Nursing Interventions to Prevent Necrotizing Eterocolitis: A State of the Science Literature Review

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NURSING INTERVENTIONS TO PREVENT NECROTIZING ENTEROCOLITIS: A STATE OF THE SCIENCE LITERATURE REVIEW

by

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ABSTRACT

The purpose of this review of literature is to understand the current state of the science and to make recommendations for practice and research in regards to the gastrointestinal condition affecting premature infants, necrotizing enterocolitis (NEC). Emphasis is placed on reviewing the literature to identify prevention strategies nurses can use to reduce the incidence, morbidity and mortality of NEC. The introduction will focus on discussing the problem of NEC including its risk factors, pathophysiology, and disease presentation. The findings sections will focus on the most promising and researched areas of intervention. The discussion section will focus on how this knowledge can be translated into practice and what nurses can do about it.

The research will be conducted through nursing databases with conceptual primary sources that will further expand upon the selected studies on this topic.

DEDICATIONS

First and foremost, I would like to thank my Lord and Savior Jesus Christ. It is because of Him that I can do all things – including writing a thesis during nursing school while juggling a pregnancy and large family. He is also the reason I am in nursing school and felt called to write about this population.

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Next, I would like to dedicate this thesis to my five beautiful children Ava, Gianna, Maddox, Alivia, and Liam for bringing me unrelenting joy, happiness, and purpose every single day and inspiring me to help other families experience the same.

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Much love,
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Introduction

Necrotizing enterocolitis (NEC) is a devastating disease that is neither a uniform nor a well-defined entity and is associated with high morbidity and mortality (Gordon, Swanson, & Attridge, 2007). Even with early diagnosis, still 25-33% of all infants with NEC will die and those who survive are plagued with short and long-term co-morbidities (Thompson & Bizzaro, 2008). The high morbidity and mortality of NEC has made NEC an area of active research, however, researchers have yet to understand the pathogenesis of this disease; its exact cause and etiology are still unknown (Ganguli & Walker, 2012). Additionally, treatment options are often unsuccessful and there is little improvement of outcomes even after early diagnosis. Research and attention needs to be redirected to NEC prophylaxis and the reproducibility of promising studies and interventions.

Disease Background

Necrotizing enterocolitis is an acquired gastrointestinal (GI) disease that mainly affects premature infants (Noerr, 2003). It is characterized by diffuse necrotic injury to the mucosal and submucosal layers of the bowel, resulting in bowel wall necrosis leading to perforation (Fox & Godavitarne, 2012). The condition can occur anywhere in the GI tract but most commonly occurs in the right lower quadrant effecting the jejunum, ileum, and cecum (Bradshaw, 2009).

Researchers have yet to fully understand the pathogenesis of this disease (Ganguli & Walker, 2012). However, research has shown that NEC is probably multifactorial in origin (Bilali, Bartsocas & Velonakis, 2012). Blood flow, intestinal barrier function immaturity, and

bacterial colonization of the newborn's GI tract have been identified as primary factors that lead to the development of NEC (Bradshaw, 2009). The most current research explains the pathophysiology of NEC as likely secondary to innate immune responses to intestinal microbiota by the premature infant's intestinal tract, leading to inflammation and injury (Tanner et al, 2015). Additionally, research has shown other GI disorders in this population may have been historically misdiagnosed as NEC, offering an explanation for the confusion and disparity between etiology, presentation, and treatment of NEC thus far (Gordon et al, 2007).

The presentation of NEC varies widely. Symptoms of NEC may be sudden and profound or insidious and subtle (Noerr, 2003). Additionally, disease presentation varies depending on the stage of the disease, so NEC is best defined along a continuum from suspected cases to infants with advanced disease (Noerr). Signs and symptoms of NEC during early onset are often nonspecific and may resemble symptoms of sepsis such as apnea (with or without bradycardia), temperature instability, and lethargy (Luton, 2013). Other nonspecific signs of NEC may include feeding intolerance, sepsis, or GI bleeding, all of which may be caused by stress or other conditions of prematurity (Noerr). In an attempt to improve reporting and the management of NEC, a tool known as Bell's staging was developed in 1978 by Bell and colleagues which was later modified in 1979 and again in 1986 by Walsh and Kliegman and is displayed in Table 1 (Gordon et al, 2007). Although clinicians agree that Bell's staging needs to be updated further, it is still widely accepted and no other staging system has been universally been accepted (Gordon et al).

Table 1. Modified Bell's staging for NEC. (Adapted from Walsh and Kliegman, 1987).

Review of Bell's stages	***Clinical findings***	***Radiographic findings***	***Gastrointestinal findings***
Stage I	Apnea and bradycardia, temperature instability	Normal gas pattern or mild ileus	Gastric residuals, occult blood in stool, mild abdominal distention
Stage II A	Apnea and bradycardia, temperature instability	Ileus gas pattern with one or more dilated loops and focal pneumatosis	Grossly bloody stools, prominent abdominal distention, absent bowel sounds
Stage II B	Thrombocytopenia and mild metabolic acidosis	Widespread pneumatosis, ascites, portal-venous gas	Abdominal wall edema with palpable loops and tenderness
Stage III A	Mixed acidosis, oliguria, hypotension, coagulopathy	Prominent bowel loops, worsening ascites, no free air	Worsening wall edema, erythema and induration
Stage III B	Shock, deterioration in laboratory values and vital signs	Pneumoperitoneum	Perforated bowel

According to modified Bell's staging, there is a classic triad of symptoms including abdominal distension, bloody stools, and bilious gastric aspirate or emesis accompanied by any

of these conditions; pneumatosis intestinalis, portal venous gas, or pneumoperitoneum (Luton, 2013). At least one of the symptoms must be present along with one positive radiographic finding that meets diagnostic criteria for NEC, with abdominal distention usually being the first to occur (Luton). The diagnostic criteria defined in Bell's staging can often lead to misdiagnosis of NEC because it shares many similar diagnostic findings with other acquired neonatal intestinal diseases (ANIDs). As such, some ANIDs lead to the final diagnosis of NEC and some do not (Gordon et al, 2007). Researchers are beginning to question if the misdiagnosis of NEC and other ANIDs has been the cause for so many disparities in trial results, leading to more confusion about NEC.

The risk factors for NEC seem endless, however, the only consistent recognized risk factor is prematurity (Luton, 2013). Related risk factors specifically for premature infants include a birth weight of less than 1000 grams, gestational age (the highest at risk are babies with the lowest gestational age), non-standardized feeding practices, non-standardized management of feeding intolerance, use of infant formula, use of H2 blockers, choriamnionitis, sepsis, number of infections, first course of antibiotics being equal to or over five days, patent ductus arteriosus, indomethacin and glucocorticoid treatment (especially in the first week of life), absence of an umbilical arterial catheter, mechanical ventilation, packed red blood cell (PRBC) transfusions, HIV positive mother, maternal antenatal cocaine use, perinatal asphyxia, Apgar score of less than seven after five minutes, black race, male, antenatal glucocorticoids, morphine infusion, and cesarean section (Gephart et al, 2012).

Although less than ten percent of NEC cases occurs in late preterm and term infants, it is important to differentiate between the risk factors for these infants from those of early preterm infants (Gephart et al, 2012). Risk factors for late pre-term and term infants include cyanotic

congenital heart disease, polycythemia, intrauterine growth restriction, formula feeding, maternal hypertensive disease, HIV positive mother, umbilical catheters, exchange transfusions, perinatal asphyxia, mechanical ventilation, sepsis, maternal illicit drug use, respiratory distress syndrome, and an Apgar score of less than seven after five minutes (Gephart et al).

Despite the overwhelming number of risk factors, this list is not universally agreed upon nor is it exhaustive of every prenatal, intrapartum, and postnatal risk factor. However, the majority of these risk factors are related to one or more of the following primary risk factors that NEC researchers have identified, which include blood flow, intestinal barrier function, and bacterial colonization of the newborn's GI tract (Bradshaw, 2009).

The incidence of developing NEC is inversely proportional to gestational age and birth weight (Bradshaw, 2009). Therefore, the most premature infants, extremely low birth weight (ELBW), defined as weighing less than 750 grams, and very low birth weight (VLBW), defined as weighing 750-1000 grams, are the most susceptible (Lin & Stoll, 2006). It is estimated around seven percent of infants in the United States weighing 1500 grams or less develop the disease (Wright & Miller, 2012). Globally, NEC incidence rates vary widely in this population with statistics ranging from 1% to 28% (Caplan & Jilling, 2001). These numbers are significant because one in ten (15 million) premature births occur each year worldwide (Kinney, Lawn, Howson, & Belizan, 2012).

True to the inverse proportion of gestational age and birth weight, countries that report a low incidence of NEC also tend to experience a lower rate of preterm births (Noerr, 2003). Countries whose NEC incidence rates are similar to those of the United States include Canada and Australia (Luig & Lui, 2005; Sankaran et al, 2004).

For many years, clinicians saw little progress in NEC prevention, and no definitive progress in treatment was achieved (Gordon et al, 2007). Especially because of increased viability at lower gestational ages, the number of infants at risk has increased. Fortunately, it seems as if some advances are being made. In 2005, the Centers for Disease Control (CDC) rated NEC as the tenth most common cause of death for all infants (CDC, 2005). Most recently in 2013, the CDC dropped NEC to the 11th most common cause of death for all infants which equates to a reduced percentage of all births to 0.4% (CDC, 2005; CDC, 2013).

Morbidity and mortality of NEC is directly correlated with the stage of NEC based on Bell's modified staging criteria and the choice of therapy (Carter, 2007). The overall mortality for all patients with NEC is 28% (Hull et al, 2014). The choice of therapies for the treatment of NEC can be divided into two categories: surgical and medical (Carter). Medically managed NEC mortality is 21% overall, with significantly lower mortality in neonates of larger birth weight (Hull et al). Medical management of patients with NEC includes restricted oral intake accompanied by gastric decompression. Additionally, patients are given total parenteral nutrition, receive appropriate antibiotic coverage, and receive close clinical and laboratory monitoring with serial abdominal X-rays every six to eight hours to detect intestinal perforation (Huda, 2014).

