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The Role of Human Milk in Decreasing Necrotizing Enterocolitis Through Modulation of the Infant Gut Microbiome: A Scoping Review

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Abstract

Background: Necrotizing enterocolitis is associated with a high incidence of morbidity and mortality in premature infants. Human milk minimizes necrotizing enterocolitis risk, although the mechanism of protection is not thoroughly understood. Increasingly, dysbiosis of the infant gut microbiome, which is affected by infant diet, is hypothesized to play a role in necrotizing enterocolitis pathophysiology.

Research aim: The aim of this scoping review was to summarize the state of the science regarding the hypothesis that the gut microbiome composition is a mediator of the relationship between human milk and decreased incidence of necrotizing enterocolitis within a sample of human infants.

Methods: Electronic databases and reference lists were searched for peer-reviewed primary research articles addressing the link between human milk, gut microbiome composition, and subsequent incidence of necrotizing enterocolitis among human infants.

Results: A total of four studies met criteria for inclusion in this review. Of these, evidence supporting the link between human milk, gut microbiome composition, and necrotizing enterocolitis was found in two (50%) studies.

Conclusion: Some evidence linking all three variables is provided in this review. Given the small number of available studies, and the limitations of those studies, more research is urgently needed to thoroughly understand the protection against necrotizing enterocolitis gained through the provision of human milk.

Keywords

breastfeeding, human milk, microbiota, necrotizing enterocolitis, nutrition, premature infant diseases, prematurity

Background

Necrotizing enterocolitis is a devastating intestinal disease with an unknown etiology that primarily affects premature infants and is associated with an increased risk of morbidity and mortality (Pammi et al., 2017). Though prevalence varies geographically, it is estimated that at least 7% of infants born < 1500 g will be diagnosed with necrotizing enterocolitis (Pammi et al., 2017). Loss of bacterial diversity and increased abundance of pathogenic bacteria, referred to as intestinal dysbiosis, has been associated with necrotizing enterocolitis in premature infants (Neu & Pammi, 2017; Pammi et al., 2017).

An exclusive human milk diet serves as the most effective method for the prevention of necrotizing enterocolitis (Maffei & Schanler, 2017; Patel & Kim, 2018). Evidence that human milk and direct breastfeeding modulate the development of the infant gut microbiome is provided by a growing body of literature (Ho et al., 2018). Therefore,

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researchers have hypothesized that gut microbiome composition mediates the relationship between human milk and the reduced risk of necrotizing enterocolitis (Gregory et al., 2016).

Understanding the mechanisms of how human milk protects against the development of necrotizing enterocolitis (NEC) can expand understanding of the etiology of the disease and lead to novel methods of prevention, diagnosis, and management. However, there is limited human-subjects research linking infant diet with intestinal dysbiosis observed preceding or during NEC. The aim of this scoping review was to summarize the state of the science regarding the hypothesis that gut microbiome composition is a mediator of the relationship between human milk and decreased incidence of NEC within human infants.

Key Messages

- The ratio of commensal bacteria to pathogenic bacteria in the infant gut microbiome appears to be associated with the proportion of human milk received.
- Changes in gut microbiome composition are associated with necrotizing enterocolitis in premature infants.
- There is limited evidence supporting the hypothesis that human milk minimizes the risk of necrotizing enterocolitis through modulation of the infant gut microbiome, warranting continued investigation.

Methods

Design

A scoping review was conducted to examine our stated hypothesis. The aim of a scoping review is to map all available evidence on a selected topic and identify gaps and limitations within that literature (Humphrey-Murto et al., 2017; Tricco et al., 2018). Since there are few methodological restrictions for study inclusion, a scoping review is an appropriate methodology to apply to emerging topics of scientific interest, namely the mechanistic processes by which human milk confers protection against NEC as discussed in this review (Pham et al., 2014).

Sample

Any primary research articles that investigated the focus of this review were included. Publications that did not include NEC incidence as an outcome measure or that did not analyze the association between infant gut microbiome composition and infant diet were excluded. There were no restrictions placed on the gestational age, birth weight, or medical diagnoses of participants when evaluating studies for inclusion. Literature reviews, animal studies, medication trials, protocols, workshop summaries, case studies, commentaries, abstract-only publications, studies unrelated to NEC or human milk, and studies that were not published in English also were excluded. After removing duplicates, the initial search yielded a total of 131 articles to be screened for inclusion (Figure 1). Four studies ultimately met all inclusion criteria and were included in this review.

