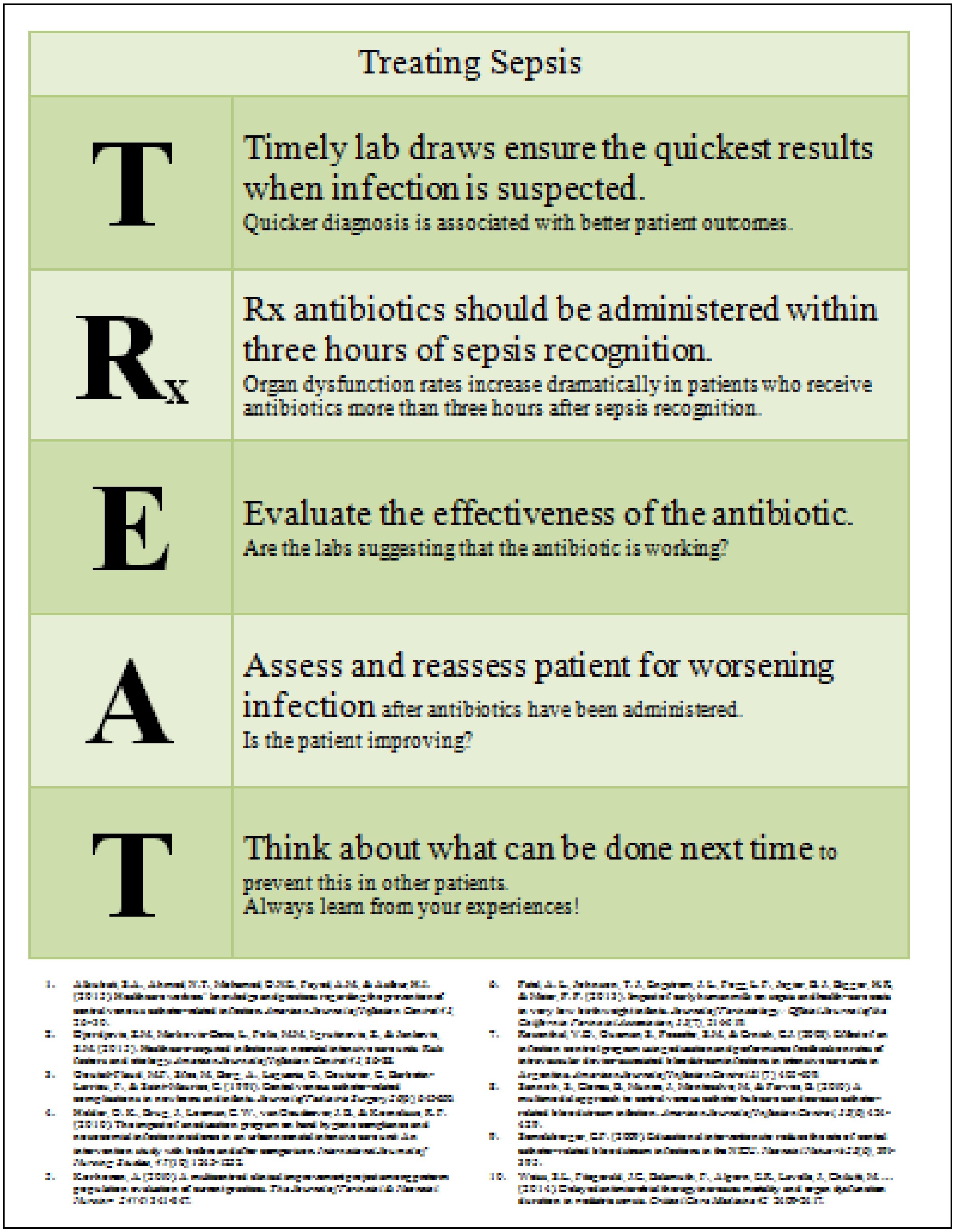
Figure 1: Reference Sheet with Evidence-Based Recommendations (8.5x11”). Side A.