Surgical NEC mortality is 35% overall and, unlike that of medical NEC, does not consistently improve with larger birth weight (Hull et al, 2014). Unfortunately, 52% percent of VLBW neonates with NEC undergo surgery, which is accompanied by a substantial increase in mortality (Hull et al). Not surprisingly, because infants with surgical NEC have lower birth weights, younger gestational age, and lower Apgar scores, operative intervention rather than medical management is more common (Carter). Emergency surgical intervention is undertaken

in all cases of pneumoperitoneum (Carter). Surgery is also indicated if the infant is clinically deteriorating despite maximal medical treatment, if an abdominal mass is detected, if the preterm infant has signs of persistent intestinal obstruction, sepsis, or has an intestinal stricture (Huda). Other relative indications for surgery are increased abdominal tenderness, distension, discoloration, or the persistence of portal vein gas (Huda). When surgery is indicated, various strategies are available. Surgical interventions include primary peritoneal drainage, laparotomy with resection and enterostomy, resection with primary anastomosis, proximal diverting jejunostomy, clip and drop technique laparotomy, and primary peritoneal drainage (Huda). Laparotomy was the more frequent method of treatment (69%), and of those managed by drainage, 46%, also had a laparotomy (Hull et al). The laparotomy alone, and drainage with laparotomy groups, had similar mortalities while treatment by drainage alone was associated with the highest mortality (Hull et al).

Even with early detection and survival after NEC, the illness and its therapies are associated with many long-term problems (Carter, 2007). The most common complications of infants with NEC include feeding intolerance, higher incidence of nosocomial infections, lower levels of nutrient intake, slower growth, longer durations of intensive care hospital stay, and surgery-related complications such as strictures and obstructions (McGuire, 2015). Short and long-term problems of infants with NEC, particularly severe NEC requiring surgical intervention, is a high incidence of significant long-term neurological disability, growth delay, cystic periventricular leukomalacia, bronchopulmonary dysplasia and short gut syndrome (McGuire; Fox & Godavitarne, 2012; Huda).

In addition to the global priority of addressing the significant morbidity and mortality of NEC, it is important to recognize the immediate economic cost of NEC. Necrotizing enterocolitis

accounts for almost 20% of NICU annual costs, an estimated $6.5 million in additional hospital costs per year in the US alone (Gephart et al, 2012; Rodriguez & Caplan, 2015). The average length of stay for medical NEC costs $73,700 and is 22 days more than for other premature infants (Gephart et al). If NEC cannot be managed medically and the affected neonate requires surgery, the average hospital stay is an additional 60 days and costs an additional $186,200 (Gephart et al). Furthermore, it has been estimated that it costs the US $1.5 million every five years for the ongoing outpatient care that NEC survivors require to manage the severe sequelae of the disease (Ganguli & Walker, 2012). These estimates do not factor in lost work and productivity costs of the parents of a baby with NEC. The primary and secondary conditions associated with NEC cost societal money, resources, victim and familial quality of life, and the lives of those who don't survive.

Problem

Necrotizing enterocolitis is a devastating disease that is neither a uniform nor a well-defined entity, but is associated with high morbidity and mortality (Gordon et al, 2007). Even with early diagnosis, still 25-33% of all infants with NEC will die. Those who survive are plagued with short and long-term co-morbidities (Thompson & Bizzaro, 2008). This made NEC an area of active research, however, researchers have still yet to understand the pathogenesis of this disease, and its exact cause and etiology remain unknown (Ganguli & Walker, 2012). Additionally, treatment options are often unsuccessful and there is little improvement of outcomes even after early diagnosis. Research and attention needs to be redirected to NEC prophylaxis through the repetition of promising studies and interventions.

Purpose

Because NEC is still an area of active research, it is challenging for health care professionals to stay up to date on the latest research and practice accordingly. Although many aspects of NEC require more research, it is important for health care professionals to understand and implement current evidenced-based practice (EBP) guidelines. The objective of this thesis is to provide an integrated review of the literature that provides the reader with a current picture of the state of the science on NEC with a primary focus on preventative strategies and nursing interventions. Any conclusions and findings explored herein may help provide translation of current knowledge into nursing practice and promote further research on NEC.

Methods

An initial review of the literature was performed by searching multiple electronic databases with the following inclusion criteria. The article must have been written in English, published in a peer reviewed journal, and available in full text. The following search terms were used: "necrotizing enterocolitis" and "NEC". Relevant articles contributing to the base of knowledge on NEC were reviewed and selected. However, because of the abundance of research and variety of topics, further parameters were selected for the discussion and findings section. The focus of the paper is to give nurses the most recent research on NEC, so the term "nurs*" was added with the publication restriction year of 2010 or later. An ancestry and descendant method was also used and relevant articles were discovered with this approach. This search strategy resulted in 110 articles from the following databases: Cumulative Index of Nursing and Allied Health (CINHAL), CINHAL Plus with Full Text, MEDLINE, Alternate HealthWatch, Biological & Agricultural Index Plus, PsycINFO, ScienceDirect, Dynamed, and Science Citation

Index. Articles were evaluated for their relevance to the topic and quality of research resulting in the elimination of 56 articles. The remaining articles 54 articles were read and analyzed. Thirty were used for general background information on NEC and 24 were categorized relating to several aspects associated with NEC. The categories were selected by summarizing the main idea of the article and grouping main ideas together. There were five articles relating to breastmilk, four on bacteria/probiotics, four on feeding practices, three on transfusion-related NEC, six on better understanding and diagnosing of NEC, one on H2 blockers, and one on quality improvement methods. Article findings are summarized and original research is discussed and critiqued below.

Findings

Breastmilk

Breastmilk has been shown to be the most effective intervention to reduce NEC and it should be the gold standard in the preterm population (Luton, 2013). Implementing breastmilk alone has shown to cut NEC incidence by over half because it helps defend the neonate against the multiple contributing factors to NEC and, contrarily, exclusively formula-fed infants in this population are six to ten times more likely to have confirmed NEC (Gephart et al, 2012; Thompson & Bizarro, 2008). The following are just some examples of how breastmilk helps reduce NEC incidence: breastmilk contains interleukin 10, which is an anti-inflammatory cytokine that reduces the activation of the cytokine cascade; it supplies IgA which helps prevent bacterial translocation across intestinal mucosa; it contains a protein called oral lactoferrin known to improve immunologic function; it contains prebiotics, possibly from the mother's GI tract and/or passed through breast milk, that help facilitate the digestion and replication of

protective bacteria and microbes that protect the neonate by interacting with intestinal cellular receptors that modulate the inflammatory response; breastmilk also contains epidermal growth factors, significant because infants diagnosed with NEC have decreased epidermal growth factors; and breastmilk has detectable levels of PAF-acetylhydrolase which prevent intestinal damage (Thompson & Bizzarro; Wright & Miller, 2012; Mshvildadze, Neu, & Mai, 2009; Frost & Caplan, 2013). Furthermore, breastmilk contains biofactors, including nutritional components, enzymes, hormones, antioxidants, soluble CD14, growth factors, immunoglobulins, glycoproteins, oligosaccharides and cytokines, all of which have overlapping functions and work synergistically to provide antimicrobial, anti-inflammatory, and antioxidant protection; together these biofactors modulate the infant's immune response, enhance intestinal maturation, and promote bifidogenic GI microflora (Rodriguez & Caplan, 2015).

Feeding the premature infant its own mother's expressed milk is the gold standard of care (Luton, 2013). The milk, especially colostrum, expressed by women who deliver ELBW infants has higher concentrations of many protective biofactors than milk expressed at term (Rodriguez & Caplan, 2015). While feeding every preterm infant breastmilk sounds simple, it is not always used or available; some mothers have underlying health conditions, do not make enough milk, or choose not to provide milk (Nelson, 2013). Thus, the next best nutrition to the preterm infant's own expressed mother's milk is banked human donor milk (Nelson). Since previous research has already identified breastmilk as having protective benefits against NEC, donor milk and barriers to its implementation has become the latest area of active research in regards to breastmilk.

Nelson (2013) discussed the benefits of human donor milk for preterm infants by method of literature review. For preterm infants in particular, feeding breastmilk over formula lowers rates of sepsis, NEC, and retinopathy of prematurity, and improves neurodevelopmental

outcomes. Nelson also reports that, according to a Cochrane Neonatal Review of eight trials comparing formula with human donor milk, formula increases growth rates short term but increases NEC risk. This finding led researchers to add bovine-based fortifiers to human milk to try to increase growth rates. Although human milk fortifiers have lower rates of NEC, most NICUs continue to use bovine-based fortifiers in human milk due to cost.

Nelson addressed the pasteurization process of human donor milk. Donors are first screened for viruses and illness that can be transmitted through breastmilk, and then through a process called the Holder method, in which breastmilk is pasteurized. Unfortunately, the pasteurization process causes some loss of live cells (IgA and lysozyme specifically); however, even with these losses, the value of human donor milk outweighs the use of formula for preterm infant. Nelson admits more research is needed on alternative pasteurization techniques, fortifiers, and an in-depth cost analysis of providing pasteurized human donor. Nelson, however, cites evidence from a systematic review and meta-analysis that there was a decrease of NEC by 79% with a sole diet of donor milk, and concludes that, therefore, the greatest clinical benefit of pasteurized human donor milk for preterm infants is the protective effect against NEC (Nelson).

Gibbins, Wong, Unger, and O'Connor (2013) co-published an article reviewing current literature focusing on the practice considerations of donor human milk for preterm infants. The article highlights benefits of breastmilk previously discussed and identifies the problems women face who have given birth to a preterm infant. These women may have low milk volumes due to stress, lack of support, immaturity of mammary secretory cells, and other factors related to preterm birth, including maternal illness. Other obstacles these women may possibly face are a lack of a breast pump, geographical and language barriers, and difficulties with storing and transporting milk. It is important to identify all obstacles to obtaining the preterm infant's

mother's own milk because, as previously discussed, the mother's own milk is the gold standard (Luton, 2013) and the perception of using bodily fluids from a stranger can be uncomfortable. Gibbins and colleagues revisit the history of wet nurses since ancient times, and that the concept of milk banks has been around since the early 1900s. However, with the emergence of HIV in the early 1980s, many milk banks closed and donor milk usage and research was limited. Thankfully, with improved knowledge and advances in technology milk banking has increased. Currently, The Human Milk Banking Association of North America (HMBANA) is the leader in establishing guidelines and education to promote milk banking, and provides milk to primarily hospitalized patients. Gibbins and colleagues also educate the reader on what exactly is pasteurized donor breastmilk, the process the milk undergoes, and the effect pasteurization has on the milk. The article touches on evidence for the use of donor milk for preterm infants, such as the reduction of NEC, improved immunity, and many long-term health benefits. Gibbins and colleagues note the risk of using donor milk: because it comes primarily from mothers of term infants and therefore has a lower protein content than milk from mothers of preterm infants, it contributes to slower growth in the preterm population (Gibbins et al.).

According to Carrol and Herman (2012), the strategy of using pasteurized human donor milk is to ensure VLBW infants are fed breastmilk exclusively to reduce the incidence of NEC, improve enteral feed tolerance and gastric emptying, achieve the rapid establishment of full enteral feeding, and reduce medication usage to treat gastroesophageal reflux. The American Association of Pediatrics (AAP) and the World Association of Perinatal Medicine insist on banked donor milk as a standard component of care for the preterm infant population (Carrol & Herman, 2012).