Data Collection

Our study search and initial screening process was performed by the first author and replicated by a second author (VG). Both authors searched six electronic databases within a 3-month period from October 1, 2019 to January 1, 2020: PubMed, MEDLINE, GLOBAL HEALTH, EMBASE, CINAHL, and EBSCO Academic Premier. MeSH search terms were used where possible with Boolean phrases including: "human milk OR breastfeeding" AND "microbiome OR bacterial diversity" AND "necrotizing enterocolitis OR NEC." No limits were placed on date of publication. Both authors screened article lists by title and abstract for relevance and basic inclusion criteria (e.g., article type, human study). After the initial screening, the first author then read the full texts of the remaining publications to determine final eligibility for inclusion. The reference lists of included articles were also reviewed by the first author and VG for potential articles meeting inclusion criteria.

Data Analysis

Data from chosen articles were extracted and summarized in a table created by the first author and were shared with and reviewed by the co-authors. The aims and results of the reviewed studies were summarized according to how participants were grouped in each respective study (i.e., diet-type cohorts or necrotizing enterocolitis-case cohorts). One author (JAD) abstracted the following data from each article to facilitate comparisons between studies and to evaluate methodologic rigor: (1) operationalization of human milk consumption among participants (i.e., use MOM vs. pasteurized donor human milk; classification of diet according to volume as a categorical or continuous variable); (2) consideration and measurement of potentially influential bioactive components in human milk samples; (3) methods used to diagnose NEC (i.e., Modified Bell's Staging Criteria vs. biomarkers); (4) methods used for microbiome analysis (i.e., sample type; timing and frequency of sample collection; ribonucleic acid (RNA) sequencing vs. metabolomics-based approaches); (5) characteristics of the participants in the study sample (i.e., gestational age; exclusion criteria); and (6) study design and sample size (i.e., prospective vs. retrospective/post-hoc). These data were summarized in tabular format and evaluated collaboratively by co-authors.