Preventing Sepsis	
S	Signs and symptoms of sepsis in neonates are nonspecific and can include: ❖ Temperature changes ❖ Breathing difficulties ❖ Diarrhea ❖ Hypoglycemia ❖ Reduced activity ❖ Seizures ❖ Bradycardia or tachycardia
E	Encourage human milk consumption. Increasing milk consumption by 10mL/kg is associated with a 19% decrease in risk of developing sepsis.
P	Premature, low birth weight, post-operative, and neonates with CVCs are at the highest risk of developing sepsis and should be assess for signs and symptoms of sepsis frequently.
S	Stay clean by washing your hands and encourage visitors to stay clean as well. Hand washing is associated with decreased rates of neonatal sepsis.
I	Inspect CVC site for signs of infection routinely and clean the site with 2% Chlorhexidine in 70% isopropyl alcohol. Chlorhexidine kills bacteria surrounding the entry point of the CVC.
S	Speak up if you see a CVC insertion being performed incorrectly. An improperly inserted CVC can increase a patient's risk of infection.

Appendix B

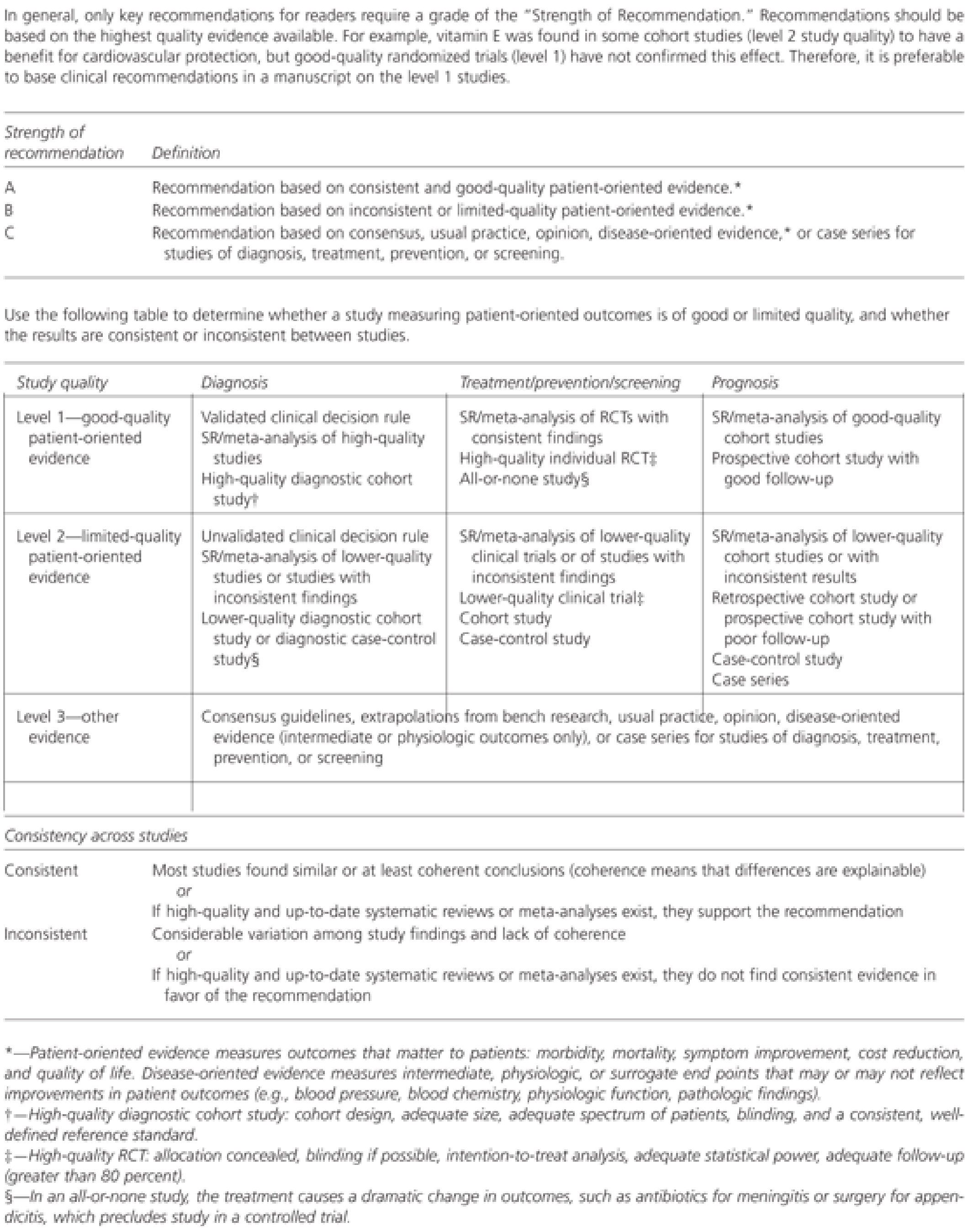
Figure 2: Reference Sheet with Evidence-Based Recommendations (8.5x11”). Side B.