With these recommendations from the World Association of Perinatal Medicine, Australia is investigating how to introduce donor human milk to the NICU. Carrol and Herman (2012) highlight what they learned from a United States NICU so it can be applied to the implementation of human donor milk in Australia. They did this by administering a qualitative research study with both open and close-ended questions in a survey format. The purpose of the study was to research the perceptions and knowledge of a multi-disciplinary NICU team (including neonatologists, respiratory therapists, nurses, and lactation consultants) regarding pasteurized human donor milk. The study was part of a quality improvement initiative to reduce NEC rates and it captured the acceptance of the multidisciplinary NICU team both at implementation of pasteurized donor human milk and after using the donor milk for six months. Carrol and Herman hypothesized that, even though the empirical research supports human donor milk when the mother's own milk is not available, the perceptions and practices of the multi-disciplinary team collectively shapes the culture of acceptance and implementation of pasteurized human donor milk.

No formal education was provided before or during the study to the team. At implementation, 100% of the neonatologists, respiratory therapists, and lactation consultants replied yes they thought donor milk was a suitable infant feeding option in NICU, however 36% of surveyed nurses had some reservations about donor milk use, or did not agree to the use of donor milk. During the beginning of the study, only 79% of respondents were prepared to recommend donor milk to parents but after six months that proportion increased to a total of 93%. This overall increase in readiness to recommend donor milk to parents can be attributed to the increase in acceptance of donor milk among nursing staff because of their exposure to the positive outcomes in the infants. The positive perceived benefits for the unit included a decrease

in NEC (reported by 75% of respondents); improved feed tolerance (reported by 55% of respondents); and 15% of respondents even reported extra benefits of donor milk such as reduced constipation and a reduction of blood in the stools.

Carrol and Herman concluded that perceptions clinicians have about donor milk will likely change as a result of being exposed to it, and that purposeful education regarding donor milk is very much needed and wanted by NICU clinicians.

In a qualitative study looking at implications for nurses implementing donor milk for use in the hospital, Rosembaum (2012) conducted interviews with three separate hospitals currently using donor milk and summarized the findings. In all three hospitals, cost was the greatest barrier to implementing donor milk. Donor milk was not reimbursed by insurance companies and costs $3.00 to $5.00 per ounce with additional costs for shipping. In comparison, ready-to feed formula retails for 70.8 to 83 cents per ounce, and is commonly provided free to the hospitals. Still, one hospital absorbed the cost and reserved donor milk for only the most critical babies, one hospital pays for the first 12 ounces and then bills the parents, and the last hospital acquired funding to establish a separate milk lab for preparation of the pasteurized donor milk. The last hospital viewed donor milk as a dietary issue. Rosembaum states that when comparing the cost of NEC to that of donor milk, the cost of donor milk is small and should be considered because it is an effective prevention strategy against NEC.

The AAP recommends all preterm and compromised infants receive their mother's milk, and if it is not available, pasteurized human milk should be used (Andrew et al, 2014). With the increased acceptance and use of donor milk, the demand for donor milk is increasing. Andrew and colleagues recognize this need and estimate that nine million ounces are required to meet the needs of NICUs nationwide, leaving a critical shortage of human donor milk (Andrew et al).

There are currently only 12 HMBANA milk banks operating in the United States, and only 149 donor human milk depots are available to provide milk to the HMBANA milk banks. The depots are where the moms can drop off their milk to donate and the banks are where the milk is pasteurized by HMBANA. The authors propose that if every hospital established a donor human milk depot, the supply of donor milk would increase dramatically, which would reduce the shortage. Addressing the issue of donor milk shortage and implementing more milk depots are vital to the success of using donor milk as a preventative measure against NEC (Andrew et al).

In a 2015 study, Rodriquez and Caplan (2015) explore new ideas to combat NEC. Their article published in the *Journal of Perinatal & Neonatal Nursing* offers both evidence from current studies and proposes theoretical perspectives. Of particular importance here, Rodriquez and Caplan review the promising findings of oropharyngeal administration of mother's milk to prevent NEC in extremely low-birth weight infants, giving a new outlook on breastmilk and NEC.

Preterm infants commonly lack the ability to take feeds by mouth and must have their nutrition given through a nasogastric (NG) tube (Rodriguez & Caplan, 2015). In the first days of life, clinical instability of extremely low birth weight infants often prevents them from even receiving enteral feeds. However, when enteral feeds are administered the infant’s oropharynx is bypassed and not usually exposed to the many beneficial properties of breastmilk, as this paper has previously highlighted, for several weeks post-birth. As a potential preventative strategy against NEC, researchers have begun to experiment with oropharyngeal administration of mother's milk (placing drops of milk directly onto the oral mucosa) with the intention to expose the infant's oropharynx to the protective factors of breastmilk. So far the results from the studies are promising. The evidence suggests oropharyngeal administration of mother's milk provides

protection against bacteremia, NEC, and ventilator-associated pneumonia. In fact, in one study, after one year of implementing the protocol, the incidence of NEC was reduced by 22% in ELBW infants. The article boasts that the most compelling finding was that treated infants reached full enteral feedings (150 mL/kg/d) ten days earlier than placebo-treated controls, suggesting possible maturational effects on the intestine. Earlier attainment of full enteral feeds as a result of the oropharyngeal administration of mother's milk also has impacted the maturation of oral feeding skills, resulted in improved growth, and enhanced breast-feeding outcomes. Last, treated infants received significantly fewer days of parenteral nutrition, and late-term sepsis decreased – significant because both are risk factors for NEC. With further research, oropharyngeal administration of mother's milk may become an additional strategy to prevent NEC (Rodriguez & Caplan).

Bacteria/Probiotics

As discussed, NEC is multifactorial in origin, and bacterial colonization of the newborn's GI tract has been identified as one of the primary factors that lead to the development of NEC (Bradshaw, 2009). Supporting evidence includes that there has never been a reported case of NEC in utero or in stillborn infants because the GI tract of a normal fetus is sterile (Bradshaw). Usually during the birth process and beyond, the infant is exposed to microbes needed to colonize the GI tract, leading to a dense, diverse, and commensal bacterial community (Bradshaw). This bacterial community allows for the availability of critical nutrients, and stimulates the GI mucosa to develop innate and adaptive immune responses (Mshvildadze et al, 2009). Term infants, especially those who are vaginally delivered and breast fed, are colonized by a high number of beneficial bacteria such as bifidobacteria and lactobacilli (Frost & Caplan, 2013; Mshvildadze et al). However, preterm infants are more likely to have lower numbers of

beneficial bacteria and higher numbers of potentially pathogenic bacteria such as enterobacteria, e.coli, bacteriodes species, enterococci, streptococci, clostridia, staphylococci, and klebsiella (Mshvildadze et al.). Last, although the majority of NEC cases are sporadic, the occurrence of clusters indicates an infectious component to the disease (Wendleboe, 2010). These observations imply bacterial colonization is partially responsible for the etiology of NEC (Thompson & Bizarro, 2008). To counteract the pathogenic bacteria and to promote colonization of beneficial bacteria, researchers have experimented with the use of probiotics. The following research studies look at the role of bacteria in NEC and/or the use of probiotics as a preventive measure against NEC.

In 2010, a research study published in the *American Journal of Infection Control* by Wendelboe, Smelser, Lucero, and McDonald examined the possibility of a microbiologic cause of a cluster of NEC cases after the cluster was found in a NICU in New Mexico in 2007. Between the dates of January 1, 2007, to February 13, 2007, 16.9% or eleven cases of NEC were identified (compared with 3.3 of 100 infants and 2.4 of 100 infants in 2006 and 2005) (Wendelboe et al). This led to an investigation of the unit by personnel from the New Mexico Department of Health, the hospital in which the cluster occurred, and the Centers for Disease Control and Prevention. Investigators performed a chart and laboratory review for neonates with a diagnosis of NEC during the outbreak period, to identify the cause of the cluster and evaluate risk factors. During this time the hospital instituted enhanced environmental cleaning, cohorting of infants and nurses, and increased attention to hand hygiene. Additionally, commercial feeding products in the unit were tested for bacterial contamination. Investigators found the patients had a median of five disease risk factors, four distinct pathogens were detected in blood or stool specimens from four different patients, and one sample of human milk fortifier (HMF) tested

contained a colony count of Bacillus cereus at the US Food and Drug Administration's upper microbiologic limit for contamination. Seven (65%) patients received HMF before symptom onset, and nine (82%) patients received one or more types of liquid formula. Even though evidence suggests a microbiologic cause, investigators concluded a microbiologic cause could not be clearly identified and the cluster might have resolved spontaneously (Wendleboe et al, 2010).

In attempt to answer the question of whether or not administering probiotic treatment to infants under 1500 g decreases the incidence of necrotizing enterocolitis, Rohan and Wainwright (2014) conducted a systematic literature review and published their findings in the *Journal of Neonatal Nursing*. To execute the literature review, Rohan and Wainwright used four databases to find the available evidence: Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), British Nursing Index (BNI) and Embase. They identified seven randomized controlled studies regarding probiotic use for NEC in this population (Rohan and Wainwright, 2014). Information from professional bodies such as the Neonatal Nurses Association, Department of Health and the British Dietetic Association was also searched, but no new evidence was found (Rohan and Wainwright, 2014). The table below summarizes the findings of the seven randomized control studies.

Author(s)	Country of origin	Probiotic used	Sample total	Decrease or increase of NEC	Incidence of NEC. Study vs. control group
Dani et al.,	Italy	Lactobacillus GG once	580 babies	No	1.4% V 2.8%

2002	Multicenter	a day for until discharge	<1500 g <33weeks	decrease in NEC	(No P value available)
Lin et al., 2005	Taiwan	Lactobacillus acidophilus and Bifidobacterium infantis twice a day until discharge	367 babies <1500 g	Decrease in NEC	≥stage 2 NEC/Death: P .0095% V 12.8%
Bin-Nun et al., 2005	Israel	Bifidobacteria infantis, Strepococcus thermophilus and Bifidobacteria bifidus. daily until 36 weeks corrected	145 babies <1500 g	Decrease in NEC	Cases of NEC: P .034% V16.4%
Lin et al., 2008	Taiwan Multicenter	Bifidobacterium bifidum and Lactobacillus acidophilus twice a day for 6 weeks	434 babies <1500 g	Decrease in NEC	≥stage 2 NEC/Death: P .002
Samantha et al., 2009	India	Bifidobacteria infantis, Bifidobacteria bifidum, Bifidobacterium longum and	186 babies <1500 g <32 weeks	Decrease in the incidence but not the	Cases of NEC: P .0425.4%V 15.8%≥stage

		Lactobacillus acidophilus twice a day until discharge.		severity	2 NEC/Death: P .62
Braga et al., 2011	Brazil	Lactobacillus casei Bifidobacterium breve daily until day 30.	231 babies	Decrease in NEC	≥stage 2 NEC0% V 3.6%
Sari et al., 2011	Turkey	L sporogens daily until discharge	221 babies <1500 g <33weeks	No decrease in NEC	NEC/Death:P .5158.2% V11.7%

After reviewing the research, Rohan and Wainwright (2014) found there was no consistency among the studies in the type or combination of probiotics used, the timing of introduction, and frequency and duration of administration. There is an overlap between some of the studies in the type of probiotic used, but there is no consistency in the combination and strength of the dose. In studies where only one probiotic was used there was no significant statistical change in the incidence or severity of NEC. In studies where two or more probiotics were used in combination, however, a decrease in the incidence of NEC was seen. Last, one of the research studies administered a triple dose of probiotics, which saw an improvement in the incidence of NEC, but not the severity of the disease (Rohan and Wainwright).

