5-2022

Necrotizing Enterocolitis Rates in Preterm Infants

Alexis Howard
University of Arkansas, Fayetteville

Elanor Mann School of Nursing, University of Arkansas

Breast Milk and Donor Milk Impact on Necrotizing Enterocolitis Rates in Preterm Infants

Alexis Howard

Dr. Hope Ballentine

Abstract

Breast milk and donor human milk is used in the prevention of necrotizing enterocolitis (NEC) in preterm infants born prior to 37 weeks gestation and those with very low birth weight. This process occurs through direct breast feeding and tube feeding. The aim of this study was to compare the use of breast milk and donor milk to the use of formula feed in preterm infants. A systematic review was conducted using articles collected from CINAHL and PubMed and was guided by PRISMA guidelines. A total of 15 studies that met criteria were analyzed by purpose, variables, study design, population characteristics, and results. In total 629 donor human milk banks, 2557 cases analyzed, 6487 preterm infants, 227 very preterm infants, 926 low birth weight infants, 24,302 very low birth weight infants, and 3174 extremely low birth weight infants from eight different regions were studied. The analysis reveals a decreased incidence of necrotizing enterocolitis in neonates born before 37 weeks gestation when breast/human milk and donor milk were used in comparison to preterm formula feed. However, further research needs to be conducted to understand the pathophysiology of the disease for true preventive care and proper intervention of the disorder to occur.

Introduction

According to Thakkar and Lakhoo (2018 p. 227 – 230), necrotizing enterocolitis (NEC) is now the most common emergency requiring surgery in the neonatal setting. NEC is a gastrointestinal problem that causes inflammation in the intestinal tissue and eventual necrotization of the intestine. A perforation in the intestine can also form leading to bacteria leaking into the bloodstream or abdomen. NEC is classified into four different categories based on what caused the condition and when symptoms started. The most common type of NEC falls into the “classic” category. Within this category infants are born before 28 weeks and NEC

occurs three to six weeks following birth. In most instances, the condition occurs through sudden development, without warning, but the infant remains in a stable state. The “transfusion-associated” category consists of infants who need a blood transfusion to treat anemia and develop NEC within three days of receiving the blood transfusion. “Atypical” NEC is rare and occurs in the infant prior to the first feed or within the first week of life. The last category is termed “term infant” and is usually associated with a birth defect such as a congenital heart condition, low oxygen levels at birth, or gastroschisis. About 85% of infants affected by NEC are premature. Those most at risk are born at a gestation age of less than 34 weeks, fed with enteral nutrition, and fall into the category of extremely low birth weight weighing less than 1000 grams. Over the past decade, there has been increased focus on the relationship between breast milk, donor milk, and formula feeding on the rates of NEC in premature infants.

Although the pathophysiology of the disease is still not completely understood, factors believed to contribute to necrotizing enterocolitis are relatively well-defined. Some of the contributing factors that make a premature infant prone to developing NEC are bacterial colonization, immature immune system, immature intestinal tract, too little blood flow or oxygen to the intestines, and formula feeding (Sanchez & Kadrofske, 2019). The impact on the neonate may range from simple medical monitoring and treatment to a surgical intervention. Medical necrotizing enterocolitis consists of supportive management techniques including stopping enteral feedings and providing parenteral nutrition, administration of broad-spectrum antibiotics, and intestinal decompression by nasogastric suctioning. Surgical management will often consist of either an exploratory laparotomy with possible bowel resection and percutaneous ostomy placement or peritoneal drain placement.

Because NEC in premature neonates is so prevalent, it is necessary to establish an effective prevention and intervention treatment, and education base for parents and nurses to provide the most effective care. It is vital for the future wellbeing of premature neonates that this prevention and intervention be observed and documented. Conducting studies and understanding this prevention and treatment option will help create a base of information for the most effective options against necrotizing enterocolitis.

PICOT Research Question

For preterm infants how does the use of breast/human milk and donor milk impact the morbidity and mortality of necrotizing enterocolitis compared with formula feeding?

Methods

Study Design

A systematic review of research was conducted on the effect breast (human) milk and donor milk has on necrotizing enterocolitis in neonates compared to those receiving formula feed. This review was completed with the use of articles collected from PubMed and CINAHL and was guided by PRISMA guidelines to complete the different phases of the literature review.

Information Sources

I independently searched CINAHL and PubMed databases. An electronic search of the databases CINAHL and PubMed were conducted using subject headings. Following the subject headings, a keyword search was conducted to produce more specific articles.