Treating Sepsis	
T	Timely lab draws ensure the quickest results when infection is suspected. Quicker diagnosis is associated with better patient outcomes.
Rx	Rx antibiotics should be administered within three hours of sepsis recognition. Organ dysfunction rates increase dramatically in patients who receive antibiotics more than three hours after sepsis recognition.
E	Evaluate the effectiveness of the antibiotic. Are the labs suggesting that the antibiotic is working?
A	Assess and reassess patient for worsening infection after antibiotics have been administered. Is the patient improving?
T	Think about what can be done next time to prevent this in other patients. Always learn from your experiences!

Appendix C

Figure 3: Strength of Recommendation Taxonomy (SORT)



In general, only key recommendations for readers require a grade of the "Strength of Recommendation." Recommendations should be based on the highest quality evidence available. For example, vitamin E was found in some cohort studies (level 2 study quality) to have a benefit for cardiovascular protection, but good-quality randomized trials (level 1) have not confirmed this effect. Therefore, it is preferable to base clinical recommendations in a manuscript on the level 1 studies.

Strength of recommendation	*Definition*
A	Recommendation based on consistent and good-quality patient-oriented evidence.*
B	Recommendation based on inconsistent or limited-quality patient-oriented evidence.*
C	Recommendation based on consensus, usual practice, opinion, disease-oriented evidence,* or case series for studies of diagnosis, treatment, prevention, or screening.

Use the following table to determine whether a study measuring patient-oriented outcomes is of good or limited quality, and whether the results are consistent or inconsistent between studies.

Study quality	*Diagnosis*	*Treatment/prevention/screening*	*Prognosis*
Level 1—good-quality patient-oriented evidence	Validated clinical decision rule SR/meta-analysis of high-quality studies High-quality diagnostic cohort study†	SR/meta-analysis of RCTs with consistent findings High-quality individual RCT‡ All-or-none study§	SR/meta-analysis of good-quality cohort studies Prospective cohort study with good follow-up
Level 2—limited-quality patient-oriented evidence	Unvalidated clinical decision rule SR/meta-analysis of lower-quality studies or studies with inconsistent findings Lower-quality diagnostic cohort study or diagnostic case-control study§	SR/meta-analysis of lower-quality clinical trials or of studies with inconsistent findings Lower-quality clinical trial‡ Cohort study Case-control study	SR/meta-analysis of lower-quality cohort studies or with inconsistent results Retrospective cohort study or prospective cohort study with poor follow-up Case-control study Case series
Level 3—other evidence	Consensus guidelines, extrapolations from bench research, usual practice, opinion, disease-oriented evidence (intermediate or physiologic outcomes only), or case series for studies of diagnosis, treatment, prevention, or screening		

Consistency across studies	
Consistent	Most studies found similar or at least coherent conclusions (coherence means that differences are explainable) *or* If high-quality and up-to-date systematic reviews or meta-analyses exist, they support the recommendation
Inconsistent	Considerable variation among study findings and lack of coherence *or* If high-quality and up-to-date systematic reviews or meta-analyses exist, they do not find consistent evidence in favor of the recommendation

*—*Patient-oriented evidence measures outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life. Disease-oriented evidence measures intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes (e.g., blood pressure, blood chemistry, physiologic function, pathologic findings).*

†—*High-quality diagnostic cohort study: cohort design, adequate size, adequate spectrum of patients, blinding, and a consistent, well-defined reference standard.*