Ulbricht and colleagues (2011) had similar questions regarding the use of probiotics so they conducted a meta-analysis by performing a systematic review to compare the efficacy and safety of prophylactic enteral probiotics administration versus placebo or no treatment in the

prevention of severe NEC and/or sepsis in preterm infants. The standard search strategy for the Cochrane Neonatal review group was performed by two review authors. Searches were made of MEDLINE (1966 to December 2006), Embase (1980-December 2006), CENTRAL (Cochrane Library, Issue 3, 2006), and abstracts of annual meetings of the Society for Pediatric Research (1995–2006). Only randomized or quasi-randomized controlled trials that enrolled preterm infants with gestational age of < 37 weeks and/or birth weight of < 2500 g were considered. Trials were included if they involved enteral administration of any live microbial supplement (probiotics) and measured at least one pre-specified clinical outcome. Standard methods of the Cochrane Collaboration and its Neonatal Group were used to assess the methodological quality of the trials. Retrieved articles were assessed for eligibility. When data was incomplete, the primary investigators were contacted for further information and clarification. When appropriate, data of individual trials were combined using meta-analytical techniques to provide a pooled estimate of effect, assuming a fixed-effect model. Nine eligible trials, using randomizing and consisting of 1425 infants, were included. Included trials were highly variable with regard to enrollment criteria (such as birth weight and gestational age), baseline risk of NEC in the control groups, timing, dose, formulation of the probiotics, and feeding regimens (Ulbricht et al).

Ulbricht et al. (2011) found enteral probiotics supplementation significantly reduced the incidence of severe NEC (stage II or more; typical RR: 0.32 [95% CI: 0.17, 0.60]) and mortality (typical RR: 0.43 [95% CI: 0.25, 0.75]). There was no evidence of significant reduction of nosocomial sepsis (typical RR: 0.93 [95% CI 0.73, 1.19]) or days on total parenteral nutrition (WMD: –1.9 [95% CI: –4.6, 0.77]). The included trials reported no systemic infection with the probiotics supplemental organism. The statistical test of heterogeneity for NEC, mortality, and

sepsis produced insignificant results, but the researchers concluded that enteral supplementation of probiotics reduced the risk of severe NEC and mortality in preterm infants.

In another literature review of the research on using probiotics to prevent necrotizing enterocolitis, Yowell (2014) questions why clinicians have yet to change their practice. Yowell found evidence to support probiotic use and shows the potential for success, but argues that even after looking at the evidence, a standard of treatment cannot be implemented until more conclusive research is available. She concludes the hesitation comes because there has not been a consensus on the type of probiotic or specific regimen regarding administration and preparation. Her suggestion for implementation, where probiotics are licensed or available by special-access schemes, is that parents of all infants who met eligibility criteria from earlier trials be offered probiotics after adequate quality control of the reconstituted product. She suggests clinicians inform parents that the strategy is new and will be used only with their consent (Yowell).

Feeding Practices

The current evidenced-based practice guidelines for NEC recommended by the US Department of Health and Human Services in regards to feeding practices include the recommendation that enteral fasting, defined as delaying the introduction of enteral feeds until after five to seven postnatal days, not be used as a strategy to decrease NEC risk. Also, when the infant is judged ready to tolerate feeding advancement, feeding volumes should be advanced by 15 to 35ml/kg/day (National Guideline Clearinghouse, 2015).

Cosh (2012) summarized the results of a three-year study funded by the charity Action Medical Research and published in the *Journal Pediatrics*. Cosh found sooner is better for feeding milk to preterm infants. The study reported beginning enteral milk feeds from day two, as opposed to day six, was associated with less chance of cholestatic jaundice, less time requiring

parenteral nutrition, less time of high dependency care required, and improved standard deviation score for weight at discharge. Cosh concluded beginning full enteral feeds earlier, on day two, does not pose an increased risk of developing NEC (Cosh).

Feeding preterm infants only the mother's own milk or donor human breastmilk can be challenging. As a last resort for this population, infant formula is used. Historically, NEC rates are significantly higher with the use of infant formula despite drastic improvements in its quality and composition. In attempt to improve outcomes of low-birth weight infants who are exclusively formula fed, Hale (2014) looks at the effect of dilute versus full-strength formula. Hale's summary is based on a Cochrane systematic review involving 102 preterm or low-birth-weight infants that included patient data from three randomized or quasi-randomized trials. Past studies revealed that the risk of increased residual feedings remaining in the stomach is potentially due to the variations in osmolality between formula and breast milk. The osmolality of breast milk from mothers of term infants is 300 mOsm/kg, the breast milk of mothers of preterm infants is 276 mOsm/kg, and the variable osmolality of formula is 250 to 350 mOsm/kg (Hale, 2014). This is significant because feeding intolerance may present as residual feedings remaining in the stomach and may serve as a precursor for the development of NEC. Additionally, residual formula in the stomach has the potential to damage the bowel mucosa or influence the development of the gut, further putting the formula-fed infant at risk for development of NEC (Hale, 2014).

Researchers thought by decreasing the osmolality of the formula, they could, in return, decrease the intolerance to formula feeding. Hale's review focuses on offering formula to infants in an alternative way by feeding infants diluted formula rather than full-strength formula in order to reduce the variations in osmolality between breastmilk and formula (Hale, 2014).

The findings of these studies suggest that infants receiving diluted formula rather than full-strength formula achieved full nutritional intake earlier and had fewer incidents of feeding intolerance (Hale, 2014). Hale believes the cause of this outcome may correlate to a lower incidence of feeding intolerance. However, assessment of these studies resulted in no findings of decreased NEC. Feeding infants diluted formula rather than full-strength formula is not an effective strategy to reduce or prevent NEC (Hale, 2014).

McGuire, Young, and Morgan (2015) conducted a literature review to evaluate current evidence to prevent NEC. They focused on several feeding strategies, though their methods were not disclosed. The following paragraphs include their findings.

One of their findings was that, while many studies have attempted to identify a specific feeding protocol to reduce the risk of NEC, there is a lack of evidence that specific methods of delivering enteral nutrition to very preterm infants affects important outcomes (McGuire et al). However, a systematic review of observational studies has shown that the use of a feeding protocol, irrespective of its specific recommendations, may of itself reduce the risk of NEC (McGuire et al).

Immunoglobulin supplementation has been thought to duplicate the immunoglobulins naturally found in breastmilk and reduce the preterm infant's susceptibility to NEC. Breastmilk supplies immunoglobulin-A (IgA) which helps prevent bacterial translocation across intestinal mucosa (Thompson & Bizarro, 2008). Unfortunately, randomized controlled trials of enteric immunoglobulin supplementation for very preterm or VLBW infants have not found any evidence of an effect on the incidence of NEC. However, most trials have used immunoglobulin-G, whereas enteral immunoglobulin-A prophylaxis (which is more costly) is likely to be the more biologically appropriate intervention (McGuire et al).

Another area of debate is the timing to begin enteral feedings and the rate. Research shows the incidence of NEC tends to be higher in neonatal units where enteral feeding is introduced earlier and feeding volumes are advanced quickly. In response, clinicians began to delay feedings but research also shows delaying feeds is not good either (McGuire et al). Current evidenced-based practice guidelines recommended that enteral fasting not be used as a strategy to decrease NEC risk (National Guideline Clearinghouse, 2015). Conservative feeding volumes are recommended. The range of recommended feeding volumes varies greatly, but after the infant is judged ready to tolerate feeding advancement, the recommended feeding volume should be advanced by 15 to 35ml/kg/day (National Guideline Clearinghouse, 2015).

Researchers have identified lactoferrin, an antimicrobial glycoprotein present in colostrum and breast milk, as a key component of innate response to infection (McGuire et al). Lactoferrin has broad microbicidal activity against Gram-positive cocci, Gram-negative bacilli, and Candida species. Lactoferrin also has probiotic properties, creating an enteric environment for the growth of beneficial bacteria and reducing colonization by pathogenic species. When studying very preterm infants, researchers have found these infants have low lactoferrin levels and this deficiency is exacerbated by delay in establishing enteral feeding (McGuire et al).

An Italian multi-center trial examined whether enteral supplementation with exogenous (bovine) lactoferrin for up to 6 weeks, either alone or in combination with a probiotic lactobacillus, reduced the risk of NEC and invasive nosocomial infection in very preterm infants (McGuire et al). Lactoferrin supplementation reduced the incidence of invasive nosocomial infection by two thirds compared with controls. However, the incidence of NEC was decreased in the lactoferrin plus probiotic group only (McGuire et al). Lactoferrin needs to be studied further as a possible NEC prevention strategy.

Very preterm or VLBW infants who develop NEC have lower plasma levels of the amino acids glutamine and arginine compared with gestation-comparable infants who do not develop NEC (McGuire et al). Therefore the addition of these amino acids in attempt to reduce the incidence of NEC has been recently studied.

Glutamine is a conditionally essential amino acid and is the preferred respiratory fuel for rapidly proliferating cells such as enterocytes (McGuire et al). Glutamine is abundant in human milk -- but present only in much lower levels in cow milk formula, and absent in standard parenteral nutrition solutions. Researchers think glutamine supplementation may reduce mucosal damage and lower the risk of invasive infection and death. However, a Cochrane review and meta-analysis of randomized controlled trials did not find any evidence that the routine use of glutamine supplementation affects important clinical outcomes including the risk of VLBW infants developing NEC. Current research efforts have moved to assessing the potential of glutamine supplementation as a rescue therapy for accelerating recovery in infants with established NEC (McGuire et al).

Arginine is another amino acid involved in the generation of nitric oxide, a key mediator of intestinal vasomotor tone (McGuire et al.). It has been suggested that enteral arginine supplementation may enhance endothelial nitric oxide generation and thereby improve intestinal perfusion. So far only one trial has tested arginine, but optimistically it found a reduced incidence of NEC in infants who received the amino acid. Large multi-center trials are needed to confirm this finding (McGuire et al.).

