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The Use of Probiotics in Preventing Necrotizing Enterocolitis

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Prematurity is not a new phenomena. Advances in medical technology has allowed for increased survival of the smallest infants with the earliest age being 22 to 23 weeks gestation. Despite the medical advances, these tiny infants are at risk for numerous postnatal complications. Complications of prematurity can affect many body systems and include infection, intraventricular hemorrhage, chronic lung disease, osteopenia, retinopathy of prematurity and necrotizing enterocolitis (Angert, 2009). Prevention is crucial in all these disease states, in particular the use of probiotics in preventing necrotizing enterocolitis. Bifidobacteria and lactobacilli are the common intestinal flora found in term, breastfed infants. Preterm infants lack this normal flora.   Probiotics such as Bifidobacteria and Lactobacillus are live microbial supplements that are intended to colonize and normalize the intestines of premature infants in an effort to prevent the overgrowth of pathogenic organisms which can lead to necrotizing enterocolitis.   "The evidence that probiotics reduce mortality rates is as conclusive as that for surfactant for respiratory distress syndrome, cooling for hypoxic ischemic encephalopathy, or antenatal corticosteroids for threatened preterm labor" (Tarnow-Mordi, Wilkinson, Trivedi, & Brok, 2010, p. 1069).

Definition and Description of the Disease

Necrotizing enterocolitis (NEC) is a common gastrointestinal emergency that affects as many as 14% of very low birth weight (VLBW) preterm infants in the neonatal intensive care unit (NICU) (Lin et al., 2008).   The mortality rate for infants diagnosed

with NEC is 20-50% with higher mortality rates corresponding to greater bowel involvement (Gibbins, Maddalena, & Golec, 2008). The exact cause of NEC remains unknown but many factors are believed to contribute to NEC. These include prematurity, enteral feeding, intestinal ischemia and bacterial colonization (Lin et al., 2008).   The incidence of NEC is inversely related to birth weight and gestation. Medical management of NEC is aimed at preventing progression. If NEC is suspected, enteral feeds are stopped, IV fluids are started, nasogastric decompression is initiated, and IV antibiotics started. Lab values and serial abdominal x-rays are conducted. In some cases NEC progresses despite medical management and surgery is needed for peritoneal drainage or bowel resection (Ladd and Ngo, 2009).

Four risk factors are believed to contribute to NEC. The first risk factor is prematurity. NEC occurs in 5-10% of all infants less than 1500 grams at birth. The second risk factor is enteral feedings. Although NEC occurs weeks after feedings are started, it usually occurs when full feeding amounts are achieved. Infection is the next risk factor although no specific bacterium has been pinpointed. Normal intestinal flora consisting of lactobacilli and bifidobacerium are not evident in preterm infants until three to four weeks after birth. This lack of normal flora is attributed to late start of enteral feedings and use of broad-spectrum antibiotics. Mucosal injury or ischemia is the fourth risk factor but it is unclear if ischemia is the cause of NEC as in asphyxia or the result of NEC from the mucosal inflammation (Gibbs, Lin and Holzman (2007).

Hammerman and Kaplan (2006) explain the microflora of infant intestines and how probiotics can help with restoring normal flora and thereby reduce the incidence of NEC. A newborn gut is sterile until birth. A normal, full term, breastfed newborn will

colonize a variety of intestinal bacteria with bifidobacteria being the dominant one. The

preterm infant has a much different colonization due to the delayed start of feedings and

use of broad-spectrum antibiotics, with a smaller number of bacterial strains. Those that

are present are usually pathogenic and include klebsiella, enterobacter and clostridium

organisms. The appearance of the normal bifidobacteria usually does not occur in the

preterm infants until 2-3 weeks after birth, making the preterm infant more susceptible to

NEC. Underwood, et al. concluded probiotics did increase bifidobacteria in the preterm

infants (2009). In addition, many probiotic clinical trials have been conducted outside

the United States, which have shown a significant decrease in the incidence of NEC in

preterm infants greater than 1000 grams (Ladd and Ngo, 2009).

