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THE PROTECTIVE ROLE OF HUMAN BREAST MILK AGAINST NECROTIZING ENTEROCOLITIS IN PRETERM INFANTS: A LITERATURE REVIEW

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ABSTRACT

Necrotizing enterocolitis (NEC) is a life-threatening gastrointestinal disease that predominantly affects preterm infants, with high rates of morbidity and mortality. Human breast milk (HBM) has long been recognized as the most effective nutritional intervention for preventing NEC due to its unique bioactive components such as immunoglobulins, lactoferrin, glutamine, vitamins, and human milk oligosaccharides (HMOs), which act through mechanisms including strengthening the intestinal barrier, modulating immune responses, and regulating the gut microbiota. This narrative review aims to synthesize recent evidence on the protective role of HBM against NEC, with particular emphasis on the function of HMOs, probiotics, and complementary nutritional interventions designed to replicate or enhance HBM's bioactivity. The methods applied in this review followed a narrative literature search in PubMed, Scopus, and Google Scholar for studies published between 2015 and 2025 on the effects of breastfeeding on NEC risk in preterm infants, using predefined eligibility criteria. The findings indicate that HBM significantly reduces NEC incidence, while supplemental interventions such as prebiotics and probiotics may serve as complementary strategies, particularly when the availability of mother's own milk is limited. Overall, HBM remains the primary protective factor against NEC, and optimizing its provision in neonatal care is critical for improving outcomes among preterm infants.

Keywords: Human Breast Milk (HBM), Necrotizing Enterocolitis (NEC), Preterm Infants, Probiotics, HMOs

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INTRODUCTION

Necrotizing enterocolitis (NEC) is a severe gastrointestinal disease and one of the leading causes of morbidity and mortality among neonates, particularly preterm infants. It is characterized by inflammation and necrosis of the intestinal wall, which may lead to perforation and systemic complications (Duess et al., 2023). Approximately 85% of NEC cases occur in infants born before 35 weeks of gestation (Shulhan et al., 2017). Globally, a meta-analysis of 27 cohort studies involving over 574,000 neonates estimated the incidence of NEC among very low birth weight (VLBW) infants to be 7% (95% CI: 6–8%) (Alsaied et al., 2020). In Indonesia, data from tertiary referral hospitals report a prevalence of 6–8% among preterm LBW infants, consistent with global estimates (Iftinan et al., 2023).Well-recognized risk factors include prematurity, immaturity of the intestinal mucosal barrier, dysbiosis of the gut microbiota, and the use of formula feeding instead of human breast milk (HBM), all of which contribute to the development of NEC (Campos-Martinez et al., 2022).

One of the most critical mechanisms underlying NEC is the immaturity of the innate immune system in preterm infants, which compromises mucosal defense against pathogenic bacteria and triggers intestinal inflammation (Luthfi Taufik & Lestari, 2021; Shaw et al., 2021). In this context, HBM emerges as the optimal nutritional source during early life, associated with lower infection rates and improved survival. Its bioactive components—such as secretory immunoglobulin A (sIgA), lactoferrin, anti-inflammatory cytokines, and human milk oligosaccharides (HMOs)—modulate immune responses and suppress NEC-associated pathogens (Altobelli et al., 2020). Among HMOs, disialyllacto-N-tetraose (DSLNT) has been identified as a key protective molecule, with evidence showing its role in reducing NEC severity through prebiotic and immunomodulatory mechanisms (Hassinger et al., 2020; Masi et al., 2024).

Nevertheless, despite its well-documented protective effects, 1–3% of preterm infants exclusively fed with HBM still develop NEC (Shulhan et al., 2017). This highlights that the mechanisms underlying HBM's protection are not yet fully understood and that NEC remains a multifactorial and complex disease. Moreover, the choice of milk type becomes a critical aspect of NEC prevention, particularly in neonatal intensive care units (NICUs), where donor human milk (DHM) is often used as an alternative when mother's own milk (MOM) is unavailable. DHM generally contains lower levels of protective bioactive components compared to MOM. This difference may influence the effectiveness of NEC prevention (Parker et al., 2024).