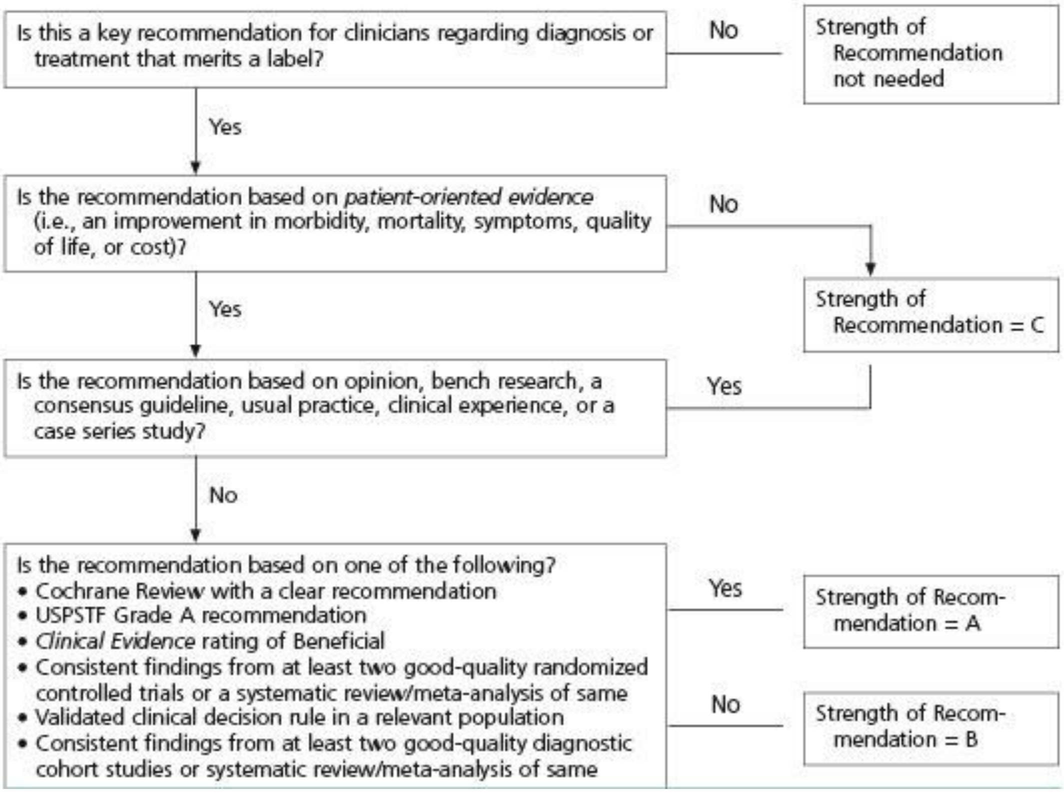
‡—*High-quality RCT: allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80 percent).*

§—*In an all-or-none study, the treatment causes a dramatic change in outcomes, such as antibiotics for meningitis or surgery for appendicitis, which precludes study in a controlled trial.*

Note: Retrieved from Ebell et al.(2004).

Appendix D

Figure 4: Strength of Recommendation Based on a Body of Evidence


Is this a key recommendation for clinicians regarding diagnosis or treatment that merits a label?
No
Strength of Recommendation not needed
Yes
Is the recommendation based on *patient-oriented evidence* (i.e., an improvement in morbidity, mortality, symptoms, quality of life, or cost)?
No
Strength of Recommendation = C
Yes
Is the recommendation based on opinion, bench research, a consensus guideline, usual practice, clinical experience, or a case series study?
Yes
No
Is the recommendation based on one of the following?
• Cochrane Review with a clear recommendation
• USPSTF Grade A recommendation
• *Clinical Evidence* rating of Beneficial
• Consistent findings from at least two good-quality randomized controlled trials or a systematic review/meta-analysis of same
• Validated clinical decision rule in a relevant population
• Consistent findings from at least two good-quality diagnostic cohort studies or systematic review/meta-analysis of same
Yes
Strength of Recom-mendation = A
No
Strength of Recom-mendation = B

Note: Retrieved from Ebell et al.(2004).