To date, there have not been any large randomized controlled trials that have assessed the effect of probiotics on the risk of NEC in very preterm infants, but several such trials are being developed (McGuire et al.).

Moyses, Johnson, Leaf, and Cornelius (2013) understand the importance of adequate nutritional intake in preterm infants to promote growth and development, and published their findings in the *American Journal of Clinical Nutrition.* Moyses et al. conducted a systematic review and meta-analyses concerning the use of early parenteral nutrition in preterm infants. The authors explore the advisability of using early parenteral nutrition (PN) as one potential strategy to achieve adequate nutrition and growth in this population. The group's systematic review included randomized controlled trials (RCTs) and observational studies. Eight RCTs and 13 observational studies met the inclusion criteria (n = 553 and 1796 infants). The authors report there is no evidence from the studies that show early PN significantly increases the risk of NEC or mortality overall (Moyses et al).

Transfusion Related NEC

Hypoperfusion and subsequent ischemic-hypoxic injury to the GI tract has been identified as one of the major contributing factors of NEC (Thompson & Bizarro, 2008). Many times this complex cannot be avoided as it may occur as a result of uncontrollable factors such as placental abruption, but it may also occur after interventions such as packed red blood cell (PRBC) transfusion (Luton, 2013). Research related to adverse outcomes associated with transfusions among preterm infants is limited; however, data suggests increased mortality rates if a transfusion is received (Marin & Strickland, 2013). Retrospective studies examining transfusion-related necrotizing enterocolitis (TR-NEC) reported between 25% and 35% incidence, and a temporal association exists with TR-NEC onset occurring within 48 hours after transfusion. (Marin & Strickland). Therefore, the administration of enteral feedings during PRBC transfusion has been postulated to play a role in the development of TR-NEC (Marin & Strickland). It is thought that stored blood transfusion contributes to NEC by two primary

mechanisms, vasoconstriction and the inflammatory response (Luton, 2013). However, the true effects of PRBC transfusion volume and duration, the administration of multiple transfusions on mesenteric oxygenation and perfusion, and the effects of the age of blood transfused on mesenteric tissue oxygenation, are unknown (Marin & Strickland, 2013).

It is important to recognize PRBC transfusion as a risk factor because, while it does follow the inverse relationship of increased chance of NEC in relation to prematurity as evidenced by infants with low birth weights less than 1500 g, low gestational ages at birth, and greater intensive care needs making these infants more likely to develop TR-NEC, it also affects atypical population groups (Marin & Strickland, 2013). For example, some infants who develop transfusion-associated necrotizing enterocolitis do not display other typical NEC risk factors besides prematurity, preterm infants of older postnatal age are more likely to develop NEC after transfusion, and VLBW infants who developed late-onset NEC (>4 weeks of age) had received more than one PRBC transfusion (Luton, 2013; Marin & Strickland). Last, cases of NEC resulting after PRBC transfusion are more severe and require a higher rate of surgical intervention (Luton, 2013). Meta-analyses have shown the correlation between PRBC transfusion and NEC. Since PRBC transfusions are done out of necessity, researchers have focused on the major modifiable components surrounding blood transfusions to reduce the risk for TR-NEC (Marin & Strickland). The modifiable components may involve concurrent feeding administration, transfusion administration (duration and volume), and close observation of the preterm infant during these events (Marin & Strickland).

A 2014 retrospective cohort study was conducted by DeReinzo and colleagues that looked at feeding practices and other risk factors for developing transfusion-associated necrotizing enterocolitis. The purpose of the study was to evaluate the effectiveness of initiating

a peri-transfusion feeding protocol. The recommended protocol specifies that oral food and fluids are to be withheld from infants for four hours before, during, and after transfusion, at which time feeds are restarted at 50% of the original volume for 12 hours and then advanced to the original volume (DeRienzo et al, 2014).

DiRienzo's cohort included all inborn VLBW infants admitted to the Duke intensive care nursery from 2002 to 2010. NEC was defined using Bell's modified criteria IIA and higher, and TR-NEC as NEC occurring within 48 hours of a packed red blood cell transfusion. Demographic and laboratory data for TR-NEC vs. other NEC infants were compared regarding the incidence of TR-NEC pre/post implementation of the facility's peri-transfusion feeding protocol. The pre-transfusion hematocrit and PRBC unit age with TR-NEC was also considered (DeRienzo et al, 2014).

A total of 1380 VLBW infants were identified, of whom 148 (10.7%) developed NEC (DeRienzo et al, 2014). They found a significant reduction in incidence of NEC from 126/1065 (12%) to 22/315 (7%) ($P = 0.01$) in the pre- and post-protocol cohorts respectively. When measured by overall incidence in the VLBW population, a non-significant reduction in TR-NEC from 51/1065 (5%) to 9/315 (3%) ($P = 0.16$) was found. When measured as prevalence among infants developing NEC, no difference was found in TR-NEC within 24, 48, or 72 hours of transfusion. Within the NEC cohort, however, TR-NEC infants were of lower birth weight and were significantly more likely to develop surgical NEC—37/60 (62%) vs. 36/88 (41%), $P = 0.02$. Additionally, among only TR-NEC infants, transfusions given within 48 hours of NEC had a significant lower mean pre-transfusion hematocrit than all other transfusions given prior to their NEC episodes (28% vs. 33%, $P < 0.001$) (DeRienzo et al).

Marin and colleagues (2013) hypothesized the variation in mesenteric oxygenation patterns surrounding transfusions could be the mechanism correlating NEC to PRBC transfusions. In their study, Marin and colleagues used near-infrared spectroscopy to investigate and compare oxygenation patterns of four VLBW infants who developed TR-NEC to four VLBW infants with similar gestational age who were transfused but did not develop NEC (non-NEC). Cerebral and mesenteric patterns were recorded before, during, and 48 hours after RBC transfusion using near-infrared spectroscopy technology. Percentage change from mean baseline regional oxygen saturation values and cerebrosplanchnic oxygenation ratios were analyzed. The researchers found that all TR-NEC infants (24-29 weeks' gestation; 705-1080 g) demonstrated greater variation in mesenteric oxygenation patterns surrounding transfusions than non-NEC infants (27.6-30 weeks' gestation; 980-1210 g), and TR-NEC infants received larger mean volumes of total blood (8.77 mL/kg) than non-NEC infants (0.5 mL/kg). In conclusion, their study showed the infants who developed TR-NEC had more pronounced wide fluctuations and decreases in mesenteric oxygenation patterns even before TR-NEC onset than non-TR-NEC infants, and greater total volume of infused blood was associated with TR-NEC in preterm infants (Marin et al).

Mohamed and Shah (2012), as well, recognized several studies have reported the possibility of an association between recent exposure to PRBC transfusion and development of NEC. Mohamed and Shah systematically reviewed and meta-analyzed the association between transfusion and NEC, identified predictors of TR-NEC, and assess the impact of TR-NEC on outcomes. They conducted their review by searching Medline, Embase, CINAHL, and bibliographies of identified articles for studies assessing association with recent (within 48 hours) exposure to transfusion and NEC. The two reviewers independently collected data and

assessed the quality of the studies for bias in sample selection, exposure assessment, confounders, analyses, outcome assessments, and attrition. Meta-analyses were performed by using a random effect model; odds ratio and 95% confidence interval were calculated. Mohamed and Shah included eleven retrospective case-control studies and one cohort study of moderate risk of bias. Ten case-control studies had NEC control patients not associated with transfusion. Overall, their meta-analysis found recent exposure to transfusion was associated with NEC (Mohamed & Shah).

Additionally, Mohamed and Shah found that neonates who developed TR-NEC were younger by 1.5 weeks, were 528 g lower birth weight, were more likely to have patent ductus arteriosus, and were more likely receiving ventilator support. They also concurred with other studies that TR-NEC infants had higher risk of mortality (Mohamed &Shah, 2012). Last, a potential strategy to reduce TR-NEC by withholding feedings during PRBC administration was tested in two pre-post comparative studies included in their meta-analysis, and they found of 20 patients, a reported reduction of TR-NEC was achieved after withholding feeds during transfusion (Mohamed & Shah).

Better Understanding and Diagnosing NEC

The more researchers and clinicians understand about NEC, the better they can prevent it and treat it. Moreover, better measures are needed to identify infants at risk for developing NEC and to facilitate communication about risk across transitions (Gephart et al, 2014). Understanding and identifying risk factors helps clinicians discriminate modifiable risk factors and intervene appropriately in regards to NEC. In addition to finding neonates at risk for NEC and intervening, diagnosing NEC early with new technologies is equally important. Recent areas of research to both better understand the pathogenesis of NEC and tools to diagnose NEC earlier

will be discussed, and include NEC clinical risk index tools, infrared thermal imaging, monitoring the pattern of microbial progression, and intra-abdominal pressure measurement.

Gephart and colleagues developed two studies, the first to clearly define NEC risk and develop a clinical risk index for NEC risk specifically called the Gut Check NEC (Gephart et al, 2013), and the second study to test the accuracy of the NEC clinical risk index tool (Gephart et al, 2014).

The objective of the first study by Gephart and colleagues (2013) was to develop and test a clinical risk index tool they developed called Gut Check NEC, which is comprised of NEC risk factors believed by the experts to be most relevant for a NEC risk index. Their purpose was also to describe the derivation, validation, and calibration testing of this clinical NEC risk index to confirm its content validity, and to determine the level of agreement among experts about NEC risk factors in premature infants. Using an electronic Delphi method (e-Delphi), online electronic surveys and e-mail communication, supported by an interactive study website, were used. The participants in the study consisted of 35 nurses and physicians from four countries and across the United States who rated themselves as at least moderately expert about NEC risk. Three rounds of surveys and qualitative thematic analysis of experts' comments were completed, and surveys continued until criteria for consensus and/or stability were met (Gephart et al, 2013).

Of 64 initial items on the NEC clinical risk index, 43 items (representing 33 risk factors) were retained (final Gut Check NEC Content Validity Index [CVI] = .77). Two broad themes about NEC risk emerged from 242 comments: the impact of individual physiologic vulnerability and variation in NICU clinicians' practices. Controversy arose over the impact of treatments on NEC, including probiotics, packed red blood cell transfusions, and patent ductus arteriosus (PDA) management using indomethacin (Gephart et al, 2013).

In the second study by Gephart and colleagues (2014), Gut Check NEC was tested and validated by comparing risk factors of infants without NEC to infants with medical NEC, surgical NEC, and those who died from NEC. Discrimination was then tested in a case-control matched validation set and an un-matched calibration set using receiver operating characteristic curves (Gephart et al, 2014).