The sequelae of infants who survive NEC include short-gut syndrome, poor

growth, prolonged initial hospitalization, multiple re-hospitalizations and poor long-term

neurodevelopment (Martin & Walker, 2008). Preventing NEC is instrumental in

decreasing the morbidity and mortality from this gastrointestinal emergency. Evidence

based studies have shown a decrease in NEC in breast fed babies and conservative

trophic feedings. Other experimental methods of prevention include antenatal steroids,

enteral antibiotics, and probiotics (Ladd and Ngo, 2009). The use of probiotics is an

inexpensive, safe and effective treatment for the prevention of NEC.

Current Review of Evidence-Based Literature

The literature was searched for information about the use of probiotics in the

prevention of necrotizing enterocolitis. An electronic search of CINAHL and MEDLINE

databases was performed using keywords necrotizing enterocolitis and probiotics.   The time frame searched was from 2000 to 2010.

Hammerman and Kaplan (2006) compare four clinical trials that used probiotics in preterm infants and evaluated the incidence of NEC. Three out of the four studies demonstrated a decreased incidence of NEC with relative risk: 0.395 (95% CI, 0.279-0.559) and P < 0.001. One of the four studies showed a decrease in mortality from probiotic use. The overall result was not significant with a relative risk of 0.896 (95% CI, 0.709-1.132) and P = 0.388. None of the four studies showed a significant increase or decrease in sepsis with overall relative risk: 1.02 (95% CI, 0.801-1.302) and P = 0.913. Finally the authors concluded probiotics are a safe, noninvasive, disease-preventing option that should be considered a treatment option in neonatology. "Their efficacy in preventing NEC renders them a most attractive addition to the clinical armamentarium. To date, very few other strategies have been proven definitively to be efficacious in decreasing the incidence of NEC (Hammerman and Kaplan, 2006, p. 282).

In the summary of their multicenter randomized controlled trial, Lin et al. begin with presenting the problem of NEC and the possible contributing factors. The authors explain that previous clinical trials found probiotics decreased the incidence of NEC but these trials failed to define optimal strains, timing, dosage and duration. The hypothesis was clearly stated. The method was a prospective, randomized, masked, controlled trial involving seven NICU's in Taiwan. The population included 443 preterm infants with birth weight less than 1500 grams and they were randomized to a group that received Infloran, a probiotic, with breast milk twice per day or a group that received breast milk alone. Inclusion and exclusion criteria were defined. Parental consent was obtained and

approval was given by the IRB before initiation of the study. Death or NEC occurred in

4 out of 217 infants in the study group and 20 out of 217 in the control group. The NNT

to prevent one case of NEC was 20 infants and the NNT to prevent 1 death or case of

NEC was 14. A post-hoc analysis was done to evaluate for bias or center variations.

Final conclusions support the use of the probiotics containing B bifidum and L

acidophilus for six weeks to decrease the incidence of NEC in VLBW preterm infants.

Underwood, et al. explain how the preterm infant lacks the important normal

bacteria that are needed for growth and good health. Discussion of the variety of

outcomes from previous probiotic studies reveals that the differences occurred based on

the infants gestational age and the type of probiotic used. The team of researchers

investigated three groups, two of the groups received two different commercially

produced probiotics and the third group received a placebo. This was a double blind,

placebo-controlled, randomized study that evaluated the effect of probiotics on weight

gain, fecal microbiota and fecal short-chain fatty acid content of the preterm population.

The study was IRB approved and parental consent was obtained. Inclusion and exclusion

criteria were identified. The data collection and analysis was scientifically thorough.

