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ENTEROCOLITIS IN VERY LOW BIRTH WEIGHT PRE-TERM

Breast Milk Exposure and the Incidence of Necrotizing Enterocolitis in Very Low Birth Weight
Pre-Term Infants

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Abstract:

Purpose: To determine what degree of exposure to breast milk feeding is protective against Necrotizing Enterocolitis (NEC) in very low birthweight (VLBW) preterm infants.

Data Sources: This is a secondary data analysis of 56 VLBW preterm infants diagnosed with NEC and 56 age-matched VLBW infants who served as controls. All infants were born between 1997 and 2009 and cared for in the Newborn Intensive Care Unit (NICU). Infants were born at or before 29 weeks gestation and with a birth weight less than 1500 grams. Data included the volume fed daily and type of feeding along with demographic birth data.

Methods: The percentage of total volume of feeding that was breast milk versus infant formula was calculated over time frames of three weeks, two weeks, one week, six days, five days, four days, three days, two days and one day before the NEC diagnosis date in case infants. Odds ratios were used to determine the relationship between mean percent of breast milk feeding and the occurrence of NEC.

Results: In a preliminary odds ratio, breast milk feeding was protective against NEC at a threshold of 50%. When over 50% of the total feeding volume consisted of breast milk versus infant formula, infants were nearly half as likely to develop NEC. This finding was clinically significant and underscores the importance of breast milk in NEC protection. However, the sample size available to this study proved to be too small to be statistically significant.

Implications for Practice: Preterm infants in the NICU should receive the highest possible percentage of breast milk feedings. Strategies to increase the provision of breast milk need to be a priority.

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Conclusions: Our findings demonstrate that if at risk infants receive at least 50% breast milk by volume, then the risk for NEC may be decreased by 50-66%. Further analysis involving a larger sample of preterm infants is needed to support this finding.

Key Words: very low birth weight, preterm infants, prematurity, necrotizing enterocolitis, NEC, infection, breast milk, breastfeeding, breast pumping, at risk infants

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Breast Milk Exposure and the Incidence of Necrotizing Enterocolitis in Very Low Birth Weight Pre-Term Infants**Background**

Necrotizing Enterocolitis (NEC) is a devastating, multifactorial, gastrointestinal disease that affects between one and three infants per 1000 live births (Premji, 2005). As a multifactorial disease, there is no one definitive cause, making NEC difficult for healthcare providers to effectively detect and treat. With mortality rates between 20% and 30% (Neu, 2013) research on NEC is vital to the development of evidence-based practice strategies to help healthcare professionals prevent the disease before it begins. A recent study by Patel et. al describes an increase in NEC related deaths from 2003 to 2011, while deaths related to other neonatal illnesses have declined (Patel, 2015). This finding highlights the need for research related to NEC prevention.

NEC often first presents with generalized lethargy and cardio-respiratory decline associated with increasing oxygen requirements. Abdominal symptoms of NEC include abdominal distention, bile colored (green) gastric aspirates, lack of gastric motility, lethargy and signs of infection. Infants with NEC also present with anemia, metabolic acidosis, thrombocytopenia, neutropenia and hyponatremia. Radiographically, infants with NEC present with pneumatosis due to gas in the bowel, thickened bowel walls and dilated bowel loops (Sharma, 2013). NEC involves an inappropriate or exaggerated inflammatory response in the preterm bowel. This inflammatory response results in bowel injury is characterized by pneumatosis, distension, and under the worst circumstances, bowel perforation that is different from spontaneous perforation. This tissue necrosis can result from several factors that have been

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associated with an overwhelming inflammatory response in the bowel: Aggressive advancement of feedings, viral infection (Sharma, 2013), severe anemia (as defined by hemoglobin less than 8) leading to hypoxic injury (Patel, 2016), genetic predisposition in the TLR4 gene (Kenton et. Al, 2014). Maternal factors that are associated with NEC include chorioamnionitis (Been, 2013) and premature rupture of membranes (Drenckpohl, 2010).