Necrotizing enterocolitis carries not only high morbidity and mortality but also poses a significant economic and long-term health burden. Approximately 20–40% of affected infants require surgical intervention, and mortality rates may rise to 50% in severe cases. The financial impact is considerable, with treatment costs for surgical NEC estimated to exceed US$ 300,000 per infant. Beyond the acute phase, survivors are at risk of long-term complications, including growth failure, neurodevelopmental delays, and short bowel syndrome (Shulhan et al., 2017). These consequences underscore the importance of preventive strategies and highlight the value of reviewing current evidence on the protective mechanisms of HBM in preterm infants.

Therefore, this review will address four key aspects: (1) the epidemiology and risk factors of NEC, (2) the pathophysiology of NEC in preterm neonates, (3) the bioactivity

and protective mechanisms of HBM components against NEC, and (4) complementary nutritional strategies that enhance the efficacy of HBM. Ultimately, this review aims to provide insights that support clinical practice by emphasizing the importance of exclusive breastfeeding for preterm infants, particularly in the early days of life, as a preventive strategy against NEC.

RESEARCH METHODS

This structured narrative review was conducted following the methodological principles outlined by Paré & Kitsiou (2017). The review focused on studies evaluating the impact of human breast milk (HBM) on the risk of necrotizing enterocolitis (NEC) in preterm infants. This narrative review synthesizes current evidence from studies published between 2015-2025. Literature searches were performed in major scientific databases, including PubMed, Scopus, and Google Scholar, using the following keywords: "breastfeeding," "human breast milk," "human milk," "necrotizing enterocolitis," "preterm," "probiotic," "HMOs," "prebiotic," and "risk factors."

The eligibility criteria were established to ensure the inclusion of relevant and high-quality evidence. Inclusion criteria comprised original research articles that investigated the relationship between HBM feeding and NEC incidence in preterm infants, published in English or Indonesian, and available in full text. Accepted study designs included randomized controlled trials (RCTs), cohort studies, case–control studies, and systematic reviews with clearly defined primary data. Exclusion criteria included opinion pieces, editorials, commentaries, and publications with very small sample sizes or insufficient methodological rigor.

RESULT AND DISCUSSION

Epidemiology of NEC

Epidemiologically, necrotizing enterocolitis (NEC) remains a major clinical challenge among preterm infants worldwide. The incidence of NEC is estimated to affect 3–15% of preterm neonates, with higher risk observed in very low birth weight (VLBW) infants (<1,500 g) (Kaban et al., 2022). A meta-analysis reported that 7 out of 100 low birth weight (LBW) infants admitted to neonatal intensive care units (NICUs) are at risk of developing NEC with mortality rates ranging from 23–30%, and rising up to 50% in severe cases (Alsaied et al., 2020). In Indonesia, similar patterns have been reported. A study at Dr. Cipto Mangunkusumo General Hospital (Jakarta) found an incidence of 8.6% among preterm infants in 2019, with a survival rate of only 27.27% (Kaban et al., 2022) Prematurity and LBW remain the most significant risk factors due to intestinal immaturity, underdeveloped immune responses, and altered microbial colonization (Campos-Martinez et al., 2022). Survivors frequently face severe long-term complications, including short bowel syndrome (SBS), sepsis, and growth or neurodevelopmental impairments, highlighting the urgent need for preventive strategies

Etiology of NEC

The exact etiology of NEC remains incompletely understood; however, there is a broad consensus that intestinal immaturity and dysbiosis of the gut microbiota play a central role in its pathogenesis. Preterm infants possess an underdeveloped immune system and a highly permeable intestinal barrier, which increases susceptibility to bacterial

translocation and excessive inflammatory responses (Savarino et al., 2021). Gut dysbiosis—characterized by an overrepresentation of pathogenic bacteria such as Enterobacteriaceae and reduced populations of protective commensals such as *Bifidobacteria*—triggers mucosal inflammation. This imbalance promotes the release of inflammatory mediators and reactive oxygen species (ROS), ultimately leading to enterocyte injury and necrosis (Shaw et al., 2021).

In addition to prematurity and microbial dysbiosis, several perinatal and neonatal risk factors exacerbate NEC susceptibility. These include neonatal sepsis, chorioamnionitis, perinatal asphyxia, meconium aspiration syndrome, and maternal drug exposure such as cocaine. Prolonged use of broad-spectrum antibiotics during the perinatal period may also disrupt microbial colonization and further increase the risk. Histopathological studies indicate that the terminal ileum and ascending colon are the most frequently affected sites of cellular apoptosis in NEC, reflecting their vulnerability to hypoxia, ischemia, and bacterial invasion (Kanuri et al., 2023; Shaw et al., 2021).