The first result of the study revealed the actual make up of the probiotics differed from

their advertised labels. The study revealed no significant difference in weight gain

between the placebo and intervention groups. Final stool samples revealed a significant

difference in the bacteria between the intervention and placebo groups. The intervention

groups showed a large colonization of bifidobacteria, similar to a term breast-fed infant,

whereas the placebo group showed low counts of bifidobacteria, typical of a preterm

infant. This was the first study in the United States to compare two probiotic products to

a placebo. The study revealed different make up in the advertised versus actual

compositions of the probiotics. Although the study revealed advantageous differences in

the fecal bacteria composition between the intervention and control groups, it also

revealed the issue of purity of probiotics and questioned their use in the vulnerable

preterm population. Finally the authors recommended more large, multi-centered trials

before the widespread use of probiotics is implemented in the preterm population.

Final analysis revealed two meta-analysis articles. The first is *Probiotics for

Prevention of Necrotizing Enterocolitis in Preterm Infants (2008)*. In this Cochran

review AlFaleh and Bassler compare probiotic versus placebo or no treatment in the

prevention of NEC and/or sepsis in preterm infants. Standard Cochrane search strategy

was used and only quasi-randomized or randomized trials were included. Inclusion

criteria was preterm infants less than 37 weeks and/or less than 2500 grams. Nine trials,

consisting of 1425 infants were included. Specific data related to VLBW infants could

not be extrapolated. The meta-analysis revealed probiotics decreased the incidence of

stage II or greater NEC with a relative risk of 0.32 (95% CI, 0.17-0.60. Probiotics also

reduced mortality from NEC with the relative risk 0.43 (95% CI, 0.25-0.75). No

significant change in sepsis incidence was noted, relative risk 0.93 (95% CI, 0.70-1.19).

Final analysis did reveal that probiotics did significantly reduce the incidence of severe

NEC and a practice change was recommended for preterm infants greater than 1000

grams.

The second article is *Updated Meta-analysis of Probiotics for Preventing

Necrotizing Enterocolitis in Preterm Neonates (*2010) by Deshpand, Rao, Patole, &

Bulsara. Cochrane Central register, Medline, Embase and Cinahl databases were

searched with a total of eleven (N = 2176) trials included in the meta-analysis. A greater

number of infants in the control group (no probiotics) developed NEC compared with the

group that received the probiotics, with a relative risk: 0.35 (95% CI, 0.23-0.55) and P <

0.00001. The number need to treat (NNT) to prevent one case of NEC was 25. Probiotic

use did not show a significant decrease in sepsis, with relative risk 0.98 (95% CI, 0.81-

1.18) and P = 0.80. Probiotic use also showed a significant decrease in mortality, with

relative risk 0.42 (95% CI, 0.29-0.62 and P < 0.00001. NNT to prevent 1 death was 20.

A sensitivity analysis of five trials (N = 1717) revealed decreased NEC in the probiotic

group with relative risk of 0.29 (95% CI, 0.17 – 0.59) and P < 0.00001 and a decreased

mortality with relative risk 0.39 (95% CI, 0.25-0.59) and P < 0.00001. All the included

trials had a Jadad quality score of =/> 3. "Overall, the results of our updated systemic

review and meta-analysis (11 good quality RCT's and N = 2176) confirm the dramatic

benefits of probiotic supplements in reducing the risk for death and for definite NEC in

preterm VLBW neonates", with VLBW infants defined as less than 1500 grams.

(Deshpand, et al, 2010, p. 925).

Diagnosing NEC

Necrotizing enterocolitis is an inflammatory bowel disease that mainly affects

preterm infants. The exact pathophysiology of NEC remains unknown but it is thought to

be a multi-factorial process. Intestinal ischemia with reperfusion, bacteria in the gut and

enteral feedings can activate inflammatory mediators, which are thought to contribute to

the pathophysiology of NEC. Once the inflammatory mediators are activated, the

premature infant is unable to modulate this response. This is the common pathway for

the disease, which can lead to bowel injury and or death. Although the exact cause of

NEC remains unknown, the key to decreasing the incidence of this catastrophic disease is

prevention. Trials on different feeding strategies have been investigated, comparing

earlier feeding introduction to delayed feeding. Neither feeding plan proved to decrease

the incidence of NEC. Other randomized controlled trials have investigated the use of

IGA and IGG in the prevention of NEC with no significant reduction noted.

