




Maternal breastmilk, infant gut microbiome and the impact on preterm infant health

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Abstract

Aim: This narrative review summarises the benefits of maternal breastmilk to both the infant and the mother, specifically the benefits that relate to modification of the infant microbiome, and how this might vary in the preterm infant.

Methods: We used PubMed to primarily identify papers, reviews, case series and editorials published in English until May 2020. Based on this, we report on the components of breastmilk, their associated hypothesised benefits and the implications for clinical practice.

Results: Breastmilk is recommended as the exclusive diet for newborn infants because it has numerous nutritional and immunological benefits. Additionally, exposure to the maternal breastmilk microbiome may confer a lasting effect on gut health. In the preterm infant, breastmilk is associated with a significant reduction in necrotising enterocolitis, an inflammatory gastrointestinal disease and reduction in other key morbidities, together with improved neurodevelopmental outcomes.

Conclusion: These impacts have long-term benefits for the child (and the mother) even after weaning. This benefit is likely due, in part, to modification of the infant gut microbiome by breastmilk microbes and bioactive components, and provide potential areas for research and novel therapies in preterm and other high-risk infants.

1 | BREASTMILK

Human breastmilk is the optimal food for newborn infants and is recommended by the World Health Organisation as exclusive diet until at least 6 months of age, at which stage complementary foods can be added and breastfeeding maintained throughout infancy and early childhood.¹ The first stage of lactation (the first few days post-natally) provides colostrum, a low volume immune rich substance, of which the primary benefit is transfer of immunological factors and trophic priming of the infant gut, rather than as a source of nutrients

per se.² Maternal milk supply is thereafter inherently linked to demand from the infant who provides feedback to the mother to up- or down-regulate milk production as needed. Breastmilk provides a strategy for transfer of both nutrition (macro- and micronutrients) and many functional components and bioactive molecules including long-chain polyunsaturated fatty acids, immune cells, human milk oligosaccharides (HMOs), cytokines and growth factors. In addition, it ensures continued exposure to a mother-baby specific, vertically transmitted, milk-oriented microbiota, which is further influenced by retrograde transfer of microbiota from the infants' oral cavity.³

Abbreviations: EGF, epidermal growth factor; HMO, human milk oligosaccharide; LOS, late-onset sepsis; MOM, mother's own milk (maternal breastmilk); NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; SCFA, short chain fatty acids; sIgA, secretory IgA; TLR, Toll-like receptor.

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2 | BREASTFEEDING: EARLY INFLUENCES ON LATER HEALTH

2.1 | Infant benefits

Mothers' own breastmilk (MOM) offers continued protection against multiple infections even after breastfeeding has ceased, and several studies have documented lower rates of infant otitis media, gastroenteritis and respiratory infections.⁴ Longer-term, breastfeeding is associated with enhanced cognitive development, and reduced risk of cardiovascular disease, obesity and type 2 diabetes.⁵

Infants who grow slowly in utero often demonstrate catch-up growth after birth, which may increase risks for later metabolic syndrome. Breastfeeding has been shown to be protective perhaps because the infant can provide feedback to the mother about their energy and growth requirements, and maternal milk supply can be regulated to meet demands.⁵ There is also evidence that breastfeeding is associated with a 20%-30% reduction in childhood obesity, which remains significant after correcting for potential confounders such as parental obesity,⁴ which may involve a variety of mechanisms modulated by nutrient composition (eg, fatty acid profiles), functional components (eg, growth factors) or impacts on gut microbiota. In addition, MOM is associated with reduced rates of cardiovascular disease, asthma and allergy in childhood, type 2 diabetes, and is positively correlated with improved cognitive development.

2.2 | Maternal benefits

In addition to the many short- and long-term benefits of MOM for the infant, there are several associated benefits for the mother. Breastfeeding results in favourable maternal metabolic changes that persist after weaning, including lower rates of hypertension, hyperlipidaemia and cardiovascular disease.⁶ Studies have also shown protective effects of breastfeeding against cancers of reproductive tissues including breast and ovary that may be due to the reduced lifetime exposure to oestrogen. A meta-analysis in 2002 showed a reduction in risk of breast cancer by 4.3% for every year of breastfeeding,⁶ and a further study showed a 28% reduction in risk of ovarian cancer for mothers who breastfed for at least 12 months compared to those who never breastfed.⁷

2.3 | Breastmilk composition

Hormones, growth factors, chemokines and cytokines all interact to regulate development and function of the early neonatal immune system and have both direct and indirect effects on antimicrobial activity and modulation of immune function whilst conferring significant anti-inflammatory benefits.² Maternal nutritional status has an impact on immunomodulatory components of MOM along with infant growth trajectories.⁸ Transfer of several functional components in MOM is key to the development of immune function and