Pathophysiology of NEC

The pathogenesis of NEC is multifactorial, with major contributions from pathogenic bacterial invasion, immune immaturity, intestinal barrier dysfunction, and impaired perfusion. Bacterial invasion, particularly by *Clostridium* and *Staphylococcus* species, triggers a strong inflammatory response in the intestine, characterized by the production of free radicals and the activation of cellular apoptosis pathways (Duess et al., 2023). Massive epithelial damage due to apoptosis leads to the loss of intestinal barrier integrity, allowing bacteria and toxins to spread into the systemic circulation and cause widespread organ injury (Kanuri et al., 2023). The accumulation of bacteria in the intestinal lumen activates inflammatory responses through Toll-Like Receptor 4 (TLR4) on the surface of enterocytes, which recognizes lipopolysaccharides (LPS) from Gram-negative bacterial cell walls. TLR4 activation primarily stimulates the production of pro-inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α), which subsequently induces cellular apoptosis through various mechanisms, including the production of Reactive Oxygen Species (ROS) that damage cellular components (Duess et al., 2023).

This inflammatory process results in extensive mucosal injury and the loss of intestinal barrier integrity, allowing bacteria and toxins to enter the systemic circulation and trigger sepsis. Moreover, poor intestinal blood perfusion and epithelial immaturity in preterm infants also contribute to the development of NEC. The repetitive cycle of pathology, repair, and regeneration of the intestinal epithelium due to bacterial infection and other risk factors leads to chronic mechanical injury of the intestinal barrier, which further exacerbates inflammation and prolongs the disease course (Kanuri et al., 2023; Shaw et al., 2021).

Histopathological features of NEC are typically characterized by acute intestinal inflammation, enterocyte apoptosis, decreased epithelial cell proliferation, mucosal edema, submucosal hemorrhage, villous distortion, and crypt abnormalities of Lieberkühn (Shaw et al., 2021) Although bowel resection is a common therapeutic intervention in NEC cases, it can lead to Short Bowel Syndrome (SBS). Nevertheless, histological findings often show intestinal repair following resection. This recovery is characterized by villous lengthening,

crypt deepening, and an increased rate of epithelial cell proliferation, which collectively enhance the intestinal absorptive capacity (Savarino et al., 2021).

Clinical manifestations of NEC reflect mucosal injury and systemic inflammation. Symptoms generally appear during the second to third week of life in preterm infants, beginning with nonspecific signs that can progress to severe systemic conditions. According to the findings of Savarino et al. (2021), the most common early sign is feeding intolerance, manifested by abdominal distension in 83.2% of cases, followed by gastric residuals (33.3%) and gastrointestinal bleeding (27.7%). Other systemic signs such as bilious vomiting, apnea, lethargy, and hypothermia are also frequently present. Radiological examination may reveal pneumatosis intestinalis, which is the presence of gas within the intestinal wall and is considered a hallmark diagnostic finding of NEC (Niño et al., 2016).

Role and Composition of Breast Milk

Preterm infants who receive breast milk have a lower incidence of NEC compared to those who don't (Altobelli et al., 2020). This makes breast milk the most effective preventive measure. Below is a description of several major components of breast milk and their functions in supporting intestinal health in preterm infants and preventing NEC *(Table 1)*:

1. Lipids

Lipids in breast milk, particularly Long-Chain Polyunsaturated Fatty Acids (LC-PUFAs) such as DHA and ARA, play a direct role in supporting various physiological functions in early life, including the synthesis of signaling molecules, lipid membrane development, and organogenesis. LC-PUFAs also reduce the risk of inflammation and support the formation of an intact epithelial barrier, thereby lowering the risk of NEC(Sami et al., 2023).

2. Lactoferrin

Lactoferrin is a major whey protein component in breast milk that enhances the immune system, regulates inflammation, and stimulates intestinal epithelial regeneration. It functions by binding iron and directly interacting with microbes and immune cells to prevent pathogen growth (Sami et al., 2023).

3. Carbohydrates (Lactose)

The primary carbohydrate in breast milk is lactose, which serves as a major energy source and facilitates the absorption of calcium and magnesium. Additionally, breast milk contains oligosaccharides that act as prebiotics and prevent pathogenic colonization in the infant's gut (Wijaya, 2019).