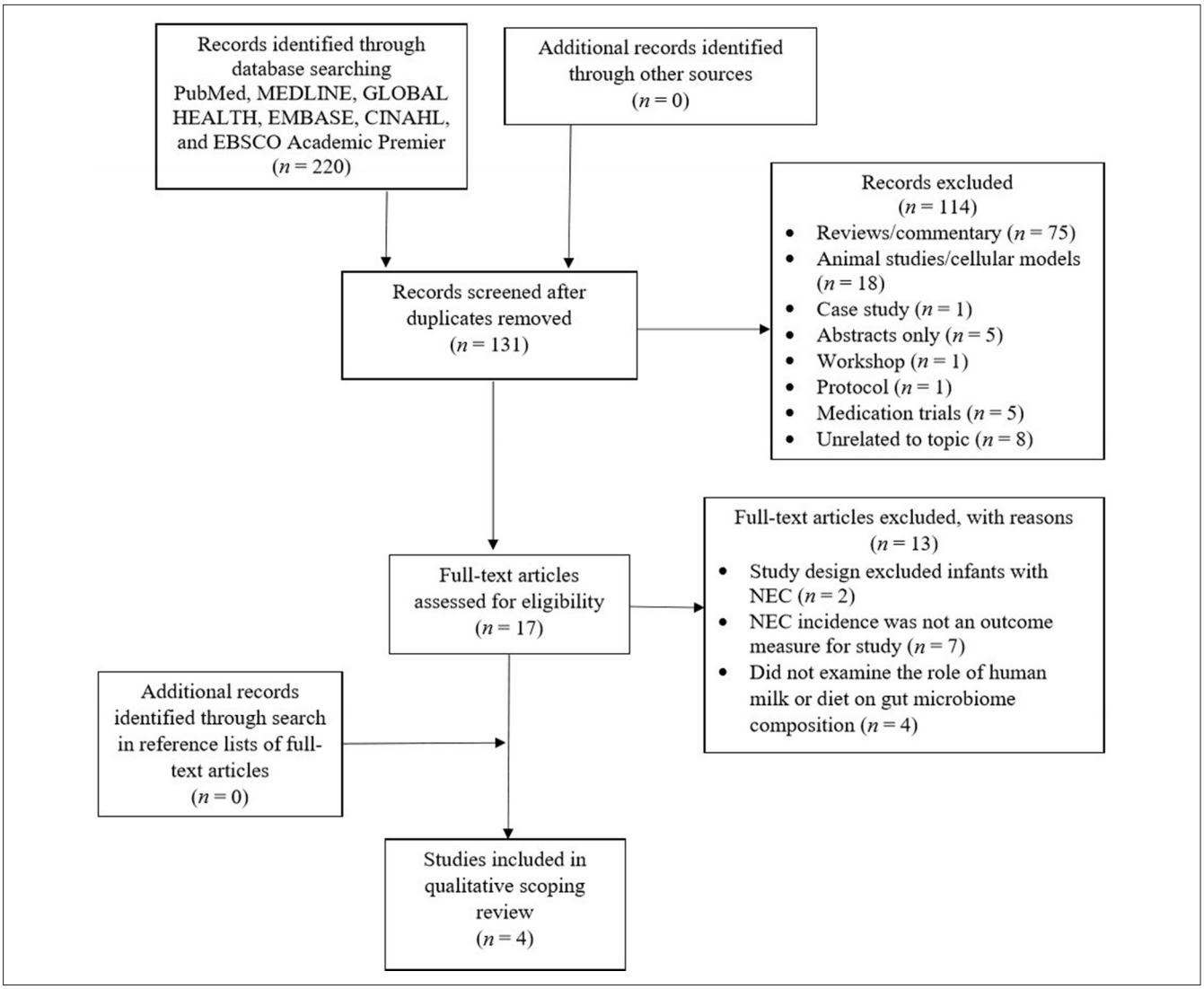

Figure 1. PRISMA Flow Diagram of Scoping Review Search Strategy.

The included articles were critically appraised with the consideration of current evidence regarding: (1) Human milk use for vulnerable infant populations; (2) variation in the bioactive composition of human milk/mother's own milk; (3) NEC in human infants; and (4) evaluation of infant gut microbiome composition. Specifically, operationalization of human milk was evaluated according to the evidence that *exclusive* human milk diets yield the most benefit in the prevention of NEC and that the variation of human milk/mother's own milk (MOM) composition is associated with maternal and environmental factors (i.e., genetics; feeding mode; pasteurization) and could predispose an infant to NEC. The critical evaluation of the methods used for diagnosis of NEC, as well as evaluation of sample demographics, study design, and sample size, was performed in accordance with the current methodological standards described in the literature, which encompasses research investigating NEC incidence, diagnosis, and treatment utilizing samples of both premature and full-term infants. Methods for gut microbiome analysis were evaluated according to current omics-based approaches presented in neonatal and infant gut microbiome literature.

Results

Characteristics of the Sample

The sample demographics, study design, and aims of the reviewed studies are summarized in Table 1. The researchers of three (75%) studies explicitly excluded infants diagnosed with structural defects associated with increased risk of NEC (Ford et al., 2019; Gopalakrishna et al., 2019; Heida et al., 2016). One (25%) of the studies included infants who received pasteurized donor human milk in addition to raw

Table 1. Designs and Settings of the Reviewed Studies (*N* = 4).

1st Author (year) Country	Sample (*N*)	Design	Aims
Ford et al. (2019) United States	VLBW infants (117) MOM cohort *n* = 74 > 50% MOM feeds PDHM cohort *n* = 43 > 50% PDHM feeds	Prospective longitudinal two-group comparison	Compare groups: 1. Microbiome composition and development 2. Cases of ≥ Stage IIA NEC
Gopalakrishna et al. (2019) United States	Infants < 31 weeks GA Post-diagnosis sample (69) ≥ stage IIA NEC *n* = 30 no-NEC *n* = 39 Longitudinal sample (MOM-fed only) (23) ≥ Stage IIA NEC *n* = 10 no-NEC *n* = 13	Two-group comparison Retrospective/prospective	Describe association between diet and presence of IgA+ bacteria Compare NEC/no-NEC groups: 1. Ratio of IgA+ to IgA− bacteria 2. Diversity of IgA+ bacteria 3. Shifts in bacterial taxa 4. IgA+ bacterial taxa
1st Author (year) Country	Population (*N*)	Design	Aims
Heida et al. (2016) Netherlands	VLBW premature infants < 32 weeks GA and < 1200 g (32) ≥ Stage IIA NEC *n* = 10 no-NEC *n* = 22	Prospective longitudinal two-group comparison	Compare NEC/no-NEC groups: 1. Microbiome composition 2. Proportion of diet containing MOM
Parm et al. (2015) Estonia	Premature infants < 32 weeks GA (159) TPN *n* = 41 no enteral feeds Formula *n* = 70 no MOM feeds MOM *n* = 48 ≥11% MOM feeds	Post-hoc analysis three-group comparison	Compare diet groups: 1. Cases of ≥ Stage IIA NEC in first 7 days of life 2. Microbiome colonization with pathogenic bacterial taxa