Search Strategy

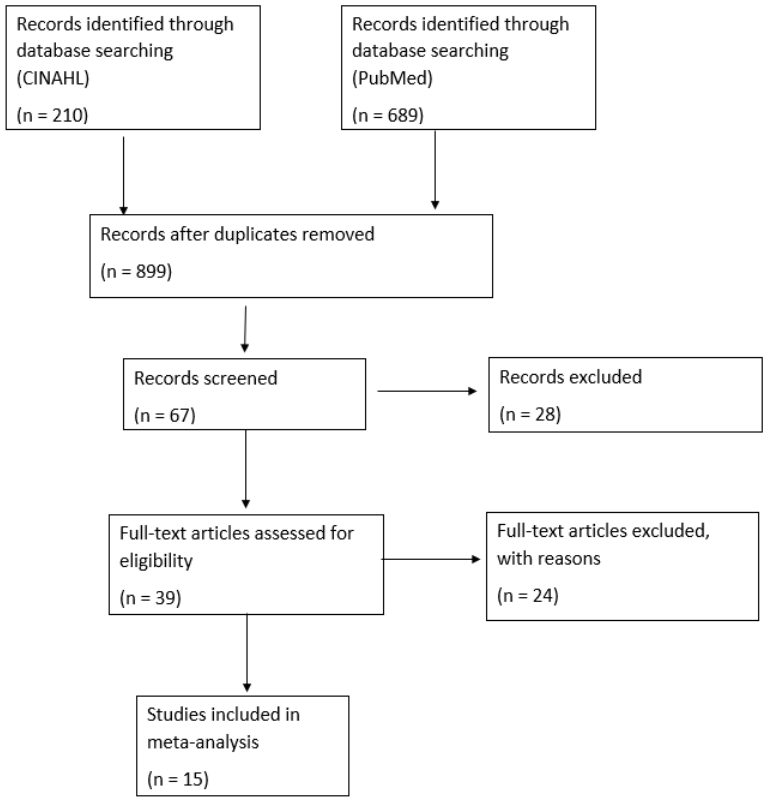
Search terms that were used, based on the research question, include *necrotizing enterocolitis* OR *NEC* OR *necrotising enterocolitis* AND *human milk* OR *breast milk* OR *formula* OR *breastfeeding*. CINAHL and PubMed subject titles were used to search the database.

Search limiters in CINAHL and PubMed include English language, publish date within the last five years, and human subjects.

Inclusion/Exclusion Criteria

Articles that did not include the following PICOT key elements were excluded: (a) The study was conducted on infants with a gestational age equal to or less than 37 weeks (Population); (b) the study investigated the use of breast milk and donor milk as a clinical prevention technique for necrotizing enterocolitis (Intervention or Issue of Interest); (c) the study compared groups that received breast milk and donor milk in comparison to formula feed (Comparison); and (d) outcomes measured must include NEC morbidity or mortality rates (Outcome).

Figure 1



Data Extraction

Information on author, publication year, conceptual framework, design/method, sample & setting, major variables studied, measurement, data analysis, findings, and appraisal worth to practice were all observed from the 15 articles listed. To ensure data accuracy, the articles were reviewed by myself and the universities research librarian. After comparing the data pulled by the two researchers, any incompatible data discrepancies were resolved.

Search Results

After searching CINAHL, the initial search compiled 210 articles with no duplicates noted. Abstracts and titles of articles were reviewed narrowing it down to 52 articles. Next, the full text of the remaining articles was reviewed and articles that did not meet the inclusion criteria were excluded. This resulted in seven primary full-text articles that were used for review. See Appendix A.

After searching PubMed, the initial search compiled 689 articles with no duplicates noted. Abstracts and titles of articles were reviewed narrowing it down to 15 articles. Next, the full text of the remaining articles was reviewed and articles that did not meet the inclusion criteria were excluded. This resulted in eight primary full-text articles that were used for review. See Appendix A.

Results

Characteristics of Studies

In the 15 studies chosen, there were a combined total of 629 donor human milk banks, 2557 cases analyzed, 6487 preterm infants, 227 very preterm infants, 926 low birth weight infants, 24,302 very low birth weight infants, and 3174 extremely low birth weight infants from eight different regions: various states within the United States, England, Mexico, Italy, Spain,

France, Netherlands, and China. The age range of these participants varied from preterm neonates within the range of 28 to 37 weeks old. Not all studies reported specific age of participants but reported the range of participant ages. The studies feature a meta-analysis (Altobelli et al., 2020), a retrospective case control study (Baños-Peláez et al., 2021), a single center, observational and retrospective cohort study (Canizo Vázquez et al., 2019), a retrospective chart review (Chowning et al., 2016), a quality improvement observational study (Cohen et al., 2021), a multicenter, double blinded randomized clinical trial (Corpeleijn et al., 2016), a retrospective quality improvement initiative (Feinberg et al., 2017), a multicenter retrospective cohort study (Hair, et al., 2016), a descriptive analysis (Kantorowska et al., 2016), a randomized control intervention trial (Lapidaire et al., 2021), a systematic review and meta-analysis (Miller et al., 2018), a meta-analysis including a double blinded randomized control trial and retrospective cohort study (Patel, A., & Kim, J., 2017)**,** a prospective nationwide population-based study (Rozé et al., 2017), a retrospective single-center chart review (Sato et al., 2019), and a comprehensive literature search of randomized control trials (Zhang et al., 2020). More information can be found in the table located in search results.