Prophylactic antibiotics have also been considered but the risks outweigh the benefits.

Only three preventative treatment strategies have been shown to give some protection

against NEC and are the only promising preventative measures in the prevention of NEC

(Gibbins, Maddalena and Golec, 2008):

- The exclusive use of maternal breast milk

- Standardized feeding protocols, specifically advancing feedings cautiously

     by a priori decisions not just early versus delayed feeding

- Prophylactic probiotics

The clinical presentation of NEC can be very non-specific and insidious or it can

present as a catastrophic emergency leading to shock and possibly death in a short time

period. The signs and symptoms include apnea, bradycardia, oxygen desaturation,

lethargy, irritability, temperature instability, abdominal distention, abdominal tenderness,

absent bowel sounds, feeding intolerance, abdominal wall cellulitis, blood in the stool,

emesis, and increased gastric residuals. Diagnostic laboratory abnormalities include

metabolic acidosis, thrombocytopenia, leucopenia, leukocytosis with increased band

cells, glucose instability, hyponatremia, coagulation abnormalities, and increased C-

reactive protein. Finally radiographic abnormalities include intestinal dilatation, presence

of fixed loop of the dilated bowel, thickening of the intestinal wall, ascites, air in the

portal venous system pneumatosis intestinalis, which is the accumulation of hydrogen gas

in the bowel wall by fermentation of carbohydrates by gas-producing organisms and

pneumopeironeum (Thompson and Bizzarro, 2008).

A staging system for classifying NEC was introduced by Bell and colleagues in

1978. This staging system breaks NEC down into 3 stages. Stage I is suspected NEC and

includes the symptoms of temperature instability, apnea and bradycardia, lethargy,

increased gastric residuals, mild abdominal distention, emesis, and bloody stools.

Radiographic findings would show normal or mild intestinal dilatation or mild ileus.

Stage II is Definitive NEC and includes all the symptoms of stage one and in addition

there is an absence of bowel sounds, abdominal tenderness, mild metabolic acidosis and

mild thrombocytopenia.   Radiographic studies show intestinal dilatation, ileus or

pneumatosis intestinalis. Finally stage 3 NEC is the most severe and includes all the

symptoms of stage I and II and in addition there is severe apnea and bradycardia,

respiratory and metabolic acidosis, neutropenia, thrombocytopenia and disseminated

intravascular coagulation (Gibbins, et al, 2008).   Bell's NEC classification system is

further divided in to class A and B in each stage as listed below in Table 1 (Hughes, Baez

& McGrath, 2009).

TABLE 1

Stage I: suspected NEC
A. Systemic signs are nonspecific, including apnea, bradycardia, lethargy, and temperature instability.
B. Intestinal finding include feeding intolerance, recurrent gastric residuals, and guaiac-positive stools.
C. Radiographic findings are normal or nonspecific.
In stage IB, the diagnosis is the same as stage IA, with the addition of grossly bloody stool.
Stage II is the definite diagnosis of NEC.
Stage IIA: mild NEC
A. Systemic signs are similar to those in stage I.
B. Intestinal findings include prominent abdominal distention with or without tenderness, absent bowel sounds, and gross blood in stools.
C. Radiographic findings include ileus, with dilated loops with focal areas of pneumatosis intestinalis.
Stage IIB: moderate NEC
A. System signs include stage I signs plus mild acidosis and thrombocytopenia.
B. Intestinal findings include increasing distention, abdominal wall edema, and tenderness with or without a palpable mass.
C. Radiographic findings include extensive pneumatosis and early ascites intrahepatic portal venous gas may be present.
Stage III: advanced NEC
Stage IIIA: advanced NEC
A. Systemic findings include respiratory and metabolic acidosis, assisted ventilation for apnea, decreasing blood pressure and urine output, neutropenia, and coagulopathy.
B. Intestinal findings include spreading edema, erythema, or discoloration, and induration of the abdominal wall.
C. Radiographic findings include prominent ascites, paucity of bowel gas, and possibly a persistent sentinel loop.
Stage IIIB: advanced NEC
A. Systemic findings reveal generalized edema deteriorating vital signs and laboratory indices, refractory hypotension, shock syndrome, disseminated intravascular coagulation, and electrolyte imbalance.
B. Intestinal findings reveal a tense, discolored abdomen and ascites.
C. Radiographic findings commonly show absent bowel gas and often evidence of intraperitoneal free air.