Key notes

- Maternal breastmilk confers significant nutritional and immunological benefits to the term and preterm neonate.
- The single most important factor in modifying the infant gut microbiome is maternal breastmilk.
- Breastmilk reduces the risk of necrotising enterocolitis in preterm infants and is associated with improved neurodevelopmental outcomes.

immune-protection of the neonate. These proteins and other compounds generally resist digestion or degradation in the stomach and are therefore available for direct action in the gut. These include secretory IgA (sIgA), human milk oligosaccharides (HMOs), lactoferrin and lysozyme, which have been implicated in both short-term health and longer-term modification of growth and body composition in children.⁸ In addition, cytokines (including TNF- α , IFN- γ , TGF- β and IL-1 β) and growth factors (including epidermal growth factor and erythropoietin) are some of the bioactive factors transferred via MOM (Figure 1).⁹ IL-1 β leads to an innate inflammatory response in enterocytes, with increased pro-inflammatory IL-8 and stimulation of the NF- κ B pathway. Breastmilk can attenuate this IL-1 β activation of IL-8.¹⁰

Oral and breastmilk microbiota tend to be dominated by skin and enteric bacteria, mainly Bifidobacteria and *Lactobacillus* spp. Microbes colonising the infant upper small intestine will be influenced by multiple mechanisms including swallowed oral microbes and by microbes in the breastmilk (arrow 1). Bioactive components from breastmilk include sIgA, lactoferrin, lysozyme, HMOs, growth factors and cytokines. sIgA is produced by plasma cells in the lamina propria and translocated to the gut lumen where it binds pathogenic bacteria and promotes bacterial clearance. Commensal bacteria are transferred to gut-associated lymphoid tissue both bound and unbound to IgA and induce sIgA production (arrow 2). Lactoferrin has antimicrobial properties and binds T cells, causing proliferation and growth promotion of key bacteria (arrow 3). Short chain fatty acids (SCFAs), produced by microbiota, improve IEC tight junction integrity (arrow 4). Furthermore, lactoferrin interacts with lysozyme (arrow 5), also present in high amounts in breastmilk, allowing the lysozyme to degrade bacterial membranes. Some microbes preferentially promoted by breastmilk components such as HMOs (arrow 6), favour the growth of *Bifidobacterium* spp. In addition, HMOs are translocated into the systemic circulation (arrow 7) and both promote and inhibit growth of regulatory T cells (arrow 8). Antigen presentation leads to effector and regulatory T-cell differentiation and production of cytokines including IL-1 β , TNF- α , TGF- β and IL8 (arrow 9). Cytokines in breastmilk act to ameliorate the pro-inflammatory response to infection and pathogens (arrow 10). Infant oral microbiota reflects microbes acquired from breastmilk and the skin/areola (arrow 11), but in turn, oral microbes will impact on bacterial

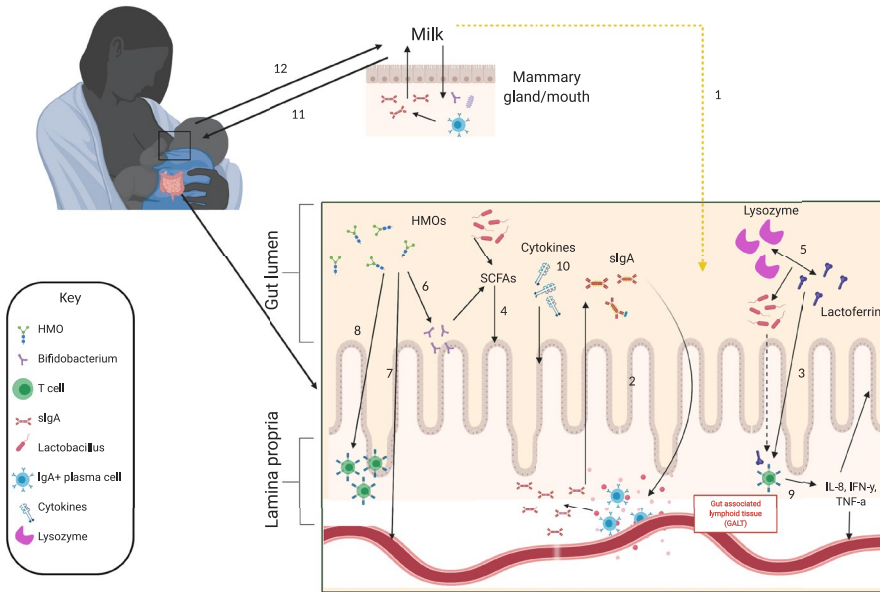


FIGURE 1 Sites of action of breastmilk components

communities in mammary gland ducts through 'back-wash' during direct breastfeeding (arrow 12).