In the articles being reviewed, researchers explore the use of milk banks and donor human milk availability in correlation to NEC rates. Altobelli et al. (2020) examines the relationship between NEC in low weight premature infants and mixed feeding vs human milk. Cohen et al. (2021) examines the correlation of donor human milk availability and its relation to the incidence rate of necrotizing enterocolitis. Kantorowska et al. (2016) examines the association between the availability of donor human milk (DHM) and changes in rates of NEC.

Researchers also examined the use of formula or fortified feed vs mother's own milk and donor milk in correlation to NEC rates. Corpeleijn et al. (2016) examines whether providing DM

instead of formula reduces the incidence of NEC, serious infection, and mortality. Feinberg et al. (2017) examines early administration of HM and probiotics role in reduction of the incidence of NEC in premature infants. Hair et al. (2016) examines the incidence of NEC and mortality in extremely premature infants pre and post initiation of an exclusive human milk-based diet (HUM) feed. Lapidaire et al. (2021) examines the chance of neonatal NEC in association to the increased use of MM and donor breast milk. Miller et al. (2018), examines the effect of human milk feeding on necrotizing enterocolitis morbidity in very low birth weight infants. Sato et al. (2019) examines the exclusive use of a human-milk diet and daily probiotic supplement in very low birth weight (VLBW) infants' and there correlation to the incidence of NEC.

The articles being reviewed explore the correlation between feed amounts and feed rates with the incidence of NEC. Baños-Peláez et al. (2021) examines the exclusive use of fortified human milk (FHM) and mother's own milk (MM) association with NEC outcomes. Canizo Vázquez et al. (2019) examines the incidence of NEC and late-onset sepsis (LOS) in very preterm infants after the introduction of donor milk (DM) when availability of MM is not enough. Chowing et al. (2016) examines whether the use of DHM in VLBW neonates affects the rate of NEC or impacted growth. Patel et al. (2017) examines the protective factors in human milk that may reduce NEC and the implementation of HUM in the neonatal intensive care unit (NICU). Roze et al. (2017) examines the relation between feeding strategies with the development of NEC and intestinal microbiota composition. Zhang et al. (2020) examines the relationship between HM and NEC.

Summary of Studies

Milk Banks and Donor Milk Availability

Promotion of the preservation of human milk and human milk donations guarantee the possibility of an improvement in the health of newborns. There was an observance of NEC risk reduction in premature infants receiving mother's own milk and donated breastmilk. The overall findings of the randomized control trials indicated a risk reduction of NEC using human milk compared to formula. The observational studies showed a risk reduction of NEC, and the protective role human milk has when it comes to the development of NEC (Altobelli et al., 2020). The promotion of human milk donations and preserving human milk guarantees an improvement in the health of premature newborns. In a study by Cohen et al. (2021) there was an increase of donor human milk availability/use in seven NICU units with a corresponding decrease in the incidence of NEC in very low birth weight infants. When data was pooled across all centers from 2009 to 2016 there was an overall reduction in NEC by approximately 40%. It was found that the incidence of NEC when DHM was not available was 5.1% compared to a significantly lower 2.9% when DHM was available. In a study by Kantorowska et al. (2016), there was an observed correlation between the increased availability of donor human milk with a decrease in the incidence of NEC in very low birth weight infants. Results showed a decrease in the combined rate of NEC in VLBW infants from 6.6% dropping to 4.3%. The availability of DHM continues to increase overtime and is associated with positive changes in decreasing NEC rates.

Formula or Fortified Feed vs Mother's Own Milk and Donor Milk

When donor human milk was introduced as the primary feeding practice when not enough of mother's own milk was available, NEC incidence was decreased in very preterm neonates born between 28 and 32 weeks (Cañizo Vázquez et al., 2019). Surgical NEC was also noted at a lower frequency in the group receiving donor human milk. In a study by Corpeleijn et

al. (2016), there was a slightly lower incidence of NEC in very low birth weight infants when donor milk was used instead of preterm formula when mother's own milk was not available during the first ten days of life. Further extension of the study and data collection were needed for sufficient results. In a study by Feinberg et al. (2017), the percentage of preterm infants who were able to receive human milk 48 hours after birth correlated with a significant reduction in NEC occurrence. Results showed a decline in NEC rate form 4.1% to 0.4% with a reduction of preterm formula feeding. In a study by Hair et al. (2016), there was an observance of a lower incidence of NEC in infants with an extremely low birth weight and gestational age <28 weeks who received an exclusive human milk-based diet. Incidence of NEC, mortality, and late-onset sepsis was significantly lower in the HUM group compared with the BOV group. In a study by Lapidaire et al. (2021), there was an observance of lower NEC rates in preterm infants with low birth weight when maternal breast milk and banked donor breast milk were used as the infants' sole diet. With a 10% increase in BBM and MBM intake, there was an association of approximately eight to 12% lower chance the neonate would develop NEC/infection and a 10% increase in the use of TF was associated with a 12% increase in NEC/infection chances. In a study by Miller et al. (2018), there was an observed significant decrease in the incidence of NEC in infants born before 28 weeks and/or had a birth weight less than 1,500 grams when human milk was used as the sole diet. The comparison of EHM vs EPTF showed there is a possible reduction in NEC with the use of EHM feedings. The comparison of any HM vs EPTF showed there is a clear effect of HM in reducing the incidence of NEC. When comparing higher vs lower doses of human milk, there was a clear reduction in the incidence of NEC with the use of a higher dose of HM. The comparison of pastured vs unpasteurized human milk has inconclusive results. This study also concluded that any amount of human milk is better than early preterm