Breast milk and its role in the development of the microbiome in the gut is one of the most strongly supported factors in NEC prevention (Sharma, 2013). Generally, there has been much research suggesting that changes in the composition of the gut microbiota play a large role in the development of NEC, however many factors may come from the environment and care that the infants receive such as breast milk feeding and availability (Gordon, 2013). Other studies suggest a genetic link involving a single nucleotide polymorphism (SNP) in a gene downstream of TLR4 called NFKB1. TLR4 is involved in the immune response including the apoptosis (programmed cell death) needed to replace compromised portions of the gastrointestinal mucosa. When this reaction is too extreme; tissue necrosis ensues. It has been noted that this SNP may play a role in NEC (Gordon, 2013).

An example of an NEC factor related to hospitalization may be giving feedings during transfusions. Many preterm infants need to receive multiple blood transfusions during their hospital stays due to anemia. These transfusions risk exposure to multiple donors and to potential viruses in the donor blood. A study by Mohammed and Shah indicates that infants transfused within 24 hours of birth are more likely to develop NEC than infants that developed non-transfusion related NEC. Gephart and McGrath reference two more studies that support the notion that withholding feedings during transfusion may be protective against risk of NEC

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(Gephart, 2012).

One strongly supported factor that has been investigated in the development of NEC is breastfeeding and or the provision of breast milk. The World Health Organization (WHO) strongly recommends that VLBW infants be fed breast milk. If the mother is unavailable or unable to produce breast milk, The WHO recommends that the infant be fed donor human milk where available (WHO, 2011). The American Academy of Pediatrics also recommends exclusive breastfeeding for six months followed by breastfeeding supplemented by additional foods for as at least 1 year (AAP, 2012). Studies have shown that breast milk plays many important roles in infant development from immune system development to colonization of the infant's gastrointestinal tract, which is thought to be sterile at birth (Patel, 2015). While an all human milk diet would be best for preterm infants, few actually receive this diet because sustaining breast milk expression while the infant is in the NICU is difficult or not possible for some mothers. An increase in provision of breast milk and breastfeeding can be a modifiable factor for many healthy mothers that is relatively attainable through parent education in the health care setting, environmental changes and public health initiatives, such as provision of breast pumps and private pumping rooms.

Advocacy for breast milk feeding is inexpensive when compared to the cost of NEC treatment and hospitalization. NEC treatment currently makes up 19% of all neonatal healthcare costs in the United States, or approximately \$500 million to \$1 billion (Neu & Walker, 2011). The average cost for the time spent in NICU for a baby that develops NEC is \$90,209 with no surgery required. Due to the surgical expense and prolonged hospitalization, the average for a baby that does require surgery is around \$133,888 (Johnson et. al, 2013). Because NEC costs are

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so high and hospital stays are so long (an average increase in stay is 60 days with surgery and 22 days without) (Johnson, et. al, 2013) even a small decrease in rates of NEC would save a significant number of healthcare dollars per year. Additionally, a key factor that is often used to judge the general health and healthcare systems of a nation is its infant mortality rates. Although the United States has the highest healthcare expenditures, this does not correlate to the best healthcare. The United States infant mortality rates are at a startling 6.17 total deaths in the first year of life per 1000 live births (CIA, 2014). This leaves the United States lagging far behind other industrialized nations in health care outcomes and costs (CIA, 2014). The government public health initiative, Healthy People 2020 would like to see a 10% drop in that number from the 2006 baseline of 6.7 deaths per 1000 live by the year 2020, while the outcome of this goal has not yet been reached, there has been significant improvement (HP, 2020).