Treatment and Prevention of NEC

Treatment of NEC is divided into two categories: medical and surgical interventions, which is based on the degree of disease as categorized by the Bell staging system. Medical treatment entails resting the bowel by stopping all enteral feedings, placing a nasogastric tube to low intermittent suction, and initiation of intravenous fluids usually total parenteral nutrition with intravenous lipids. A full septic workup including blood culture, urine culture and cerebral spinal fluid culture should be performed to identify the bacteria that may have caused NEC. After cultures are obtained, intravenous antibiotics must be initiated and would include ampicillin and vancomycin for gram-positive organism coverage, gentamicin and cefotaxime for gram-negative organisms, and metronidazole and clindamycin for anaerobic organisms (Thompson and Bizzarro, 2008). Bowel rest and antibiotics should continue for 7-14 days and antibiotics adjusted based on cultures and sensitivities. Finally, serial radiographic studies must be performed to monitor disease status. Surgical intervention is usually indicated if progression of disease has advanced to Bell's stage III. Exploratory laporatomy is done to identify and remove and necrotic bowel.

Prevention is instrumental to decreasing the incidence of NEC. There are five interventions that have proven to be instrumental in decreasing NEC. These are antenatal corticosteroids, trophic feedings, breast milk, oral antibiotics and most recently probiotics (Thompson and Bizzarro, 2008). Gibbins, Maddalena and Golec found that only three measures were proven to decrease the incidence of NEC and these are breast milk, standardized feeding protocols and probiotics (2008). Probiotics and breast milk are the two prevention measures found in both investigations.

"Probiotics are defined as live microbial supplements that colonize the intestine and provide benefit to the host. Benefits of probiotics are normalization of intestinal mucosal barrier function, protection of the gut from pathogens, decreased inflammatory processes, increased anti-inflammatory cytokines, improved enteral nutrition, and reduced infection rates secondary to bacterial translocation" (Gibbins et al, p. 147, 2009). Probiotics are thought to prevent NEC by encouraging competitive colonization, producing organic acids that decrease pH and inhibit growth of pathogens, increasing peristalsis, modulating immune response, producing anti-inflammatory cytokines, competing for pathogen binding and receptor sites, producing bactericocins, influencing intestinal mucosa to enhance mucin production, stimulating IgA production and enhancing enteral nutrition (Hughes, et al, 2009). The research that has been conducted demonstrates that the use of probiotics does reduce the incidence of NEC.

Patient and Family Counseling

An infant diagnosed with NEC can be a very scary situation for the parents of the infant. Parents should immediately be informed of their infant's change in status and the results of preliminary tests and findings. Parents need to be involved in the decision-making process and be allowed to consider all the options along the care continuum. When prognosis is grim and treatment is futile, parents need to be given some time to come to terms with the challenging diagnosis. "Referred to as 'the temporal gap,' parents are often several days behind caregivers in grasping condition and prognosis and have little or no experience on which to draw upon" (Gibbins, et al, p.150, 2009). In turn, parents will be left to make some difficult decisions, which need to be supported, and family-centered care must be central to the care of the infant.

Patient and Family Education

Both family education and family counseling must be included in the plan of care. Education is giving the family the information in a clear and concise manner. Counseling is giving families the emotional support to deal with the new diagnosis. NEC can be a potentially fatal diagnosis for a preterm infant. Early parent education about the complications of prematurity should include prevention of NEC with the use of probiotic supplementation in preterm infants. Education and prevention are key components to eliminating the problem of necrotizing enterocolitis in the preterm infant population.