formula. In a study by Sato, R., Malai, S., & Razmjouy, B. (2019), the use of donor human milk fortifier when mother's own milk was not available significantly lowered NEC rates in extremely low birth weight infants. Evidence shows support in the use of human milk-derived fortifier to reduce NEC in very low birth weight infants.

Feeding Amounts and Rates Correlation

Studies support human milk as the diet of choice in preterm infants. Studies also encourage the use of exclusive human milk feeding practices in the NICU setting to improve outcomes of the infant if they were to develop NEC. In a study by Baños-Peláez et al. (2021), there was an observance of less NEC in premature neonates born before 35 weeks when mother's own milk and fortified human milk feeding practices were utilized. The longitudinal analysis, generalized mixed and linear models, were fit to evaluate NEC associated with feeding strategies and showed that fortified human milk (FHM) and mother's own milk (MM) were significantly less likely associated with NEC. It also showed that neonates fasting on days seven and 14 had a higher overall incidence of NEC. In a study by Chowning et al. (2016), there was an observed lower rate of NEC in very low birth weight infants who received an exclusive human milk diet on more than 50% of the days spent in the NICU. In a study by Patel, A., & Kim, J. (2017), there was an observance of lowest risk of NEC in the preterm infant when mother's own milk, human milk formula, or donor human milk was used compared to preterm formula. The study also notes best practice emphasizes mother's own milk before donor human milk if available. In a study by Rozé et al. (2017), there was an observed increase in chance of the preterm infant developing NEC when a less favorable direct-breastfeeding policy and a slow rate of progression of enteral feeding were in place. Higher associations of NEC were seen in neonates receiving intermediate and slower rates of enteral feeding progression when compared

to the faster progression strategy and when intermediate direct-breastfeeding policies were in place. Therefore, support is in place regarding the use of direct-breastfeeding and a faster progression of enteral feedings to reduce the chances of preterm infants developing NEC. In a study by Zhang et al. (2020), findings demonstrated a reduction in incidence of NEC in premature infants when an exclusive human milk and partial human milk diet were used in comparison to the use of formula feed.

Discussion

All 15 studies included in this review showed the use of human milk and donor milk as more effective in preventing the development of necrotizing enterocolitis compared to formula feedings. Additional factors evaluated in a variety of the 15 studies included evaluation of the further impacts human milk and/or breast milk can have on the premature neonate. The results from these articles supported the use of HM and DHM in the reduction of late onset sepsis, infant mortality, retinopathy of prematurity, bronchopulmonary dysplasia, and increase in IQ level and growth of infants born prematurely.

Researchers should continue to gather data regarding the relationship between the use of human milk, donor milk, and formula and the incidence of necrotizing enterocolitis in the preterm neonate. Research and literature reviews regarding the effects of formula feed are important for nurses and neonatal patients. Having clinically significant feed practices in place could help with lowering the length of hospital stays, cost for families, and preventing avoidable morbidity and mortality. The results of this study give insight into the future of nursing care of neonatal necrotizing enterocolitis patients and offers a more reliable form of prevention. Part of a NICU nurse’s responsibility is to become familiar with varying forms of feeds to continually

expand their knowledge on relevant research in order to provide their patients with an individualized and effective plan of care.

Limitations and Gaps

Overall, this study presents substantial evidence regarding the relationship between the use of human milk, donor milk, and formula in the preterm neonate and the incidence of necrotizing enterocolitis. However, it is not without its gaps and limitations.

The United States, England, Mexico, Italy, Spain, France, Netherlands, and China are the only regions represented in this study. These locations drastically vary when it comes to medical advancements and access to the same resources for determining the presence of necrotizing enterocolitis in neonates. Since the sample locations differ, that should be taken into consideration in translating these findings outside the designated regions. There is a noticeable gap in the research since it excludes countries with small populations.

The number of research articles found within the CINAHL and PubMed databases regarding the topic of study became a main limitation to the review conducted. When conducting the research to gather studies for review, there were very limited studies that had addressed the use of exclusive human milk compared to exclusive formula use. Therefore, studies regarding the effectiveness of human milk in alternative aspects including donor milk and human fortifier formula were included in this study. These studies still had the main conceptual framework of determining the effectiveness of human milk in decreasing NEC incidence.