Sampled from a cohort of 58,820 infants, the randomly selected derivation set (n=35,013) revealed nine independent risk factors: gestational age, history of packed red blood cell transfusion, unit NEC rate, late-onset sepsis, multiple infections, hypotension treated with inotropic medications, Black or Hispanic race, outborn status (refers to infants transferred to that facility from another facility) and metabolic acidosis (Gephart et al, 2014). Two risk reducers of NEC were also identified: human milk feeding on both days seven and 14 of life, and probiotics. Unit NEC rate carried the most weight in the summed score. Gephart and colleagues concluded that Gut Check NEC represents weighted composite risk for NEC, and discriminates infants who develop NEC from those who do not, with very good accuracy (Gephart et al, 2014).

Infrared thermal imaging (thermography) is a non-invasive method to measure skin temperature (Rice et al, 2015). It has many different indications for use, and in the neonatal population it has been used to further understand the relationship of body temperature and perfusion, and more recently, to discover if there is an association between thermoregulation and clinical disease processes. The aim of Rice's study was to examine the feasibility of thermography for the assessment of abdominal skin temperature in ELBW infants, to compare abdominal and thoracic skin temperature, and to explore potential relationships between abdominal skin temperature and NEC. Rice and colleagues prospectively examined clinical, radiographic, and thermal imaging data in 13 ELBW infants (< 1000 gm and < 29 weeks

gestation) during the first month of life. Thermal imaging was performed using an infrared camera, with skin temperature measured over the abdomen and thorax; and then abdominal skin temperature was compared to thoracic skin temperature. The findings were further examined in infants with radiographic evidence of NEC as well as those without NEC (Rice et al, 2015).

Rice and colleagues found that thermal imaging in ELBW infants is feasible and can result in accurate measurements of skin temperature over anatomic regions. Overall, the mean abdominal skin temperature was lower than thoracic skin temperature ($p<0.05$), and this difference appears due to NEC in some infants. Infants with radiographic evidence of NEC had lower mean abdominal skin temperatures compared to infants without NEC ($p<0.5$). Therefore, Rice and colleagues concluded that thermography may be helpful for the study of thermoregulation in ELBW infants and may provide new insight into the role of regional perfusion NEC.

Since early intestinal colonization has been implicated in the pathogenesis of NEC, Zhou, et al (2015) completed a longitudinal analysis of the premature infant intestinal microbiome prior to NEC to further understand the disease. The objective of the prospective case-control study was to evaluate differences in the intestinal microbiota between unaffected controls and the microbiota prior to disease onset of infants who developed NEC. The researchers analyzed the 16S rRNA genes of 312 samples obtained from 12 NEC cases, and 26 age-matched controls with a median frequency of seven samples per subject and a median sampling interval of three days. They found that the microbiome undergoes dynamic development during the first two months of life, with day of life being the major factor contributing to the colonization process. Depending on when the infant was diagnosed with NEC, the pattern of microbial progression was different for cases and controls, the difference in the microbiota most overt in early onset NEC. In

proximity to NEC onset, the abundances of Clostridium sensu stricto from Clostridia class were significantly higher in early onset NEC subjects than controls. In late onset NEC, Escherichia/Shigella among Gammaproteobacteria, showed an increasing pattern prior to disease onset, and was significantly higher in cases than controls six days before NEC onset. Cronobacter from Gammaproteobacteria was also significantly higher in late onset NEC cases than controls one to three days prior to NEC onset. Therefore, the specific infectious agent associated with NEC may vary by the age of infant at disease onset (Zhou et al, 2015). Zhou and colleagues also found that intravenously administered antibiotics may have an impact on the microbial diversity present in fecal material.

Increased intra-abdominal pressure (IAP) is detected among most of the pediatric patients hospitalized in intensive care unit and undergoing surgery or trauma (Tanriverdi et al, 2013). This pathology causes ischemia and hypoperfusion of abdominal organs. Recently, the effect of increased IAP on NEC is under focus; the increase in IAP is thought to be related to the onset of NEC. Tanriverdi and colleagues, in their 2013 study, aimed to investigate if serial intravesical pressure (IVP) measurements (an indirect indicator of IAP) can help diagnose NEC early in order to help decide the need for surgery, and to predict the mortality of NEC. A total of 61 preterm infants with a birth weight of $\leqslant$1,500 g hospitalized in NICU were included in the study. IVP values were measured through urinary catheter by the same nurse twice daily during the preterm infant's hospitalization, and the IVP values of the preterm infants with and without NEC were compared. The breakdown of the 61 infants were as follows: group 0, the control group without NEC (n = 38); group 1, medically treated NEC patients (n = 14); and group 2, NEC patients undergoing surgery (n = 9). The median IVP measurements of group 0 were lower than the other groups (p = 0.001). No statistically significant difference in IVP measurements were

detected between group 1 and group 2 ($p = 0.155$), but a 10% increase in IVP measurement, with consecutive serial measurements, was significant in predicting the development of NEC. Furthermore, the mean IVP measurements were higher in infants with NEC who died during their follow-up at NICU compared with NEC patients who survived ($p = 0.043$). Tanriverdi and colleagues conclude that serial IVP measurements may help early of NEC diagnosis and surgery decision making; high IVP levels also may predict mortality in cases with NEC.

H2 Blockers

The use of gastric acid inhibitors (IGA) have been routinely used in the past for upper gastrointestinal bleeding or gastroesophageal reflux in preterm infants (More, Athalye-Jape, Rao, & Patole, 2013). However, the association of inhibitors of gastric acid secretion and higher incidence of NEC in VLBW infants has been well studied (More et al, 2013). Most clinicians are up to date on these findings and have discontinued ordering prophylactic H2 blockers in this population (More et al, 2013).

Researchers believe the resultant increase in gastric pH from using gastric acid inhibitors, also referred to as H2 blockers, may enhance the growth of pathogens that increase the risk of NEC. A systematic review and meta-analysis performed by More, Athalye-Jape, Rao, and Patole examined the association between IGA and NEC in preterm infants. The standard methodology of systematic reviews was followed and the following databases were searched in 2012: PubMed, Embase, Cochrane, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). They found and included one case-control and one prospective cohort study ($n = 11,346$), both evaluating H2-blockers as IGA. Meta-analysis showed a significant association between NEC and IGA (odds ratio [OR]: 1.78, 95% confidence interval [CI]: 1.4, 2.27, $p < 0.00001$). The prospective cohort study found higher incidence of infection (sepsis, pneumonia,

urinary tract infection) with IGA (37.4% versus 9.8%, OR: 5.5, 95% CI: 2.9 to 10.4, $p < 0.001$). The researchers concluded that exposure to H2 receptor antagonists may be associated with increased risk of NEC and infections in preterm infants (More et al, 2013).

Quality Improvement Methods

Rush Medical Center's NICU, despite the institution's strong lactation support and human milk feeding rates over 90% in VLBW, had an NEC epidemic -- a rise in NEC, stage ⩾2 among VLBW infants from 4% in 2005 to 2006 to 10% in 2007 to 2008 (Patel et al, 2014). This led to investigations for a common infectious etiology, heightened infection control measures, and development and implementation of quality improvement (QI) initiatives. With much tracking, chart reviews, and implementation of quality improvements methods, the NEC incidence did not decrease after implementation of the feeding protocol, but did decline significantly after changing nasogastric tube management. A new NG feeding tube system and accompanying tube maintenance practice changes had been introduced shortly before the epidemic. The new system included additional extension tubing that was not being flushed consistently after feedings, leaving residual fluid in the lumen. This highlights the unintended consequences that can result from a seemingly unrelated decision that was felt to be cost-effective and would decrease handling of infants, and the importance of multidisciplinary communication (Patel et al, 2014).

Discussion

Breastmilk

Currently, the evidence-based practice guidelines for NEC recommended by the US Department of Health assert infants should be fed with mother's own milk to decrease the risk of

NEC, and donor milk be considered, if accessible, as an alternative to formula when mother's own milk is unavailable (National Guideline Clearinghouse, 2015). Therefore, the mother's own milk should be used to feed all infants, but especially preterm infants at risk of developing NEC. Nurses are in the best position to speak with mothers about the importance of their milk and equip them with appropriate resources.

Nursing interventions for lactation support for mothers of preterm infants can include kangaroo care (skin-to-skin contact between mother and infant), simultaneous expression of milk from both breasts (using an electric pump), peer support in the hospital and community, and multidisciplinary staff training and continuous professional development to maintain skilled professional support. Mothers benefit by supplying their milk, and society benefits by reducing costs and improving patient outcomes (Gibbins et al, 2013). The most important nursing consideration is the education of families that mother's milk is always the first priority for feeding their babies, but if it is not available, properly processed donor milk is safe and effective.

If mothers are not able to supply the milk or cannot supply enough, nurses can educate families on the benefits of pasteurized human donor milk and advocate hospitals find funding for this intervention. This may be challenging because one study found that it was the nurses who were hesitant about donor milk (Carroll & Hermann, 2012). In fact, 36% of surveyed nurses in the study had some reservations about donor milk use, or did not agree to the use of donor milk (Carroll & Herrmann, 2012). This is significant! Nurses are in the best position to advocate for their patients and improve NEC outcomes. However, education of nursing staffs must be implemented to uninformed perceptions from becoming a barrier for this intervention.

Another study by Rosenbaum (2012) had similar results. The initial barrier to donor human milk in one of the hospitals she surveyed was cultural. However, after staff reviewed the

available literature and the unit invited a guest speaker from the milk bank to speak, acceptance of donor milk was achieved. Many concerns about donor milk are lifted after learning that potential donors to HMBANA banks are carefully screened before donation. Donors are screened using blood tests for infectious diseases such as HIV, Hepatitis B and C, syphilis and human T-cell lymphotropic virus. The health care providers of both the donor mother and her infant must confirm that there are no contraindications to breast milk donation. Donors must be nonsmokers, not regularly taking any medications, and not consuming alcohol or prohibited medications within a certain time period prior to donation. Donors are screened via interview in addition to completing a written screening questionnaire to evaluate the suitability of their health and lifestyle for donation. Not unlike blood donors, they are not reimbursed for their milk (Rosenbaum).

Despite barriers of incorporating pasteurized donor human milk into practice, it can still be done successfully as Rosenbaum detailed in her findings. Nurses can effectively raise awareness of the need for donor human milk and petition for the institution of a donor human milk depot in their hospital, thus facilitating donations by providing an easy drop-off location for milk donation.

The focus on donor human milk has steadily increased in recent years. While it is preferred over formula and has reduced the risk of NEC, it is not without risk. The articles mentioned above did not address all the risks of human donor milk. Although the processes of screening and pasteurization may be place, the risk of exposure to infectious diseases is a possibility as exists with donated blood, possible exposure to drugs and medications, and if not handled and stored properly, contamination. Thus far, the benefits of donor milk far outweigh the risks, and the screening process and pasteurization process are adequate, but it is important to

understand the possible risks. Other barriers to the use of donor milk include the cumbersome process of donating it, cleaning it, storing it, and paying for it.