Study Purpose

Our research question for this study is what degree of breast milk feeding is protective against NEC and at what point prior to the onset of the disease symptoms. Overall, the purpose of this study is to provide nurses and parents an evidence based goal for breast milk feeding in the prevention of NEC in VLBW preterm infants. This will contribute to existing knowledge guiding evidence based practice in the NICU especially for infants at risk for developing NEC.

Methods

This study was a secondary analysis using a retrospective cohort design. Infants in the study were previously matched to those participating in Dr. Katherine Gregory's study of urinary fatty acid binding protein as a predictor of NEC, in which she examined the presence of iFABP

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in urine samples of this same group of infants. Infants were matched on gestational age (Cohorts of under 27 weeks gestational age and of between 27 and 28 weeks gestation) and dates of treatment at Brigham and Women's Hospital (Gregory et al, 2014). Infants who developed NEC after day 28 of life and infants who were never fed enterally were excluded along with their control pair. Pairs where the the control infant either passed away or was discharged before the case diagnosis date were also removed from the study as there was not comparable feeding data in those pairs.

Study Protocol

The sum of the total volume (breast milk and infant formula) and the total volume of breast milk that each infant was fed over various time frames was calculated. Feeding data of each pair was compared over the same time frame and duration of breast milk exposure in relation to a set end point (i.e the day of life of NEC diagnosis in the case baby). A percentage was then calculated from the total feeding volume and total volume of breast milk for each infant in each time frame. Next, a mean percentage of total feeding that was breast milk was taken for the case and control groups over each time frame. Time frames included three weeks, two weeks, one week, six days, five days, four days, three days, two days and one day before NEC diagnosis date of the case baby. An odds ratio was carried out using SPSS to compare the number of case babies vs. control babies fed less than 50% breast milk and greater than or equal to 50% breast milk, as well as less than 75% and greater than or equal to 75%. Odds ratios at 50% and 75% were preformed using the means at each time frame. A t-test was then used to determine the statistical significance of the outcomes first at 50% and then at 75%. Further analysis was conducted using a McNemar test.

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Results

Sample: Data were collected from the medical records of infants cared for in the NICU at Brigham and Women's Hospital between 1997 and 2009. Study infants were all born prior to 29 weeks gestation and with a birth weight less than 1500 grams. Infants were previously matched in case-control pairs on the criteria of year of birth and gestational age. The data used for analysis includes the nursing flowsheets used to track volume fed to each infant daily and type of feeding. Infants that were never fed enterally and infants who developed NEC after day 28 of life were excluded (See Table 1 for demographic data). Control infants were matched for gestational age and birth weight. Interestingly, 40 of the control infants received breast milk at their first feeding while only 16 received formula.

Table 1. Characteristics of the Study Participants

	Case	Control
N=	56	56
Males	34	28
Females	22	28
Birth weight <835 g	27	28
Birthweight ≥835 g	29	28
Gestational Age <26 weeks	24	22
Gestational Age ≥26 weeks	32	34
Cesarean Delivery	38	41
Vaginal Delivery	18	15
1st Feed= BM	29	40
1st Feed=Infant Formula	27	16
Bell Stage 1	21	-
Bell Stage 2	14	-
Bell Stage 3	6	-
Bell Stage 4	15	-

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A T-test demonstrated that the mean percentage of breast milk exposure was significantly higher in control infants ($P=.000$) The outcome of an initial odds ratios indicated that infants fed less than 50% breast milk were at approximately two times the risk of developing NEC. The T-test of the 50% division compared with the 75% division, demonstrated that odds of developing NEC in babies fed over 50% breast milk vs, babies fed over 75% breast milk was not significantly different ($P=.603$) The odds ratio outcome was higher at each interval for the 50% division than at 75%, with the exception of 21 days before diagnosis, where the outcome for both divisions was approximately one. This result indicates that this long of a time frame did not impact risk. At one week before the date of diagnosis, the outcome of the odds ratio was 2.061 meaning that babies fed under 50% breast milk one week before the projected date of diagnosis were more than twice as likely to develop NEC, a statistically significant difference. Further analysis showed that when a McNemar test accounted for the one to one matching in the study, the difference in the odds ratio was not statistically significant. A statistical power test determined that based on the original finding, that infants at Brigham and Women's Medical Center in this time frame who were fed less than 50% breast milk were 1.86 times as likely to develop NEC as comparable infants fed 50% or more breast milk, we would need a sample size of 229 matched pairs to prove significance (see Figures 1&2).