Conclusion

Necrotizing enterocolitis continues to be the leading cause of surgery in premature infants leading to prolonged hospital stays and increased interventions of care. Research has shown a positive correlation in reducing NEC rates through the use of breast/human milk and donor milk

banks. Hospitals should be advised to establish donor milk banks and implement human milk feeding guidelines within the neonatal intensive care unit. Although the use of breast/human milk and donor milk have been correlated with the reduction in incidence of NEC, research needs to be conducted to determine the pathophysiological cause for the most effective form of prevention to take place.

References

Altobelli, E., Matteo Angeletti, P., Verrotti, A., & Petrocelli, R. (2020). The Impact of Human Milk on Necrotizing Enterocolitis: A Systematic Review and Meta-Analysis. *Nutrients*, 12(5), 1322. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7284425/

Banos-Pelaez, M., Avila-Sosa, V., Alberto Fernandez-Carrocera, L., Gonzalez-Perez, G., Carrera-Muinos, S., Antonieta Rivera-Rueda, M., Cordero-Gonzalez, G., Romero, S., Coronado-Zarco, A., Laresgoiti-Servitje, E., & Irles, C. (2021). Estimating Neonatal Necrotizing Enterocolitis Based on Feeding Practices. *Children*, 8(4), 1 – 16. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8063799/

Canizo Vazquez, D., Salas Garcia, S., Izquierdo Renau, M., & Iglesias-Platas, I. (2019). Availability of Donor Milk for Very Preterm Infants Decreased the Risk of Necrotizing Enterocolitis without Adversely Impacting Growth or Rates of Breastfeeding. *Nutrients*, 11(8), 1895. https://www.mdpi.com/2072-6643/11/8/1895/htm

Chowning, R., Radmacher, P., Lewis, S., Serke, L., Pettit, N., & Adamkin, D. (2016). A Retrospective Analysis of The Effect of Human Milk On Prevention of Necrotizing Enterocolitis and Postnatal Growth. *Journal of Perinatology*, 36, 221 – 224. https://www.nature.com/articles/jp2015179

Cleaveland Clinic. (2021). Necrotizing Enterocolitis. Retrieved fromhttps://my.clevelandclinic.org/health/diseases/10026-necrotizing-enterocolitis

Cohen, M., Steffen, E., Axelrod, R., Patel, S., Toczylowski, K., Perdon, C., Brown, D., Kaliappan, S., & Myers, M. (2021). Availability of Donor Human Milk Decreases the Incidence of Necrotizing Enterocolitis in VLBW Infants. *Advances in Neonatal Care*, 21(5), 341 – 348.

https://journals.lww.com/advancesinneonatalcare/Fulltext/2021/10000/Availability_of_Donor_Human_Milk_Decreases_the.4.aspx

Corpeleijn, W., Waard, M., & Christmann, V., et al. (2016). Effect of Donor Milk on Severe Infections and Mortality in Very Low-Birth-Weight Infants. *JAMA Pediatrics,* 170(7), 654 – 661. https://jamanetwork.com/journals/jamapediatrics/fullarticle/2518872

Feinberg, M., Miller, L., Engers, B., Bigelow, K., Lewis, A., Brinker, S., Kurland, F., Potthoff, E., Wallin, M., Pantoja, A., & Britton, J. (2017). Reduced Necrotizing Enterocolitis After an Initiative to Promote Breastfeeding and Early Human Milk Administration. *Pediatric Quality & Safety,* 2(2), 14. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6132913/

Hair, A., Peluso, A., Hawthorne, K., Perez, J., Smith, D., Khan, J., O'Donnell, A., Powers, R., Lee, M., & Abrams, S. (2016). Beyond Necrotizing Enterocolitis Prevention: Improving Outcomes with an Exclusive Human Milk-Based Diet. *Breastfeeding Medicine,* 11(2). https://www.liebertpub.com/doi/10.1089/bfm.2015.0134

Juhl, S. (2017). Necrotizing Enterocolitis – Classification and Two Initial Steps Towards Prevention. *Danish Medical Journal,* 64(6). https://ugeskriftet.dk/files/scientific_article_files/2018-08/b5362.pdf

Kantorowska, A., Wei, J., Cohen, R., Lawrence, R., Gould, J., & Lee, H. (2016). Impact of Donor Milk Availability on Breast Milk Use and Necrotizing Enterocolitis Rates. *Pediatrics,* 137(3), 39 – 39. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4771129/

Lapidaire, W., Lucas, A., Clayden, J., Clark, C., & Fewtrell, M. (2021). Human Milk Feeding and Cognitive Outcome In Preterm Infants: The Role of Infection and NEC Reduction. *Pediatric Research.* https://www.nature.com/articles/s41390-021-01367-z

Maffei, D., & Schanler, R. (2017). Human Milk is The Feeding Strategy to Prevent Necrotizing Enterocolitis. *Seminars in Perinatology*, 41(1), 36 – 40. https://www.sciencedirect.com/science/article/pii/S014600051630088X?via%3Dihub