Neonatal immunoglobulin acquisition is primarily through transplacental IgG delivery in the third trimester of pregnancy and then by IgM, IgG and IgA delivery through breastmilk. Very preterm infants miss out on transplacental delivery and are almost completely reliant on MOM for delivery of immunoglobulin until endogenous production begins. Secretory IgA (sIgA) has a predominant local mode of action in the gut and is highly effective at binding enteric pathogens and their toxins.⁹ MOM is the primary source for sIgA in the first month of life, and this maternally derived sIgA shapes the host-microbiota relationship of the preterm infant.

Lactoferrin, an iron binding protein, is one of the most abundant of innate, multi-functional molecules in MOM and has significant anti-infective capacity. Supplemental bovine lactoferrin (which has similar in vitro activity to human lactoferrin) has been shown in several small studies to reduce late-onset sepsis (LOS) in preterm infants,¹¹ but these benefits were not replicated in a recent large randomised controlled trial (RCT) of over 2200 infants.¹²

Other key molecules transferred in MOM are human milk oligosaccharides (HMOs), a family of structurally diverse, complex sugars that are the third most abundant component in MOM, but are absent from formula milk. Unable to be enzymatically digested by humans, they reach the small intestine and colon intact where they serve as metabolic substrates for potentially beneficial bacteria, especially Bifidobacteria.¹³ Increasing evidence suggests that HMOs can serve as decoy receptors and prevent pathogen attachment at the intestinal surface, lowering the risk of LOS,¹³ as well as providing nutrients for brain development. Because HMOs in MOM are altered by maternal factors including genetics, diet and body weight, and stage of lactation,¹³ HMO profiles differ between preterm and term mothers, as well as inter-individual variation which could contribute to apparent differences in the protective effects of MOM against neonatal disease.

3 | BIRTH SEEDS, BREASTMILK FEEDS

At birth, the newborn infant is immediately exposed to a vast array of microbes from the environment, but primarily from the mother (ie birth mode 'seeds' the gut), but breastmilk then 'feeds' the gastrointestinal tract both directly (maternal milk microbes) and indirectly (HMOs promoting the growth of specific bacterial species). The single most important factor influencing the neonatal microbiome is therefore MOM.¹⁴ In formula-fed infants, the microbiome is more diverse, with increased relative abundance of Bacteroidetes and Firmicutes and with increased *Clostridium difficile* when compared with breastfed infants.¹⁵ In contrast, the microbiome of breastfed infants predominantly consists of *Bifidobacterium* (*B breve*, *B longum* and *B bifidum*) and *Lactobacillus*.¹⁶

The relationship between breastmilk and the infant microbiome is complex and involves transfer of immunoglobulins, bacteria, viruses and bacteriophages (viruses which parasitise a bacterium by infecting it and reproducing inside it) from mother to infant via MOM. It has been hypothesised that in addition to this, there is subsequent retrograde feedback from infant secretions to maternal mammary tissue to adapt that microbiome (Figure 1). The maternal milk microbiome may contain hundreds of bacterial species in modestly low numbers (10^3 CFU (colony-forming units)), consisting primarily of gastrointestinal and skin microbiota, with a large degree of inter-individual variability, but the bacterial community within an individual mothers' milk appears relatively stable over time.¹⁷

Several small studies have shown that infant stool and MOM share specific bacterial strains,¹⁸ suggesting that there may be direct transfer of these core strains between mother and infant, and vice versa. However, the gut microbiome of the breastfed term infant is composed primarily of *Bifidobacterium* spp., the growth of which is supported by the provision of HMOs from MOM, rather than direct transfer a large numbers of *Bifidobacterium* spp. in milk. Studies have shown that preterm twins (or other multiples) shared a similarity in

microbiota that was not demonstrated by other infants in the same nursery, suggesting there are genetic and immunomodulatory effects at work in shaping the microbiome, combined with exposure to the same maternal microbes.¹⁹

The microbiome gradually changes to resemble that of adults by the third year of life, and the sequential acquisition of gut microbial exposure early in life has a lasting effect on gut health. Disturbance in the establishment of this microbiome is linked to increased risks of obesity, diabetes and mental health disorders, as well as immune-mediated and inflammatory conditions such as inflammatory bowel disease and atopy although there is substantial uncertainty as to whether the microbiome is causative or is a consequence of other mechanisms. Breastmilk feeding is associated with less diarrhoeal illness compared to formula-fed infants, and microbiota differences between breastfed and formula-fed infants persist beyond 6 months of age.^{20,21}

4 | BREASTMILK IN PRETERM INFANTS COMPARED WITH TERM INFANTS

Preterm infants are a vulnerable group at high risk of growth failure, immuno-compromise, neurodevelopmental delay and in the most premature, an increased risk of necrotising enterocolitis (NEC), LOS and death. The risk of these complications increases with decreasing gestational age, with very preterm infants (less than 32 weeks of gestation) being most at risk.