The key question raised by these studies is whether the substantial capital and opportunity costs of supplying donated breast milk would be better invested in promoting evidence-based practices to ensure mothers are optimally supported to express their own breast milk (McGuire et al, 2015). The challenge is to ensure that these are implemented consistently and broadly, and especially to vulnerable and socially-disadvantaged women who are less likely to provide expressed breast milk (McGuire et al).

Nurses are also on the frontlines of implementation in a new area of study -- the oropharyngeal administration of mother's milk to the ELBW infant. While promising, a significant limitation of current evidence is that data are primarily from small retrospective cohort studies, feasibility trials, or studies in which oropharyngeal colostrum was included as part of a standardized feeding protocol. Data from published studies support the premise that this intervention may be beneficial for ELBW infants, but significant weaknesses limit generalizability. Limitations include the use of small samples, retrospective analysis, an inconsistent approach (drops vs swabs), and wide variation in dosing, frequency of treatments, and duration of the treatment period. Another significant weakness is a lack of measurement of adherence to the protocol—percent of doses received out of planned doses. This is an area of research that needs more development and support from nurses to continue to improve patient outcomes.

In conclusion, supporting mothers to express breast milk for their very preterm infants may be one of the most effective and cost-effective interventions currently available for reducing

the incidence of NEC. Infant feeding practices in neonatal units, including the use of expressed breast milk, should be included in audit and benchmarking processes.

Bacteria/Probiotics

The etiology of NEC is not entirely understood, but bacterial colonization seems to be a component, and the strategy to prevent and reduce the incidence and severity of NEC by implementing the use of probiotics is extremely encouraging. Looking at the literature review performed by Rohan and Wainwright (2014) of seven randomized controlled studies, the use of probiotics in the prevention of NEC in infants <1500 g has shown to have beneficial effects. Also, a meta-analysis performed by Ulbricht and colleagues (2011) found enteral probiotics supplementation significantly reduced the incidence of severe NEC (stage II or more; typical RR: 0.32 [95% CI: 0.17, 0.60]) and mortality (typical RR: 0.43 [95% CI: 0.25, 0.75]), even though nine trials were highly variable with regard to enrollment criteria (i.e., birth weight and gestational age), baseline risk of NEC in the control groups, timing, dose, formulation of the probiotics, and feeding regimens (Ulbricht et al).

The use of probiotics as a preventive strategy against NEC may be effective. However, clinicians are still hesitant to implement probiotics because they are not without risk. One common concern is the quality and regulation of probiotics, although the included trials reported no systemic infection with the probiotic's supplemental organism and enteral supplementation of probiotics (Ulbricht et al). Additionally, the lack of consistency between trials and the lack of research in babies <1000 g can leave clinicians leery of routine probiotic implementation as well. However, an equal possibility is the benefit of reduced risk of severe NEC and mortality in preterm infants outweighing the risk of using probiotics. Although the pooled estimate from meta-analyses does indicate a substantially reduced risk of NEC and death, concern exists that

these estimates are biased by various methodological weaknesses in the primary trials. For optimal safety, further studies are required before it is safe to embark on using probiotics as a routine treatment in this high-risk vulnerable population (McGuire et al, 2015). Secondly, careful inspection of the distribution of effect size estimates of the included trials suggests that the size of the pooled estimate is due to small study and publication bias. Finally, there remains concern that questions of safety, including the risk of invasive infection with probiotic bacteria as previously mentioned, have not been addressed, and the optimal strains, dose, and frequency regimens have yet to be defined. On balance it seems appropriate and ethical at this stage to continue to support the large, good-quality, multicenter trials of probiotic supplementation that are on-going internationally and to await a more precise and less biased estimate of effect size before introducing probiotic supplementation for very preterm infants as a routine practice (McGuire et al). However, that does not mean probiotics cannot be used until such time. Yowell's (2014) suggestion for implementation where probiotics are licensed or available by special-access schemes is that parents of all infants who met eligibility criteria from earlier trials be offered probiotics after adequate quality control of the reconstituted product. She suggests clinicians inform parents that the strategy is new and will be used only with their consent. Nurses can help advocate for their patients to encourage a probiotic protocol, encourage and participate in more well-structured research on probiotic use, and educate families and witness consent to the benefits and risks of probiotic use.

Regarding the role of bacteria and infection control practices as outlined in the study done in a New Mexico NICU in 2007, nurses play a vital role in infection control practices. After the implementation of enhanced environmental cleaning, cohorting of infants and nurses, and

increased attention to hand hygiene (all infection control practices), the unit's NEC rate significantly declined (Wendleboe, 2010).

In conclusion, the infection control practices are key to containing many outbreaks, including NEC. Nurses cannot undervalue their importance. Infection control practices such as washing hands, cleaning ports, and using good sterile technique when indicated are essential to keep vulnerable patients well. Nurses have the most access to their patients and are the key educators and advocates to maintain these practices.

Feeding Practices

It is easy to see why the current feeding recommendations for NEC have such a wide range. The current research has inconsistent results and clinicians have varying opinions. Despite the variance in feeding protocols for this population, research such as McGuire, Young, and Morgan's 2015 study, has found after reviewing observational studies that the use of a feeding protocol, irrespective of its specific recommendations, may of itself reduce the risk of NEC. The careful consideration of developing the protocol increases attention to feeding and NEC and should be done in every NICU. There is no harm in careful consideration of feeding protocols, and nurses can play a vital role in advocating and implementing them.

The feeding protocol should include when to introduce feeds for neonates at risk for NEC. Previously the research showed a correlation with early feeds to a higher incidence of neonates with NEC. To compensate, clinicians used enteral fasting (defined as delaying the introduction of enteral feeds until after five to seven postnatal days). However, this has not shown to be an effective strategy. The EBP guidelines recommend enteral fasting not be used as a strategy to decrease NEC (National Guideline Clearinghouse, 2015). The results of a three year study summarized by Cosh (2012) found the sooner the better for feeding breastmilk to preterm

infants. The study stated beginning enteral milk feeds from day two as opposed to day six was associated with less chance of cholestatic jaundice, less time requiring parenteral nutrition, less time of high dependency care required, improved standard deviation score for weight at discharge, full enteral feeds earlier, and without any increased risk of developing NEC (Cosh). However, even though all babies were born before 35 weeks and had a birth weight below the tenth percentile, not all the neonates contributing to the results are the most critical and susceptible to NEC (Cosh). The exact safe time to introduce feeds to neonates at risk of developing NEC is not clearly known as research recommendations vary from two days after-birth to less than five days after birth.

Another area of research and practice regarding NEC feeding protocols is the volume and rate of advancement of feeds. One of the primary goals clinicians have for preterm babies is weight gain. Gaining weight is essential for this population, but can sometimes come at a price. Now clinicians understand even though babies gain weight faster with formula, it increases their risk of NEC. Similarly, babies gain weight faster when feeding volumes are advanced quickly, but NEC tends to be higher in neonatal units where enteral feeding is introduced earlier and feeding volumes are advanced quickly (McGuire et al). Conservative feeding volumes are thus recommended. The current evidenced-based practice guideline developed in attempt to prevent NEC states that when the infant is judged ready to tolerate feeding advancement, that feeding volume be advanced by 15 to 35 ml/kg/day (National Guideline Clearinghouse, 2015).

With the goal to promote growth and development, and to compensate for delayed feedings, slow advancement of feeds, conservative feeding volumes, and the use of early parenteral nutrition (PN) has been researched. Even though there is no evidence that shows early PN significantly increases the risk of NEC or mortality overall, the benefits and harms are still

unknown (Moyses et al, 2013). More research is needed on the use of early PN to further understand the benefits and harms before it can be routinely implemented.

Transfusion Related NEC

Recent exposure to packed red blood cell transfusion is associated with NEC in neonates, and cases of NEC resulting after PRBC transfusion are more severe and require a higher rate of surgical intervention (Luton, 2013). However, there are so many confounding variables when looking at studies regarding transfusion-related NEC (TR-NEC). One study found neonates who developed TR-NEC were younger by 1.5 weeks, were of 528 g lower birth weight, were more likely to have patent ductus arteriosus, and were more likely receiving ventilator support (Marin & Strickland, 2013). Another study reported TR-NEC infants were smaller, more likely to develop surgical NEC, and had lower mean pre-transfusion hematocrits prior to their TR-NEC transfusions compared with all other transfusions before their NEC episode: 28% vs. 33% (Luton). Last, the major confounding factor in many of the retrospective studies on TR-NEC is that concurrent changes in practice and protocol were being implemented to improve overall outcomes, including increased emphasis on use of mothers' milk and use of donor milk for all VLBW infants whose mothers consented and were not producing their own milk. Additional studies adjusting for confounders are needed. Meta-analyses have linked PRBC transfusions to NEC, but some experts argue that the neonates who get NEC get it from the transfusion or because they were more likely to get NEC anyway, because the infants with TR-NEC were more susceptible before the transfusion as evidenced by the increase in risk factors discussed.

The argument that TR-NEC occurs in infants who were more likely to get NEC in any case does not account for the fact that some infants who developed TR-NEC do not display other typical NEC risk factors besides prematurity, and preterm infants of older postnatal age are more

likely to develop NEC after transfusion (Luton, 2013). More research needs to be done to understand the mechanism of transfusion-related NEC. Until now, research has focused on identifying modifiable components surrounding blood transfusions to reduce the risk for TR-NEC (Marin & Strickland, 2013). Protocols have been developed surrounding feeding before, during and after PRBC transfusion as the administration of enteral feedings during PRBC transfusion has been postulated to play a role in the development of TR-NEC (Marin & Stricklannd). An example of a protocol for TR-NEC specifies that oral food and fluids are to be withheld from infants for four hours before, during, and after transfusion, at which time feeds are restarted at 50% of the original volume for 12 hours and then advanced to the original volume (DeRienzo et al, 2014). Unfortunately, after implementing peri-transfusion feeding protocols, the incidence of TR-NEC has not significantly changed.

The bedside nurse is in a pivotal position to recognize PRBC transfusion as an important risk factor for NEC and should intervene promptly to avert disease onset and/or progression. However, there is insufficient evidence to recommend formal changes in nursing practice for preterm infants receiving PRBC transfusions, demonstrating the need for further investigation.

Better Understanding and Diagnosing NEC

Tools to diagnose NEC earlier will continue to be tested, and research studies to better understand NEC will continue. Some of the newest areas on research on this subject, discussed above, include NEC clinical risk index tools, infrared thermal imaging, monitoring the pattern of microbial progression, and intra-abdominal pressure measurement. Although nurses may not be facilitating the research, many of the interventions discussed will become nursing responsibilities and, therefore, are included in this paper. Currently, the effectiveness of these tools need to be evaluated and a cost-benefit analysis should be done before implementation.