4. Human Milk Oligosaccharides (HMOs)

HMOs are abundant oligosaccharide components in breast milk, with concentrations that vary depending on the stage of lactation. HMOs are metabolized by gut bacteria such as *Bifidobacteria* and *Lactobacilli spp.*, aiding in the development of a healthy intestinal microbiota. They also strengthen mucosal integrity, prevent pathogen adhesion, and regulate the infant's immune response (Masi et al., 2024).

5. Essential Amino Acids

Essential amino acids serve as a primary energy source for intestinal epithelial cells. Most are protein-bound, with about 5%–10% existing in free form. The presence of

free amino acids in breast milk supports epithelial cell proliferation and prevents intestinal tissue necrosis. Several key amino acids include:

- **Glutamine**

The most abundant free essential amino acid in breast milk, particularly during the first three months of lactation. Glutamine provides energy for epithelial cell proliferation, enhances intestinal barrier function, and reduces oxidative stress. Studies show that glutamine decreases IL-1 production while increasing anti-inflammatory cytokines IL-10 and IL-4 (Sami et al., 2023).

- **L-Arginine**

A semi-essential amino acid produced by intestinal epithelial cells, used to generate nitric oxide (NO) via the arginine–nitric oxide synthase (NOS) pathway. This pathway plays a critical role in regulating intestinal blood flow and preventing tissue ischemia (Sami et al., 2023).

- **L-Tryptophan (Trp)**

An essential amino acid that enhances immune function in the gut. Its derivative, indole-3-propionic acid (IPA), regulates intestinal barrier function and reduces inflammation by activating the Pregnane-X Receptor (PXR), which in turn downregulates pro-inflammatory cytokines such as TNF-α (Sami et al., 2023).

6. Vitamin D

Vitamin D is essential for regulating the immune system and enhancing intestinal barrier function. As an immunomodulator, it binds to Vitamin D Receptors (VDR) on immune cells, inhibits Th17 differentiation, and reduces IL-17 production, thereby minimizing tissue damage and promoting anti-inflammatory responses (Sami et al., 2023).

7. Vitamin A

Vitamin A, found in high amounts in colostrum, helps maintain intestinal barrier function and regulate gut immunity. In neonates with NEC, serum vitamin A levels are lower compared to healthy infants, suggesting a potential role in improving intestinal health in preterm neonates (Wijaya, 2019).

8. Iron

Although the iron content in breast milk is relatively low, it has high bioavailability (up to 50%) due to the presence of lactose and lactoferrin, which facilitate its absorption. This contrasts with formula milk, where iron absorption is typically much less efficient (Wijaya, 2019).

9. Zinc (Zn)

Zinc is crucial for key metabolic processes, including immune regulation, oxidative stress reduction, and intestinal development. Preterm infants are often zinc-deficient since most zinc stores accumulate during the third trimester of pregnancy, making breast milk intake particularly important (Sami et al., 2023).

Table 1. Main Nutritional Composition of Mature Breast Milk (Wijaya, 2019)

Component	Average Value for Mature Breast Milk (per 100 mL)
Energy (kJ)	280
Energy (kcal)	67
Protein (g)	1.3

Fat (g)	4.2
Carbohydrates (g)	7.0
Sodium (mg)	15
Calcium (mg)	35
Phosphorus (mg)	15
Iron (µg)	76
Vitamin A (µg)	60
Vitamin C (mg)	3.8
Vitamin D (µg)	0.01

Characteristics of Breast Milk in Mothers with Preterm Infants

Breast milk produced by mothers of preterm infants has unique characteristics that are physiologically adapted to meet the developmental and protective needs of these vulnerable newborns. According to Gates et al. (2021), preterm breast milk contains higher concentrations of protein, energy, and sodium, particularly during the first week after birth. These levels gradually decline over time but continue to provide significant protective benefits. Bioactive substances such as lactoferrin, secretory immunoglobulin A (sIgA), lysozyme, and human milk oligosaccharides (HMOs) are also found in greater amounts in preterm breast milk, helping to strengthen the intestinal mucosal barrier and regulate the colonization of the infant gut microbiota (Sami et al., 2023). This composition plays an essential role in supporting intestinal growth, immune system development, and protection against infections such as NEC.