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Figure 1. Odds Ratio Outcomes at 50% Breast Milk Benchmark VS. 75% Benchmark

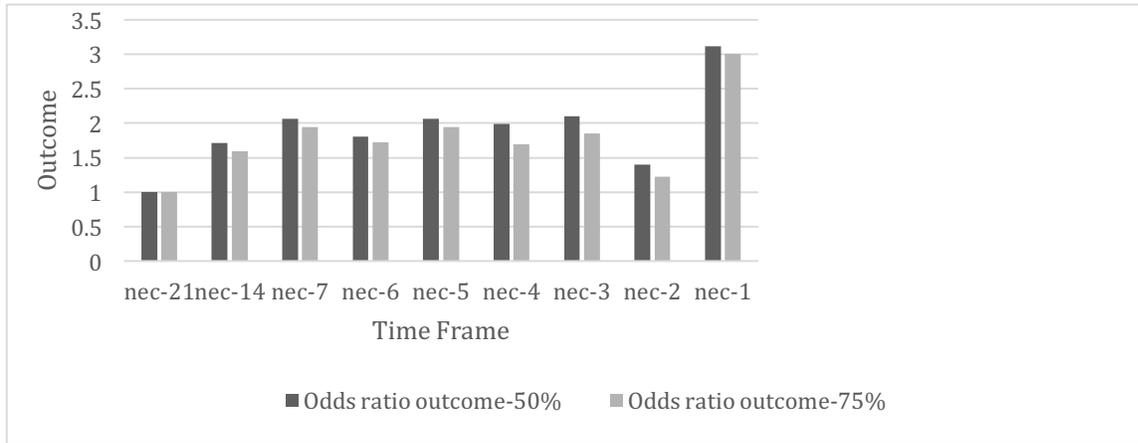


Figure 2: Numerical Odds Ratio Values at 50% Benchmark VS. 75% Benchmark

	50% Benchmark	75% Benchmark
nec-21	1	1
nec-14	1.714	1.592
nec-7	2.061	1.941
nec-6	1.81	1.727
nec-5	2.061	1.941
nec-4	1.994	1.697
nec-3	2.097	1.85
nec-2	1.404	1.228
nec-1	3.116	3

Discussion:

Our hypothesis that babies fed a greater proportion of breast milk as opposed to formula would develop NEC at a lower incidence was supported in this study. We found that a 50% benchmark was statistically significant in our initial odds ratio test which did not account for the one to one matching of pairs while a 75% benchmark was not statistically significant, with a P-

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Value of 0.603. This indicates that further increasing the percentage of breast milk feeding beyond the 50% bench mark may not further decrease the risk of NEC. One Quality Improvement Project that took place in Ireland, reported that for the first time, their unit had zero NEC cases over a one-year period after implementing 100% breast milk feeding in extremely low birth weight infants and 80% in very low birth weight infants in 2013. (Philip, 2015). What makes our study unique is the examination of the required degree of breast milk exposure, as opposed to examining breast milk feeding vs formula feeding in general. Our study suggests that 100% breast milk may not be necessary, and that 50% or greater may be enough to be protective against NEC. These findings contrast with a very similar study by Dr. Leslie Parker that compared length of hospital stay between babies fed an exclusive formula diet with babies fed at least 50% breast milk. This study found no significant difference in length of stay or cost of care between the two groups (Parker, 2012). When considered in the context of our study, this difference is surprising since NEC has been shown to increase length of stay and cost of care (Gephart, 2012). A key difference between these studies may be the gestational age of the subjects, in Parker's study, the subjects were under 32 weeks gestation while in our study the subjects included were under 29 weeks gestation (Parker, 2012). An area of further research may be the correlation between gestational age and breast milk requirements for the protective properties against NEC.