Miller, J., Tonkin, E., Damarell, R., McPhee, A., Suganuma, M., Suganuma, H., Middleton, P., Makrides, M., & Collins, C. (2018). A Systematic Review and Meta-Analysis of Human Milk Feeding and Morbidity in Very Low Birth Weight Infants. *Nutrients*, 10(6), 707. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6024377/

Patel, A., & Kim, J. (2017). Human Milk and Necrotizing Enterocolitis. *Pediatric Surgery*, 27(1), 34 – 38. https://www.sciencedirect.com/science/article/pii/S1055858617301403

Roze, J., Ancel, P., Lepage, P., Martin-Marchand, L., Nabhani, Z., Delannoy, J., Picaud, J., Lapillonne, A., Aires, J., Durox, M., Darmaun, D., Neu, J., & Butel, M. (2017). Nutritional Strategies and Gut Microbiota Composition as Risk Factors for Necrotizing Enterocolitis in Very Preterm Infants. *The American Journal of Clinical Nutrition*, 106(3), 821 – 830. https://academic.oup.com/ajcn/article/106/3/821/4822358

Sanchez, J., & Kadrofske, M. (2019). Necrotizing Enterocolitis. *Neurogastroenterology & Motility*, 31(3). https://onlinelibrary.wiley.com/doi/10.1111/nmo.13569

Sato, R., Malai, S., & Razmjouy, B. (2019). Necrotizing Enterocolitis Reduction Using an Exclusive Human-Milk Diet and Probiotic Supplementation in Infants With 1000 – 1499 Gram Birth Weight. *Nutrition in Clinical Practice*, 35(2), 331 – 334. https://aspenjournals.onlinelibrary.wiley.com/doi/full/10.1002/ncp.10394

Thakkar, H., & Lakhoo, K. (2018). Necrotizing Enterocolitis. *Paediatrics and Child Health*, 28(5), 227 – 230. https://www.sciencedirect.com/science/article/pii/S175172221830043X

Zhang, B., Xiu, W., Dai, Y., & Yang, C. (2020). Protective Effects of Different Doses of Human Milk on Neonatal Necrotizing Enterocolitis. *Medicine*, 99(37), 222166. https://journals.lww.com/md-journal/Fulltext/2020/09110/Protective_effects_of_different_doses_of_human.74.aspx

Appendix A

Final Evaluation Table								
First Author (Year)	Conceptual Framework	Design/Method	Sample & Setting	Major Variables Studied (and their Definitions)	Measurement	Data Analysis	Findings	Appraisal: Worth to Practice
Altobelli, E., Matteo Angeletti, P., Verrotti, A., & Petrocelli, R. (2020)	None	Meta-analysis	32 papers: 6 randomized control trials 26 observational studies Italy	Relationship between feeding and NEC Milk banks/Human milk Formula Preterm infants Bell score >2	Distribution of milk banks in the world Development of NEC Incidence of NEC	Meta-regression analysis using random effect models	RCTs meta-analysis: Relative risk (RR) = 0.62 (0.42–0.93). 3 OS that evaluated human milk versus mixed feeding showing that human milk has a protective role on the development of NEC: RR = 0.74 (0.63–0.91)	RCTs meta-analysis indicates a risk reduction of NEC using human milk respect to formula. The possibility of preserving human milk and promoting donations guarantees an improvement in the health of newborns.

Banos-Pelaez, M., Avila-Sosa, V., Alberto Fernandez-Carrocera, L., Gonzalez-Perez, G., Carrera-Muinos, S., Antonieta Rivera-Rueda, M., Cordero-Gonzalez, G., Romero, S., Coronado-Zarco, A., Laresgoiti-Servitje, E., & Irles, C. (2021)	None	Retrospective case-control study	192 Infants Mexico City	Neonatal necrotizing enterocolitis (NEC) Mother's own milk (MM) Fortified human milk (FHM)	Rate of NEC occurrence in preterm infants	Longitudinal analysis Generalized linear and mixed models	Neonates that were fasting on days 7 and 14 developed NEC ($p < 0.05$) Feeding strategies of exclusive MM and FHM across time were significantly less likely associated with NEC ($p<0.001$)	This study concludes feeding practices in the NICU should promote exclusive MM across the two-week critical period as a potential guideline to improve NEC outcome.

Canizo Vazquez, D., Salas Garcia, S., Izquierdo Renau, M., & Iglesias-Platas, I. (2019)	None	Single center, observational and retrospective cohort study	227 very preterm infants Barcelona	Own mother's milk (OMM) Donor milk (DM) Necrotizing enterocolitis (NEC)	Incidence of NEC in preterm infants born between 28 – 34 weeks Bell's stage 2 or higher	Chi-square and student t tests as appropriate	Incidence of NEC decreased in group 2 (9.1% vs. 3.4%, p = 0.055) Suffering NEC was four times more likely in group 1	Findings support the protective role of DM against NEC, particularly in non-extreme VPI. Did not find significant differences in the incidence of other complications of prematurity or in rates of growth or breastfeeding.