A study by Poulimeneas et al. (2021) highlighted that one of the main differences in preterm breast milk lies in its higher content of whey protein, which is more easily absorbed by the immature gastrointestinal tract. Preterm milk also contains greater amounts of essential minerals such as calcium, phosphorus, and zinc, which are crucial for bone formation and immune maturation in premature infants. However, because the composition of preterm milk changes rapidly, breast milk fortification is often recommended for very low birth weight (VLBW) infants or those born before 32 weeks of gestation.

Another notable difference is found in essential amino acid content, particularly tryptophan (Trp). Tryptophan is involved in the synthesis of serotonin and melatonin, and also plays a role in modulating the immune system and maintaining gut microbiota balance (Sami et al., 2023). Research by O'Rourke et al. (2018) showed that although preterm milk has higher total Trp levels, its free Trp levels are actually lower compared to term milk. This finding indicates differences in metabolism and immunological function in preterm infants, making the composition of preterm milk highly specific and focused on early protection.

Thus, preterm breast milk is not merely an "earlier version" of term milk but rather a biologically adaptive and therapeutic fluid, designed by the maternal body to support the defense, growth, and maturation of highly vulnerable preterm infants. The combination of nutrients, immunoprotective factors, and growth factors in preterm milk represents the most effective natural nutritional intervention for preventing neonatal morbidities, including NEC.

Protective Mechanisms of Breast Milk Against NEC

Breast milk provides protection against NEC through two main pathways: strengthening the intestinal mucosal barrier and modulating the local immune response (Sami et al., 2023). In the first pathway, key bioactive components such as glutamine, zinc, vitamins A and D, L-tryptophan, and HMOs enhance the integrity of tight junctions between intestinal epithelial cells and promote mucosal regeneration. L-tryptophan, through its metabolite indole-3-propionic acid (IPA), stimulates the production of interleukin-22 (IL-22), which supports intestinal mucosal recovery (O'Rourke et al., 2018). In addition, breast milk stimulates the production of antimicrobial peptides (AMPs) to prevent pathogenic bacterial colonization. The presence of Epidermal Growth Factor (EGF) in breast milk also accelerates healing processes and reinforces the epithelial layer as a physical barr(Syahniar & Suri, 2020)nvasion (Syahniar & Suri, 2020).

The second pathway involves modulation of the mucosal immune response, where breast milk components such as HMOs and fibers support the growth of commensal gut bacteria, particularly *Bifidobacterium* and *Lactobacillus*, which produce short-chain fatty acids (SCFAs) such as acetate and butyrate (Dombrowska-Pali et al., 2024). These SCFAs enhance the production of protective mucus, strengthen the mucosal barrier, and modulate the activation of immune cells such as dendritic cells and T cells. Furthermore, L-arginine and vitamin D in breast milk suppress the activation of proinflammatory pathways such as ERK/NF-κB, reduce the production of cytokines like TNF-α, IL-6, and IL-8, and improve immune regulation via the VDR receptor (Sami et al., 2023). The presence of probiotics in breast milk also supports the establishment of a healthy gut microbiota in infants, particularly in preterm babies who are highly susceptible to microbial imbalance. The interaction between probiotics and intestinal epithelial cells provides protective effects against NEC by enhancing barrier integrity, stimulating mucosal immunity, and inhibiting pathogenic colonization (Martinez et al., 2015).

Moreover, breast milk contributes to the inhibition of TLR4 activation, a proinflammatory immune receptor that plays a significant role in the pathogenesis of NEC (Luthfi Taufik & Lestari, 2021). Breast milk components suppress TLR4 activation by lipopolysaccharides (LPS), reduce the release of TNF-α and IL-1β, and enhance the expression of anti-inflammatory cytokines such as IL-10 (Syahniar & Suri, 2020). Thus, the protective effect of breast milk against NEC is mediated more by its bioactive components than by its microbiota alone.

The Role of HMOs in the Prevention of NEC

HMOs are major bioactive components of human breast milk that function as natural prebiotics in the neonatal gastrointestinal tract. HMOs facilitate the colonization of protective commensal bacteria, particularly *Bifidobacterium* spp., which help maintain intestinal mucosal integrity and suppress pathogenic colonization. Among the various HMOs, disialyllacto-N-tetraose (DSLNT) is one of the most prominent in the context of preventing necrotizing enterocolitis (NEC). Experimental evidence from animal models and human cohort studies has shown that low levels of DSLNT are correlated with an increased incidence of NEC, whereas its presence reduces disease severity by promoting *Bifidobacterium* dominance and attenuating intestinal inflammatory responses (Hassinger et al., 2020; Masi *et al*., 2021).