Caring for an infant with NEC involves a multi-system approach. Family education is one are that can sometimes be forgotten but is very important in the care of the infant with NEC. First, parents need to be informed immediately in the infant's change in status. Informing parents of the preliminary diagnosis including possible outcomes and options. The use of Bell's NEC classification system is a helpful tool in visually detailing the stages of NEC. The family needs to be included in the consultation process with specialists. The family will need time to come to terms with the new, potentially life-threatening diagnosis. Finally the family needs to be given all the options along the continuum of care.

Conclusion

Necrotizing enterocolitis is a devastating condition that still has no exact etiology and no specific therapy. Prematurity is a predisposing risk factor for NEC. Preterm infants are known to have altered intestinal flora. Probiotics are promising therapy in establishing normal intestinal flora in the preterm infant. The clinical trials to date have

shown some benefit in the use of probiotics for the prevention of NEC in preterm infants.

The problem is that each clinical trial has treated different populations, used different

outcome measures and used different probiotic organisms. FDA approval of probiotic

preparations that have proven to decrease the incidence of NEC could significantly help

to reduce this devastating disease. Probiotics have the potential to become a clinical

breakthrough in the prevention of necrotizing enterocolitis in the preterm infant.

Internet Resources for Families

http://www.prematurity.org

http://www.marchofdimes.org

http://www.neonatology.org

http://www.aap.org/sections/perinatal/families.html

References

Angert, Robert (2009). Care of the Very Low-birthweight Infant. *Pediatrics in Review.*

30 (1), 32-35.

AlFaleh, K. M., & Bassler, D. (2008). Probiotics for prevention of necrotizing

enterocolitis in preterm infants. *Cochrane Database of Systematic Reviews,* (1)

Askin, D. F., & Diehl-Jones, W. (2005). Improving on perfection: Breast milk and breast-

milk additives for preterm neonates. *Newborn & Infant Nursing Reviews, 5*(1), 10-

18.

Caplan, M. S. (2009). Probiotic and prebiotic supplementation for the prevention of

neonatal necrotizing enterocolitis. *Journal of Perinatology, 29*, S2-6.

Deshpande, G., Rao, S., Patole, S., & Bulsara, M. (2010). Updated meta-analysis of

probiotics for preventing necrotizing enterocolitis in preterm neonates. *Pediatrics,*

125(5), 921-930.

Gaul, J. (2008). Probiotics for the prevention of necrotizing enterocolitis. *Neonatal*

Network, 27(2), 75-80.

Gibbins, S., Maddalena, P., & Golec, L. (2008). Evidence-based care for the infant with

necrotizing enterocolitis. *Newborn & Infant Nursing Reviews, 8*(3), 144-152.

Gibbs, K., Lin, J., & Holzman, I. R. (2007). Necrotizing enterocolitis: The state of the

science. *Indian Journal of Pediatrics, 74*(1), 67-72.

Hammerman, C., & Kaplan, M. (2006). Probiotics and neonatal intestinal infection.

Current Opinion in Infectious Diseases, 19(3), 277-282.

Hughes, B., Baez, L., & McGrath, J. M. (2009). Necrotizing enterocolitis: Past trends and

current concerns. *Newborn & Infant Nursing Reviews, 9*(3), 156-162.

Indrio, F., Riezzo, G., Raimondi, F., Bisceglia, M., Cavallo, L., & Francavilla, R. (2008).

    The effects of probiotics on feeding tolerance, bowel habits, and gastrointestinal

    motility in preterm newborns. *Journal of Pediatrics, 152*(6), 801-806.

Ladd, N., & Ngo, T. (2009). Pharmacology notes. The use of probiotics in the prevention

    of necrotizing enterocolitis in preterm infants. *Baylor University Medical Center*

    Proceedings, 22(3), 287-291.