Chowning, R., Radmacher, P., Lewis, S., Serke, L., Pettit, N., & Adamkin, D. (2016)	None	Retrospective chart review	550 VLBW infants United States	Incidence of NEC Growth parameters Human milk	NEC rates	Descriptive statistics	Neonates who received HM on >50% of hospital days had equivalent growth outcomes but lower rates of NEC (NEC 3.4 vs 13.5%, P<0.001) and mortality (1.0 vs 4.2%, P=0.017).	HM should always be the diet of choice in preterm infants. HM is associated with lower rates of NEC.

Cohen, M., Steffen, E., Axelrod, R., Patel, S., Toczylowski, K., Perdon, C., Brown, D., Kaliappan, S., & Myers, M. (2021)	None	Observational Study Quality Improvement	9400 VLBW infants USA: New Jersey	NEC Donor human milk (DHM) Very Low Birth Weight (VLBW) infants Primary outcome measure was incidence of NEC in VLBW infants	Incidence of NEC Promotion of human milk feeding	Linear regression analyses Significant tests of differences $\chi 2$ analyses	The incidence of NEC when DHM was not available was 5.1% (367/7182) whereas the incidence when DHM was available (64/2218) was significantly lower (2.9%; P < .0001).	All centers, except for one (center H) that implemented DHM, showed a decrease in the percentage of NEC after implementation.

Corpeleijn, W., Waard, M., & Christmann, V., et al. (2016)	None	Multicenter double blinded RCT	373 infants Netherlands	Outcome of NEC Serious Infection Mortality Unfortified DHM vs formula	Occurrence of serious infection, NEC, or mortality in first 60 days of life	Logistic regression analysis	DHM was not associated with a decrease in the composite outcome of NEC, serious infection and morbidity (P 5 .37), or NEC 9.3% (DHM) vs 8.9% (formula) (P 5 .99). Intake of MOM was high at 89.1% (DHM) vs 84.5% (formula)	Large amounts of own mother's milk (>50% of total enteral intake) tended to be associated with a reduced risk of the cumulative incidence of serious infections, NEC, or mortality The results of this trial stress the importance of providing premature neonates with raw milk from their own mother.

Feinberg, M., Miller, L., Engers, B., Bigelow, K., Lewis, A., Brinker, S., Kurland, F., Potthoff, E., Wallin, M., Pantoja, A., & Britton, J. (2017)	None	Retrospective review	2557 cases United States	Incidence of NEC Frequency of early feedings Human Milk (HM) Donor human milk (DHM)	Percentage of infants with NEC Defined based on Bell criteria	Chi square test t-test	The NEC rate declined from 4.1% to 0.4%. NEC rates declined from 8.3% to 1.0% for VLBW infants from 2013 – 2015 compared to 2006 – 2009	Reduced NEC in population of preterm infants after successful efforts to promote breastfeeding and early use of HM. Probiotics and changes in milk preparation, storage, and fortification processes may have sustained the low incidence.

Hair, A., Peluso, A., Hawthorne, K., Perez, J., Smith, D., Khan, J., O'Donnell, A., Powers, R., Lee, M., & Abrams, S. (2016)	None	Retrospective Cohort Study	1,587 infants 768 infants BOV 819 infants HUM USA: Texas, Illinois, Florida, and California	NEC Late onset sepsis Infant mortality Human milk-based diet	Primary outcomes: NEC and mortality Secondary: late-onset sepsis, retinopathy of prematurity, broncho-pulmonary dysplasia	Chi square test Wilcoxon rank sum test	The BOV group mortality rate was 17.2% (132/768), and the HUM group rate was 13.6% (111/819; $p = 0.04$) There was a significant reduction in NEC cases in the HUM group There was a significant reduction in medical and surgical NEC ($p < 0.00005$ and $p < 0.0002$)	It was found that the use of an exclusive HUM diet in extremely premature infants (<1,250 g BW) decreased the incidence of both medical and surgical NEC Shows an association with a reduction in mortality and late-onset infections.

Kantorowska, A., Wei, J., Cohen, R., Lawrence, R., Gould, J., & Lee, H. (2016)	None	Population-based cohort study	27 – 55 hospitals Focused analysis on 22 hospitals California	NEC Availability of donor human milk in the NICU Birth weight	Percentage of VLBW infants who had NEC before and after DHM was available	Descriptive analysis Paired t-test	There was a 10% increase in breast milk feeding at NICU discharge and a concomitant 2.6% decrease in NEC rates	The availability of donor human milk has increased over time and has been associated with positive changes including increased breast milk feeding at NICU discharge and decrease in NEC rates.
Lapidaire, W., Lucas, A., Clayden, J., Clark, C., & Fewtrell, M. (2021)	None	Randomized control design	926 infants with birth weights <1850 grams England	NEC incidence IQ scores Preterm formula (PF) Term formula (TF) Banked donor breast milk (BBM)	IQ level NEC/neonatal infection rates	Logistic regression Analysis of covariance models Mediation analysis	Each 10% increase in MBM and BBM intake was associated with approximately an 8% and 12% lower chance of neonatal infection/NEC, respectively. A 10% increase in TF was associated with a 12%	Increased human milk intake, whether BBM or MBM, was associated with reduced risk of infection/ NEC. Systematic reviews suggest that the use of BBM has