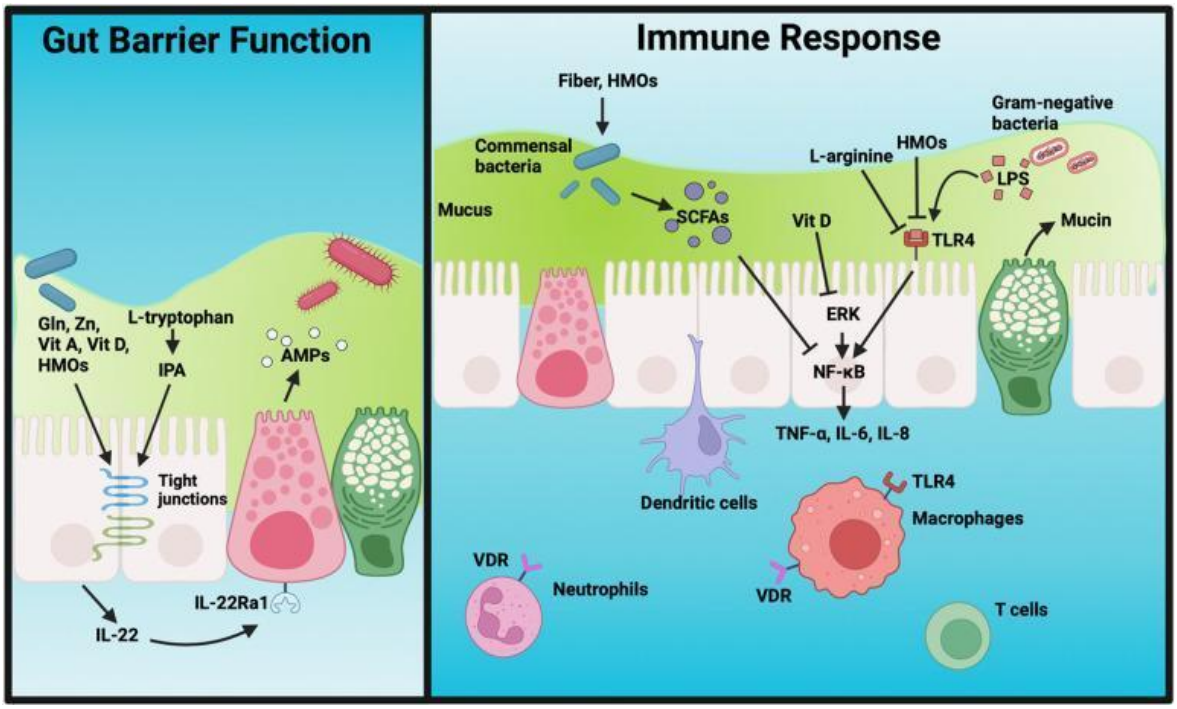

Figure 1. Protective mechanisms of breast milk against NEC through strengthening of the intestinal barrier and regulation of immune responses. (Sami et al. (2023), Licensed under CC BY 4.0.)

Furthermore, DSLNT concentrations are consistently higher in mother's own milk (MOM) compared to donor human milk (DHM), although pasteurization does not appear to significantly reduce DSLNT levels (Hassinger et al., 2020). This difference is likely attributable to the fact that DHM is often collected from mothers of term infants and during later stages of lactation, when HMO concentrations, including DSLNT, are naturally lower. Variability in DSLNT levels among mothers and the decline in concentrations over time suggest that fresh MOM provides superior protective benefits against NEC compared to DHM. Supporting this, Masi et al.(2024) demonstrated that protection against NEC is more strongly mediated by bioactive components such as DSLNT rather than by the breast milk microbiota itself. Recent policy reviews and clinical recommendations also highlight the importance of prioritizing MOM as a primary preventive strategy. Colarelli et al. (2024) emphasized that optimizing the provision of MOM—including clinical policies that account for compositional differences between MOM and DHM—should be considered an integral component of effective NEC prevention packages in NICUs. Collectively, current evidence supports DSLNT as a key protective HMO that exerts its effects through prebiotic activity and immunomodulatory mechanisms.