Abbreviations: GA = gestational age; IgA = Immunoglobulin A; IgA+ = Immunoglobulin A-bound; IgA- = Immunoglobulin A-unbound; MOM = mother's own milk; NEC = necrotizing enterocolitis; PDHM , pasteurized donor human milk; TPN = total parenteral nutrition; VLBW = very low birth weight (< 1500 gm).

MOM (Ford et al., 2019); the infants in all other studies were fed MOM or formula.

Microbiome Analysis

The methods used for microbiome analysis and the results of the reviewed studies are summarized in Table 2. NEC was classified according to the Modified Bell's Staging Criteria in all studies. Stages are assigned based on severity of signs and symptoms, with cases meeting criteria Stage IA being considered as suspected presentation of NEC and cases meeting criteria for Stage IIIB being considered as severe presentation of disease (Gephart et al., 2018). The researchers of each study considered diagnosis of NEC to be those cases that met criteria for Stage II A or greater.

The researchers of all studies utilized 16s ribosomal RNA (rRNA) sequencing for microbial analysis, which is a standardized and reliable method of microbiome measurement (Aguiar-Pulido et al., 2016). The study conducted by Gopalakrishna et al. (2019) differed from the other reviewed studies because the researchers intended to evaluate the significance of IgA antibodies on gut microbiome composition and pathophysiology of necrotizing enterocolitis. IgA antibodies, which protect against infection by binding to bacteria, cannot be produced by the infant until 4 weeks age and are derived from MOM until that time. Gopalakrishna et al. (2019) reported that IgA was derived from MOM through flow cytometry analysis of serial stool samples collected from one formula-fed infant who was less than 4 weeks old, in which the analysis revealed that IgA was absent.

Relationships Between Infant Diet, Gut Microbiome and NEC

Individual associations between (1) infant diet and gut microbiome composition; (2) infant gut microbiome composition and necrotizing enterocolitis; and/or (3) infant diet and NEC were demonstrated. Evidence supporting the link between human milk, gut microbiome composition, and NEC was found in two (50%) studies (Gopalakrishna et al., 2019; Heida et al., 2016).

Table 2. Methods and Results of the Reviewed Studies (*N* = 4).