Gephart and colleagues (2013) have attempted to construct a clinical risk index tool for clinicians to use to help them identify the infants at risk for NEC (later named Gut Check NEC). The results of their study are limited since opinions and input came from clinicians who rated themselves as at least a moderate expert of NEC. Furthermore, there was not a consensus on content, and controversy arose over the impact of treatments on NEC, including probiotics, packed red blood cell transfusions, and patent ductus arteriosus (PDA) management using indomethacin (Gephart et al, 2013). Better measures are needed to identify infants at risk for developing NEC and to facilitate communication about risk across the multidisciplinary team, however, the clinical risk index tool needs to be researched further (Gephart et al, 2014).

In the second referenced study by Gephart and colleagues, Gut Check NEC, was tested and validated (Gephart et al, 2014). Gut Check NEC discriminated infants who developed NEC from those who did not with very good accuracy. Unit NEC rate carried the most weight in the summed score. Although there are limitations to the clinical risk index tool Gephart and colleagues developed, further testing should be done to validate the accuracy of Gut Check NEC. Taking the time to identify and target modifiable NEC risk factors could reduce national NEC prevalence. Nurses can play a pivotal role by contributing their knowledge, advocating for more studies, and implementing and using the tool once it is developed.

Infrared thermal imaging (thermography) is a non-invasive method to measure skin temperature (Rice et al, 2015). Infants with radiographic evidence of NEC have lower mean abdominal skin temperatures compared to infants without NEC. This new technology will not prevent or cure NEC, but it is not invasive and may help researchers understand NEC better by providing insight to the role of regional perfusion in NEC. The financial cost to use thermography must be weighed against the value of the information that is received from

implementing this assessment tool. If implemented, nurses will be the ones the measure and record skin temperature. They will need to be properly trained to accurately use the tool and report findings of infants with lower mean abdominal skin temperatures.

Increased intra-abdominal pressure (IAP) is detected among most of the pediatric patients hospitalized in intensive care units and undergoing surgery or trauma (Tanriverdi et al, 2013). The increase in IAP is thought to be related to the onset of NEC. A 10% increase in IVP measurement was significant in predicting the development of NEC with consecutive serial measurements. The mean IVP measurements were also higher in infants with NEC who died during their follow-up at NICU as compared with NEC patients who survived. In conclusion, serial IVP measurements are non-invasive and may help in early diagnosis of NEC as well as predict mortality in cases with NEC. More research needs to be done to validate these results. The extra cost and time to implement routine IAP measurements must also be considered when evaluating the value of the data IAP measurements bring (Tanriverdi et al). Measuring IAP will become a nurse's role if IAP is implemented in the future, and nurses must develop a system to ensure measurements are consistent between providers so IAP is accurately recorded.

H2 Blockers

The use of gastric acid inhibitors (IGA) and/or H2 blockers have been routinely used in the past for upper gastrointestinal bleeding or gastroesophageal reflux in preterm infants (More et al, 2013). However, the association of inhibitors of gastric acid secretion and higher incidence of NEC in VLBW infants has been well studied. More et al (2013) also concluded there is a higher incidence of infection with IGA. As a result, exposure to H2 receptor antagonists may be associated with increased risk of NEC and infections in preterm infants and should not be

routinely used. Nurses can advocate for their patients by questioning routine orders for IGA/H2 blockers when they understand the risks vs. benefits for this population.

Quality Improvement Methods

In Rush Medical Center's NICU, the NG feeding tube system and accompanying tube maintenance practice changes had been introduced shortly before a NEC epidemic occurred (Patel et al, 2014). The new system included additional extension tubing that was not being flushed consistently after feedings, leaving residual fluid in the lumen. While this particular situation is not necessarily generalizable to other NICUs, quality improvement methods and changes in unit practices must be carefully considered before implementation. Clinicians can also learn the importance of multidisciplinary communication as evidenced by the unintended consequences that can result from a seemingly unrelated decision felt to be cost-effective. When changing equipment or materials, nurses competencies decrease. Nurses must insist they receive proper orientation and training before using new equipment or supplies to protect the safety of their patients (Patel et al, 2014).

Recommendations for Research

As demonstrated, NEC is not entirely understood. While the incidence of NEC is slowly decreasing by implementing the above recommendations, more research needs to be done. Research to further understand NEC and its cause, and well as effective strategies to prevent and treat NEC, must be performed. The challenge is the vulnerability of this population and the lack of consistency in both trials and results. One explanation for the disparities in research and confusion of NEC is that it is misdiagnosed because it shares many similar diagnostic findings as other acquired neonatal intestinal diseases (Gordon, et al 2007).

The most promising area of research is the use of probiotics. Several good multi-center trials need to be done all testing the same variables. Also, the safety and regulation of these probiotic products needs to be ensured before routine implementation.

Nurses can be of immeasurable value by participating in research studies and implementing quality improvement strategies and documenting accurate results. Each hospital could implement these recommendations for practice with the aim to improve NEC rates and track them to see if they lead to improvement using simple data collection and analysis strategies to test the impact of the recommendations.

Conclusion

Necrotizing enterocolitis is a devastating disease associated with high morbidity and mortality (Gordon, et al 2007). Treatment options are often unsuccessful and there is little improvement of outcomes even after early diagnosis. Those who survive NEC are plagued with short and long-term co-morbidities (Thompson & Bizzaro, 2008). Research and attention needs to be directed to NEC prophylaxis and the reproducibility of promising studies and interventions. Until NEC is better understood, the following recommendations need to be implemented now to decrease and prevent NEC as best as the evidence has shown how. After performing a literature on the state of the science of NEC, the following strategies are recommended for practice.

Breastmilk

- Mothers at risk for preterm delivery should be given information on the protective effects of human milk and be encouraged to express their milk. The milk, especially colostrum, expressed by women who deliver ELBW infants has higher concentrations

of many protective biofactors than milk expressed at term (Rodriguez & Caplan, 2015).

- Infants should be fed with the mother's own milk to decrease the risk of NEC. Implementing breastmilk alone has shown to cut NEC incidence by over half because it helps defend the neonate against the multiple contributing factors to NEC (Gephart et al, 2012).
- Donor milk should be considered, if accessible, as an alternative to formula when the mother's own milk is unavailable. Nelson (2013) cites evidence from a systematic review and meta-analysis that there was a decrease of NEC by 79% with a sole diet of donor milk.
- The American Association of Pediatrics and the World Association of Perinatal Medicine insist on banked donor milk as a standard component of care for the preterm infant population (Carrol & Herman, 2012). However, donor milk may not be covered by insurance; therefore, when recommending the use of donor milk, reimbursement issues may need to be considered and discussed with the family.
- Infant formula should not be used to feed preterm infants when possible. Exclusively formula-fed infants in this population are six to ten times more likely to contract NEC (Thompson & Bizzaro, 2008).

Bacteria/Probiotics

- Several studies have found enteral probiotics supplementation significantly reduced the incidence of severe NEC and mortality (Ulbricht et al., 2011). Parents of all infants who met eligibility criteria should be offered probiotics (where probiotics are licensed or available by special-access schemes and after adequate quality control of

the reconstituted product) to be used only with their informed consent (Yowell, 2014).

Feeding Practices

- Each hospital should develop and implement a NEC feeding protocol in alignment with current research based recommendations. A systematic review of observational studies has shown that the use of a feeding protocol, irrespective of its specific recommendations, may by itself reduce the risk of NEC (McGuire, Young, & Morgan, 2015).
- Enteral fasting should not be used as a strategy to decrease NEC risk. Delaying enteral nutrition may actually promote intestinal atrophy and lead to an increased infection risk, longer hospital stay, and compromised feeding success later (Ganguli & Walker, 2012).
- Fast advancement of feeding volumes is associated with an increased risk of NEC, and slow advancement of feeding volume may lengthen the need for parenteral nutrition and its associated complications. Therefore, when the infant is judged ready to tolerate feeding advancement, feeding volumes should be conservative and be advanced by 15 to 35 ml/kg/day (National Guideline Clearinghouse, 2015).

Medications

Some of the recommendations for medication use are not discussed in the paper because prescribing medications is not a role of nurses. However, it is important for nurses to be an advocate for their patients and question orders that are not in alignment with best practices. The following are evidence-based practice medications recommendations in regards to NEC prevention.

- A single course of antenatal corticosteroid should be given prior to preterm delivery (National Guideline Clearinghouse, 2015). The use of antenatal steroids is associated with a decreased risk of NEC according to metasynthesis of multiple studies (National Guideline Clearinghouse, 2015).
- Ibuprofen rather than indomethacin (both NSAIDS) should be used for closure of patent ductus arteriosus (PDA) (National Guideline Clearinghouse, 2015). Ibuprofen is associated with lower serum creatinine levels and a lower incidence of oliguria, however, both ibuprofen and indomethacin are associated with potentially serious adverse effects. The serious side effects of ibuprofen include decreased bilirubin albumin binding capacity, pulmonary hypertension, and chronic lung disease. The serious side effects from indomethacin include transient or permanent derangement of renal function, NEC, gastrointestinal hemorrhage or perforation, altered platelet function, and impairment of cerebral blood flow/cerebral blood flow velocity. In a meta-analysis examining ibuprofen versus indomethacin for closure of patent ductus arteriosus, 15 trials reported on an outcome of NEC. The risk of developing NEC was reduced for ibuprofen (National Guideline Clearinghouse, 2015). Despite this evidence, indomethacin is still routinely used in practice. Clinicians need to reevaluate their prescribing habits and align them with best practices.
- H2 blockers should not be routinely used. Inhibitors of gastric acid secretion/H2 blockers are associated with a higher incidence of NEC in VLBW infants (More et al, 2013).

Other Recommendations

- An abdominal radiograph should be performed in infants with clinical suspicion of NEC. According to modified Bell's staging, there is a classic triad of symptoms: abdominal distension, bloody stools, and bilious gastric aspirate or emesis with either pneumatosis intestinalis, portal venous gas, or pneumoperitoneum (Luton, 2013). At least one of the symptoms must be present along with one positive radiographic finding meet diagnostic criteria for NEC (Luton, 2013).
- Infants with suspected NEC should be cared for in a level III neonatal intensive care unit (NICU). With evidence of pneumoperitoneum or portal venous gas on radiographic finding, it is recommended a surgeon, in a facility in which operative intervention can be performed, evaluates the neonate (National Guideline Clearinghouse, 2015).

As discussed, NEC is associated with a high morbidity and mortality, and treatment options are often unsuccessful and there is little improvement of outcomes even after early diagnosis. NEC survivors suffer from serious short and long-term co-morbidities. Prophylactic measures are key to improve the incidence of NEC. The previously mentioned recommendations need to be implemented to decrease and prevent NEC as best as the evidence has currently shown.

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