Human Milk-Based Complementary Interventions

Although human milk (HM) is recognized as the most effective nutritional intervention for preventing necrotizing enterocolitis (NEC), challenges in its administration remain a major clinical issue. Not all mothers are able to provide exclusive HM due to factors such as low milk production, maternal medical conditions, or logistical barriers in

neonatal intensive care units (NICUs). Furthermore, despite its richness in protective bioactive components—such as oligosaccharides, immune proteins, and commensal bacteria—NEC can still occur in a subset of preterm infants with high-risk profiles. Consequently, adjunctive nutritional strategies designed to mimic or complement the bioactivity of HM have gained increasing attention, particularly through prebiotic and probiotic approaches (Colarelli et al., 2024).

Prebiotic supplementation offers fermentable substrates for gut microbiota, aiming to replicate HM's role in maintaining mucosal integrity and suppressing pathogen colonization. Common types of prebiotics—such as fructooligosaccharides (FOS), galactooligosaccharides (GOS), inulin, and lactulose—have been incorporated into infant formulas (Hassinger et al., 2020). However, clinical evidence supporting their effectiveness in NEC prevention remains limited. A recent Cochrane Review by Sharif et al. (2023) concluded that current data are insufficient to recommend routine prebiotic use in preterm or very low birth weight (VLBW) infants. Nevertheless, experimental studies have demonstrated that prebiotic-enriched formulas can produce stool microbiota profiles more closely resembling those of breastfed infants, including increased colonization by *Bifidobacterium* and *Lactobacillus* (Zhu et al., 2021). While these findings do not directly confirm NEC prevention, they underscore the potential of prebiotics to emulate HM's protective effects via gut microbiota modulation.

In contrast, probiotic supplementation has yielded more consistent results in reducing NEC incidence. Although HM microbiota is often described as "natural probiotics," a study by (Masi et al., 2024) (2024) found no significant differences in HM microbiota composition between infants with NEC and healthy controls, suggesting that HM's protective effects are primarily mediated by its bioactive components rather than its microbial content. Supplementation with specific probiotic strains—such as *Bifidobacterium longum* subsp. *infantis* and *Lactobacillus acidophilus*—has shown efficacy in lowering NEC risk. A meta-analysis by Batta et al. (2023) reported that probiotics containing *B. infantis* were more protective than combinations lacking this strain. Moreover, a clinical trial in VLBW infants demonstrated that supplementation of HM with a combination of *L. acidophilus* and *B. infantis* (Infloran™) significantly reduced NEC incidence compared with HM alone (Sajankila et al., 2023).

Nutritional interventions complementing the bioactivity of HM may serve as clinically relevant adjunctive strategies, particularly for high-risk preterm infants or in situations where maternal HM supply is limited. Nonetheless, it is important to emphasize that HM remains the primary source of protection against NEC, while adjunctive interventions such as prebiotics and probiotics function as complementary measures designed to enhance the natural protective effects of HM.

CONCLUSION

Necrotizing Enterocolitis (NEC) is a serious gastrointestinal condition in preterm infants, characterized by inflammation and intestinal tissue necrosis, with the potential to progress to perforation and sepsis. Breast milk (human milk) has been proven to provide effective protection against NEC through multiple biological mechanisms. Its nutritional and bioactive components—such as secretory IgA, lactoferrin, glutamine, vitamins A and D, and Human Milk Oligosaccharides (HMOs)—strengthen the intestinal epithelial barrier,

regulate inflammatory pathways such as TLR4 activation, and support mucosal regeneration. Among HMOs, disialyllacto-N-tetraose (DSLNT) has shown particular promise in reducing NEC risk through prebiotic and immunomodulatory mechanisms.

In clinical settings where mother's own milk (MOM) is unavailable or insufficient, donor human milk (DHM) and adjunctive strategies such as fortification, prebiotic supplementation, and probiotic therapy may help replicate HBM's protective effects. However, these interventions should be considered complementary—not substitutive. Exclusive breastfeeding remains the cornerstone of NEC prevention, supporting both intestinal development and immune defense from the earliest stages of life. Continued research is essential to refine these complementary approaches and improve outcomes in high-risk neonatal populations.

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