1st Author (year) Country	Aims	Methods	Results	Reliability & Validity
Ford et al. (2019) United States	Compare MOM and PDHM diet groups: 1. Microbiome composition 2. Cases of ≥ Stage IIA NEC	• Fecal samples collected, analyzed weekly for first 6 WOL	• MOM cohort: more diverse microbiome, higher abundance of phylum Actinobacteria, specifically genera *Bifidobacteria*, *Bacteroides*, and *Enterococcus* • PDHM cohort: higher phylum Firmicutes (large abundance of genus *Staphylococcus*) • No difference in NEC cases between groups	• Assigned to cohorts based on MOM use with 50% threshold. *M* and *SD* for MOM used to discern difference in diet between cohorts. • Initial *N* = 125; eight participants removed due to complications preventing enteral feeding. Final *N* = 117, *n* = 90 participants with adequate stool for analysis. Attrition and failure to collect adequate samples from all participants could have affected results. • Fecal samples served as adequate measure for microbiome analysis. • Weekly analysis allowed capture of microbiome changes over time. • Difference in group size (MOM cohort *n* = 74 vs. PDHM cohort *n* = 43) could increase error in results.
Gopalakrishna et al. (2019) United States	Describe association between diet and presence of IgA+ bacteria. Compare NEC/no-NEC groups: 1. Ratio of IgA+ to IgA− bacteria 2. Diversity of IgA+ bacteria 3. Shifts in bacterial taxa 4. IgA+ bacterial taxa	• Collected daily fecal samples for first 40 DOL • Analyzed fecal sample collected at time of NEC diagnosis	• IgA+ bacteria higher in MOM-fed participants in post-diagnosis cohort • Increased ratio of IgA-unbound to IgA-bound bacteria associated with NEC • Low diversity of IgA-bound bacteria associated with NEC • Increased enrichment of Enterobacteriaceae in NEC • Low IgA binding to Enterobacteriaceae associated with NEC	• Post-diagnosis sample, diet descriptions were MOM, formula, or combination. Proportion of diet consisting of MOM in combination-fed participants not disclosed and could have confounded results. • Use of fecal samples served as an adequate measure for microbiome analysis. • Using cohort of MOM-fed participants allowed investigation of significance of MOM without confounding from formula use.
Heida et al. (2016) Netherlands	Compare NEC/no-NEC groups: 1. Microbiome composition 2. MOM proportion of diet	• Fecal samples collected twice weekly for first 5 WOL • Analyzed a meconium sample and two post-meconium samples collected the week immediately before NEC dx	• NEC group greater presence and abundance of *Clostridium perfringes* at all time points ($p < 0.001$) • Higher proportion of MOM in diet associated with greater presence of lactate-producing bacilli ($p = 0.004$) and decreased risk of NEC ($p = 0.04$) • Bacterial diversity not associated with NEC or proportion of MOM received	• Proportions of diet containing MOM allowed researchers to examine significance of diet on gut microbiome composition and NEC. • Use of fecal samples served as an adequate measure for microbiome analysis. • Analysis of meconium samples and two other distinct time points allowed researchers to capture baseline characteristics of the microbiome and changes associated with diet and NEC.

(Continued)

Table 2. Continued

1st Author (year) Country	Aims	Methods	Results	Reliability & Validity
Parm et al. (2015) Estonia	Compare diet groups: 1. Cases of ≥ Stage IIA NEC in first 7 DOL 2. Microbiome colonization with pathogenic bacterial taxa	• Rectal swabs collected on admission and twice weekly until DOL 16 • Analyzed rectal samples in batches	• Colonization by *Staphylococcus haemolyticus* lower in MOM-fed cohort compared to formula and TPN cohorts • MOM cohort had higher colonization with MRSA • No difference in NEC incidence between groups	• While sample size was large, post-hoc analysis design may have increased likelihood of error related to confounding and bias. • MOM cohort included participants who received large proportions of formula, likely preventing detection of any significant effect. • Use of rectal swabs may serve as a limitation for gut microbiome analysis.

Abbreviations: DOL = days of life; IgA = Immunoglobulin A; IgA+ = Immunoglobulin A-bound; IgA- = Immunoglobulin A-unbound; MOM = mother's own milk; MRSA = methicillin resistant *staphylococcus aureus*; NEC = necrotizing enterocolitis; PDHM = pasteurized donor human milk; TPN = total parenteral nutrition; WOL = weeks of life.

With regard to infant diet and gut microbiome composition, researchers of three (75%) reviewed studies provided evidence that gut microbiome composition differed according to proportion of infant diet consisting of human milk, source of human milk (i.e., MOM or pasteurized donor human milk), and/or bioactive composition of human milk (Ford et al., 2019; Gopalakrishna et al., 2019; Heida et al., 2016). Conversely, Parm et al. (2015) found no difference in gut colonization with pathogenic bacteria between their MOM-fed cohort and their formula-fed cohort.

Researchers of two (50%) studies described an increased presence and abundance of pathogenic gut bacteria, compared to commensal gut bacteria, among participants who developed NEC (Gopalakrishna et al., 2019; Heida et al., 2016). The researchers of these two studies also included evidence of the link between infant diet and NEC, in that a greater proportion of infant diet composed of MOM was associated with decreased incidence of NEC (Heida et al., 2016) and that formula feeding was more prevalent among participants who developed NEC in the post-diagnosis sample (Gopalakrishna et al., 2019). Conversely, researchers of two studies found no differences in incidence of NEC between cohorts according to diet type (Ford et al., 2019; Parm et al., 2015).