				Maternal breast milk (MBM)			increase in the chance of infection/NEC.	a protective effect against NEC in preterm infants.
Miller, J., Tonkin, E., Damarell, R., McPhee, A., Suganuma, M., Suganuma, H., Middleton, P., Makrides, M., & Collins, C. (2018)	None	Systematic Review Meta-analysis	6 RTs 1472 infants 43 observational studies Australia	NEC Human milk (HM) Donor human milk (DHM) Preterm formula (PTF) Mother's own milk (MOM) Very low birth weight (VLBW)	Incidence of NEC Late onset sepsis Morbidity outcomes Dose amounts	Meta-analysis Observational studies	Exclusive HM vs Exclusive PTF: reduction in any NEC with EHM (ARR, 4.3%, from 2.5 to 5 fewer cases/100). Any HM vs Exclusive PTF: (APR of 3.6%, from 1.8 to 4.8 fewer cases/100). Higher vs Lower Dose HM: ARR ranging from 4.3% (0.2 more to 6.8 fewer cases/100 for RTs to 3.8% (2.6 to 4.6 fewer cases/100)	The observational studies show there is a possible reduction in any NEC with EHM compared with EPTF. There is a clear effect of any HM in reducing NEC when any human milk was compared to exclusive preterm formula. There is a clear reduction in the incidence of any NEC with

							for observational studies.	higher dose HM.
Patel, A., & Kim, J. (2017)	None	Multicenter cohort study Double-blinded randomized controlled trial	200 VLBW Infants 363 VLBW infants USA: Chicago, California	Donor Milk Human Milk NEC Prematurity	NEC rates	Meta-analyses	Double-blind: significantly fewer infants in the DHM group developed NEC (1.7%) compared to the formula group (6.6%, p = .02) This is supported by a Cochrane review of 1070 infants demonstrating that formula feeding increased the risk of NEC significantly (risk ratio 2.77,	This study strongly suggested that an all-human diet may be beneficial and that exposure to intact bovine protein in fortifier and/or formula may be harmful to preterm infants.

							95% CI: 1.40–5.46)	
Roze, J., Ancel, P., Lepage, P., Martin-Marchand, L., Nabhani, Z., Delannoy, J., Picaud, J., Lapillonne, A., Aires, J., Durox, M., Darmaun, D., Neu, J., & Butel, M. (2017)	None	Prospective nationwide population-based cohort study	3161 preterm infants France	Neonatal necrotizing enterocolitis (NEC) Feeding strategies Intestinal microbial composition	Characteristics associated with NEC: progression of enteral feeding, microbiota analysis	General linear mixed models	Slower and intermediate rates of progression of enteral feeding strategies were associated with a higher risk of NEC (95% CI: p = 0.01) and (95% CI: p = 0.02)	A slow rate of progression of enteral feeding and a less favorable direct-breastfeeding policy are associated with an increased risk of developing NEC
Sato, R., Malai, S., & Razmjouy, B. (2019)	None	Retrospective single-center chart review	140 preintervention infants 265 postintervention infants USA: California, Chicago	NEC Human Milk	NEC rates Surgical NEC rates Growth of infants	Student t-test	Comparing 140 preintervention infants with 265 postintervention infants, NEC was significantly lower in the postintervention group: 5.2% vs 1.1% (P = 0.046)	Quality-improvement initiatives utilizing an exclusive human-milk diet and daily probiotic supplementation were associated with a decreased incidence

								of NEC in infants.
Zhang, B., Xiu, W., Dai, Y., & Yang, C. (2020)	None	Meta-analysis	12 RCTs 2677 infants China	Exclusive human milk Partial human milk Mainly human milk Exclusive formula Mainly formula Any formula	Incidence of NEC	Subgroup Analysis Cochrane Collaboration Review Manager PRISMA	The incidence of NEC in the infants fed by exclusive human milk was significantly lower than that of partial human milk [risk ratio (RR) = 0.54, 95% confidence interval (95% CI): 0.36–0.79, *P* < .05]. Incidence of NEC in the infants fed by exclusive human milk was significantly lower than that of any formula (RR = 0.49, 95% CI: 0.34–0.71, *P* < .05).	The incidence of NEC in the infants fed mainly by human milk was significantly lower than that of mainly fed by formula. Data indicated that the incidence of NEC showed significant decline in the premature infants fed mainly by human milk (*P* < .05)

Melnyk, B. M., & Fineout-Overholt, E. (Eds.). (2011). *Evidence-based practice in nursing & healthcare: A guide to best practice* (2nd ed.). Lippincott Williams & Wilkins.