Limitations of this study stem from not only the retrospective nature of the study but also the multifactorial nature of NEC. Since the study was retrospective, we were unable to control many variables such as the medications that the patients received, or other health issues present. Data points were collected in only one NICU over a number of years however changes in practice

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over time were controlled for through our matching strategy. We also examined the effects of *only* one factor noted to be important in the development of NEC, which is a multifactorial disease thus, limiting the generalizability of our findings. We cannot know if changing other caregiving factors could also be important in the development of NEC. The size of our sample was also a limitation because a statistical power analysis demonstrated that to truly prove significance we would need a sample size of 229 pairs, rather than the 52 that we had. However, because the sample size is so small but incidence of NEC is so rare in the general population, 1-3 per 1,000 live births (Premji, 2005), our findings are still notable and should be considered for further evaluation.

Implications for Practice:

This study can be added to the existing evidence base surrounding the benefits of breast milk feeding. Nurses can refer to this study among others in utilizing evidence based practice to encourage mothers to proactively provide their babies with at least 50% breast milk feeding, especially in the NICU. Breast milk feeding is a nurse-led intervention that is appropriate for many patients who can be fed enterally, and has a significant impact on patient outcomes and health care costs with minimal risk. While we should aim to feed VLBW preterm infants and other infants as much breast milk as possible, it is important to recognize that with issues related to mom's work schedules and milk supply, it may not be realistic to expect 100% breast-feeding. Mothers of NICU patients should be provided with support from NICU nurses and Lactation Consultants to provide adequate breast milk. The overall outcome of this study was to determine a specific goal or cut-off for the percent of breast milk feeding that is protective against NEC. Another important implication of this study is to provide parents and NICU nurses a guideline

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benchmark percentage to set as a goal percentage of breast milk. We found that 50% breast milk feeding decreases risk of NEC, this is a reasonable goal for parents and nurses and can be followed at home and in the hospital. For example, if a baby is fed 10 times a day, then nurses can encourage mothers to feed the baby breast milk in at least 5 of those feedings. This study can also be used as evidence based practice to advocate for the availability of breast milk pumping supplies in the hospital and at home to make this goal more attainable.

Implications for Further Research:

Further research is needed to build support for the findings of this study. Primarily, a larger sample size is needed to reflect statistical significance. A statistical power analysis determined that a sample size of 229 babies with the same characteristics would be needed to prove statistical significance for the finding that VLBW babies fed less than 50% breast milk are nearly twice as likely to develop NEC. NPO days are also a factor that warrant further investigation. We excluded infants who were never fed enterally at all, but included babies had a number of NPO days. The effect of how many days a baby is NPO on development of NEC may be another important aspect to add to the existing research on NEC. Investigation into barriers to reaching a goal of 50% breast milk is also key in making this goal attainable for all mother.

Conclusions:

The 50% breast milk by total volume presents the most compelling argument for a threshold of breast milk exposure that is protective against NEC. At one week through three days before the diagnosis date, infants fed less than 50% breast milk are approximately twice as likely to be diagnosed with NEC, as indicated in an initial odds ratio test. This means that if healthcare

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providers and NICU parents can aim to feed at risk infants at least 50% breast milk out of the total volume fed, then they may be able to reduce risk for developing NEC by 50%. Promotion of breast milk feeding is significantly less expensive than the costs incurred by a NEC diagnosis. Breast feeding is also an intervention that can be led by nurses through parent education to reduce incidence of NEC. Reduced incidence of NEC could decrease hospital stay times, health care costs and infant morbidity and mortality in the NICU.

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