Discussion

NEC remains a significant cause of morbidity and mortality for premature and low birth weight infants around the world (Gephart et al., 2018). Separately, human milk has been linked with a decreased risk of NEC and the development of a commensal infant gut microbiome (Gregory et al., 2016; Pammi et al., 2017). There are many infant and environmental factors that contribute to the development of the infant gut microbiome and to the intestinal dysbiosis observed during necrotizing enterocolitis. Therefore, the nuances in the triadic relationship between human milk, gut microbiome, and NEC cannot be adequately captured by researchers who do not investigate all three variables. To account for confounding related to this variability in sample demographics and environmental exposures, researchers must simultaneously examine the influence of human milk on gut microbiome composition and the subsequent incidence of NEC using standardized and reproducible methods. In this way, the etiology of NEC and the mechanisms of protection offered by human milk can be more comprehensively understood.

In this review, we aimed to build upon the associations between human milk, gut microbiome composition, and necrotizing enterocolitis. We addressed whether current research supports a stepwise link between all three—that is, that provision of human milk/MOM is protective against the development of infant intestinal dysbiosis which, in turn, is protective against NEC. Design variation among the small number of studies included in this review precluded our ability to

definitively answer this question. However, the results of the included studies do support some components of this hypothesis.

Consistent with existing literature (Gregory et al., 2016; Pammi et al., 2017), three (75%) of the included studies (Ford et al., 2019; Gopalakrishna et al., 2019; Heida et al., 2016) support a link between MOM and the development of a commensal gut microbiome, while two (50%) studies (Gopalakrishna et al., 2019; Heida et al., 2016) demonstrated an association between NEC and MOM. The results presented by Parm et al. (2015) contradict the findings of the other included articles that described a negative correlation between human milk and both the presence and abundance of pathogenic bacteria and the incidence of necrotizing enterocolitis. Considering probable bias related to formula use within the cohort of MOM-fed infants, a plausible interpretation of these results could be that the influence of MOM on gut microbiome composition and the decreased risk of NEC is dose-dependent. The potential importance of "dose" of MOM and its corollary (i.e., any formula, volume of formula) in modulation of the infant gut microbiome and incidence of NEC also has been highlighted by the findings presented by Heida et al. (2016).

The influence of human milk on the developing infant gut microbiome was also largely mediated by its bioactive composition, in addition to the overall quantity of milk received (Gopalakrishna et al., 2019; Murphy et al., 2017; Underwood et al., 2015). As presented by Gopalakrishna et al. (2019), some infants receiving exclusive human milk diets still develop NEC. That variations in human milk bioactive composition—secondary to maternal and infant factors (i.e., secretor status, birth mode, maternal body mass index), milk handling, and pasteurization—can predispose infants to developing NEC was suggested by emerging data (Autran et al., 2018; Maffei & Schanler, 2017; Gopalakrishna et al., 2019). The bioactive composition of raw MOM includes IgA antibodies, microbes, lactoferrin, short chain fatty acids, and human milk oligosaccharides (Autran et al., 2018; Moossavi et al., 2019). While the implications of human milk microbiota on infant health are not yet understood, the other bioactive factors in raw MOM have been linked with decreased incidence of NEC (Autran et al., 2018; Gopalakrishna et al., 2019; Parm et al., 2015; Woodman et al., 2018). This evidence suggested that investigations into milk composition and factors influencing composition should be prioritized in NEC prevention efforts (Gopalakrishna et al., 2019; Underwood et al., 2015).

Modified Bell's Staging Criteria is currently the only diagnostic tool available for NEC, although the reliability of this tool has been criticized because the criteria for stages below Stage IIA are not specific to NEC (Gephart et al., 2018). Investigating the link between human milk, gut microbiome composition, and NEC could allow researchers to find gut microbiome characteristics consistently associated with NEC. This would introduce the option of using microbiome composition as a biomarker for the disease, which may improve the ability of providers to diagnose and manage NEC before the disease progresses to its most severe stages.

The resources and techniques for microbiome analysis have become more accessible for researchers, as the significance of gut microbiome composition for human health has been increasingly recognized. However, investigating the relationship between human milk, gut microbiome composition, and NEC in human infants is challenging. Evaluation is dependent on observational studies among samples of infants who may or may not develop NEC and who cannot ethically be randomized to receive formula. Through the collaboration of researchers in different locations, multi-center studies with similar patient demographics and care practices, could offer an opportunity for evaluating the significance of the influence of human milk/MOM on gut microbiome composition and the subsequent incidence of NEC in large samples of infants.