Lin, H., Hsu, C., Chen, H., Chung, M., Hsu, J., Lien, R., Tsao, L., Chen, C., & Su, B.

    (2008). Oral probiotics prevent necrotizing enterocolitis in very low birth weight

    preterm infants: A multicenter, randomized, controlled trial. *Pediatrics, 122*(4),

    693-700.

Martin, C. R., & Walker, W. A. (2008). Probiotics: Role in pathophysiology and

    prevention in necrotizing enterocolitis. *Seminars in Perinatology, 32*(2), 127-137.

Neu, J. (2007). Gastrointestinal development and meeting the nutritional needs of

    premature infants. *American Journal of Clinical Nutrition, 85*(2), 629S-634.

News. Germ-friendly. (2008). *Neonatal Intensive Care, 21*(3), 16-17.

Preemies may benefit from probiotics: May reduce risk of necrotizing enterocolitis.

    (2007). *Contemporary OB/GYN, 52*(7), 18-18.

Puntis, J. (2006). Nutritional support in the premature newborn. *Postgraduate Medical*

    Journal, 82(965), 192-198.

Rougé, C., Piloquet, H., Butel, M. J., Berger, B., Rochat, F., Ferraris, L., Des Robert, C.,

    Legrand, A., MF, N'Guyen, J., Vodovar, M., Voyer, M., Darmaun, D., & Rozé, J.

    (2009). Oral supplementation with probiotics in very-low-birth-weight preterm

infants: A randomized, double-blind, placebo-controlled trial. *American Journal of Clinical Nutrition, 89*(6), 1828-1835.

Rouse, D. J. (2009). [Commentary on] oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: A multicenter, randomized, controlled trial. *Obstetrical & Gynecological Survey, 64*(2), 84-85.

Soll, R. F. (2010). Probiotics: Are we ready for routine use? *Pediatrics, 125*(5), 1071-1072.

Srinivasjois, R., Rao, S., & Patole, S. (2009). Prebiotic supplementation of formula in preterm neonates: A systematic review and meta-analysis of randomized controlled trials. *Clinical Nutrition, 28*(3), 237-242.

Srinivasjois, R., Rao, S., & Patole, S. (2009). Prebiotic supplementation of formula in preterm neonates: A systematic review and meta-analysis of randomized controlled trials. *Clinical Nutrition, 28*(3), 237-242.

Tarnow-Mordi, W., Wilkinson, D., Trivedi, A., Sinn, J., Dutta, S., Parikh, T., & Lin, H. C. (2010). Re: ESPGHAN commentary and education that probiotics substantially reduce all-cause mortality and necrotizing enterocolitis in preterm infants. *Journal of Pediatric Gastroenterology & Nutrition, 50*(6), 694.

Tarnow-Mordi, W., Wilkinson, D., Trivedi, A., & Brok, J. (2010). Probiotics reduce all-cause mortality and necrotizing enterocolitis: It is time to change practice. *Pediatrics, 125*(5), 1068-1070.

Thompson, A. M., & Bizzarro, M. J. (2008). Necrotizing enterocolitis in newborns: Pathogenesis, prevention and management. *Drugs, 68*(9), 1227-1238.

Underwood, M. A., Salzman, N. H., Bennett, S. H., Barman, M., Mills, D. A., Marcobal,

 A., Tancredi, D. J., Bevins, C. L., & Sherman, M. P. (2009). A randomized

 placebo-controlled comparison of 2 prebiotic/probiotic combinations in preterm

 infants: Impact on weight gain, intestinal microbiota, and fecal short-chain fatty

 acids. *Journal of Pediatric Gastroenterology & Nutrition, 48*(2), 216-225.

Westerbeek, E., A, Lafeber, H. N., Knol, J., Fetter, W., & van Elburg, R. (2006). The

 intestinal bacterial colonization in preterm infants: A review of the literature.

 Clinical Nutrition, 25(3), 361-368.