Gaps in Literature

The use of pasteurized donor human milk when MOM is unavailable has become a staple of neonatal critical care (Meier et al., 2017). The results of the study conducted by Ford et al. (2019) suggest that there is not an increased risk of NEC associated with infant diets primarily consisting of pasteurized donor human milk. However, the researchers demonstrated that distinct differences in the gut microbiome composition of MOM-fed infants exist compared to the gut microbiome composition of pasteurized donor human milk-fed infants, possibly related to differences in the bioactive composition of the pasteurized donor human milk secondary to pasteurization (Ford et al., 2019). Few studies evaluating the clinical significance of MOM versus pasteurized donor human milk among exclusively human milk-fed infants exist. To comprehensively understand the short-term and long-term benefits and risks associated with the use of pasteurized donor human milk, it is necessary for more research to be conducted with the intent of investigating infant health and gut microbiome development.

In this review, researchers did not address how mode of human milk delivery could affect gut microbiome development and subsequent NEC risk. A multi-center study conducted by Rozé et al. (2017) found NICUs that had favorable direct breastfeeding policies had a lower incidence of NEC than NICUs that did not have favorable direct breastfeeding policies. This suggests that the mode of feeding may be just as critical to infant outcomes as what the infant is fed.

Direct breastfeeding, compared to other modes of human milk feeding, has also been associated with higher milk microbiota diversity (Moossavi et al., 2019) and the development of a commensal infant gut microbiome dominated by genera *Bifidobacteria* in full-term infants (Ho et al., 2018). Changes in the oral microbiomes of

premature infants have been described following direct breastfeeding and skin-to-skin contact as well (Hendricks-Muñoz et al., 2015). Therefore, future researchers should assess how the mode of feed and skin-to-skin contact correlates with gut microbiome composition and subsequent NEC incidence.

While the prevalence of NEC among infants with critical congenital heart defects is similar to premature infants (Cognata et al., 2019), the reviewed studies excluded infants born with cardiac defects. This exclusion may reflect the controversial distinction between the pathophysiology involved in "premature necrotizing enterocolitis" versus "cardiac necrotizing enterocolitis" (Spinner et al., 2020). However, infants who require cardiac surgery immediately after birth experience similar risk factors associated with intestinal dysbiosis and NEC as premature infants (Typpo et al., 2015); thus, they should be included in future research addressing the link between infant diet, microbiome composition, and NEC.

Implications for Providers

Beyond NEC, the infant gut microbiome has an extensive, multi-organ system influence on infant health and disease development. Therefore, the results of these studies, which support a relationship between MOM and the development of commensal bacteria in the preterm neonatal gut, emphasize the importance of lactation support to ensure availability of MOM for vulnerable infants. Despite known benefits of MOM in the reduction of infant morbidity and mortality, barriers persist in its provision for infants in intensive care (Davis & Spatz, 2019; Newcombe & Fry-Bowers, 2018; Patel & Kim, 2018). While MOM is widely accepted as an essential component in the care of the premature infant, awareness of and advocacy for its provision for other vulnerable populations at risk for NEC is also needed (Davis & Spatz, 2019; Newcombe & Fry-Bowers, 2018). Additionally, advocacy should not be limited to the feeding of expressed maternal milk but should also include advocating for direct breastfeeding or chestfeeding.

Limitations

Our search strategy yielded only four publications simultaneously addressing the association of human milk, infant gut microbiome composition, and subsequent NEC incidence among human infants, limiting our ability to establish conclusive links between these variables. Despite conducting and replicating the search within multiple databases, some studies may have been missed. Among the included studies, small sample sizes and variations in study design, timing and frequency of microbial analysis, type of specimen used for microbial analysis, and the operationalization of variables, including infant diet, made it difficult to establish consensus in study findings.

Conclusion

There is growing evidence to suggest that human milk influences the bacterial composition of the premature infant gut microbiome and that NEC is associated with intestinal dysbiosis. However, this review found only a small number of studies examining the link between all three variables. Given the small number of available studies and the limitations of those studies, more research is urgently needed to thoroughly understand the protection against NEC gained through the modulation of the infant gut microbiome by the provision of human milk.

Author's Note

Ms. Davis is an International Board Certified Lactation Consultant in her second semester of the PhD in Nursing program at the University of Pittsburgh.

Declaration of Conflicting Interests

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