Milk from mothers whose infants are born prematurely differs from those delivering at term. In the initial lactating period, preterm milk contains more protein, fat, free amino acids and sodium, although these decrease over time.²² Furthermore, most bioactive components in milk, including fucosylated HMOs, cytokines, growth factors and lactoferrin, are significantly higher in preterm milk and colostrum.^{13,22}

MOM has been shown to improve neurodevelopmental outcomes²² and reduces risk of NEC and retinopathy of prematurity.²³

5 | BREASTMILK AND NECROTISING ENTEROCOLITIS IN PRETERM INFANTS

Perhaps the most important benefits of breastmilk are the reduction in risk of NEC, which may be 6-10 times lower compared to those receiving formula milk feeds.²⁴ This protective benefit appears to be dose related to one study demonstrating that the risk of NEC or death after 14 days was reduced by a factor of 0.83 (CI 0.77-0.97) for every 10% increase in volume of breastmilk received.²⁵

Necrotising enterocolitis, an inflammatory condition of the gut leading to intestinal injury, occurs in up to 10% of very preterm infants with mortality rates up to 40%, making it the leading cause of death after the first 2 weeks of age in this population.²⁶ In addition, NEC results in considerable long-term morbidity including growth failure, short-bowel syndrome, cholestatic liver failure and adverse neurodevelopmental outcomes.²⁷ The rapidity of disease onset and the inability to predict those who will have a particularly fulminant course

means that there is an urgent need to develop better diagnostic and predictive tests, and interventions that may alter disease pathways.

The aetiology of NEC appears multifactorial with vascular, mucosal and toxic insults all contributing to intestinal inflammation and enterocyte injury. Multiple factors have been hypothesised to be implicated including microbial dysbiosis and abnormal bacterial colonisation, formula feeding, early use of antibiotics and genetic predisposition.^{12,29}

The potential mechanisms by which breastmilk reduces this risk are multiple, and many recent studies have focused on the role of immunomodulatory components present in milk and how these interact with and inform the gut microbiome.

6 | PHYSICAL BREASTMILK FEEDING DIFFERENCES IN PRETERM INFANTS

Breastfeeding is challenging for preterm infants as the developmental ability to coordinate suck, swallow and breathe that enables feeding directly from the breast is rarely established before 34 weeks of corrected gestational age.²⁹ Almost all MOMs that a preterm infant receives differ from that when direct breastfeeding due to the need to artificially express milk by hand or pump. This expressed milk is typically stored in a fridge or freezer in plastic containers before being fed to the infant via a nasogastric tube that 'by-passes' the oral cavity with its own unique microbiota and presence of important components such as salivary amylase.

Breastmilk expression itself changes the composition of the microbes within human milk. Azad et al showed that the milk microbiome is affected by several maternal factors and that the feeding method is associated with milk microbiota composition³. They showed that indirect feeding was associated with lower α diversity and increased β diversity compared with direct breastfeeding. Specifically, they showed that expressed breastmilk was associated with increased abundance of potential pathogens including Enterobacteriaceae and Enterococcaceae and depletion of Bifidobacteria. They suggest these data support the retrograde inoculation hypothesis, whereby the maternal milk microbiome is further altered due to feedback from neonatal secretions and other components in the infants' oral cavity.

7 | DONOR HUMAN MILK

Donor human milk (DHM) is widely used to make up any shortfall in supply of MOM and is recommended by several professional organisations.³⁰ However, the use of DHM is likely to have a different impact on the infant gut microbiome compared to MOM. DHM is pasteurised by heat techniques such as Holder pasteurisation that frequently reduces the concentrations of key components including sIgA, lactoferrin, lysozyme, growth factors, water-soluble vitamins and lipases.³⁰ HMOs, lactose, epidermal growth factor and fat-soluble vitamins tend not to be reduced, and the impact on cytokines is variable.³⁰

In addition, donors are typically mothers who delivered babies at term several months ago in whom the nutritional content, in particular protein and fat, differ from milk in the first few postnatal weeks and/or differ from mothers who delivered a preterm infant.²²

8 | IMMUNOGLOBULINS AND GROWTH FACTORS

In preterm infants, the adaptive and innate immune systems are hypothesised to interact in the development of NEC and this is exemplified by the role of immunoglobulins. Kubinak et al (2015) compared IgA bound and unbound bacterial populations in wild-type mice and MyD88-deficient mice. They found that in wild-type mice, IgA bound bacteria more closely resembled the host mucosal microbiota than faecal communities and found that in MyD88-deficient mice, IgA preferentially bound bacteria associated with disease onset, such as Enterobacteriaceae.³¹ These findings were replicated in a recent study in human infants, which found that a reduction in the IgA bound bacterial population was seen in those infants who went on to develop NEC.³² The authors hypothesised the combined function of IgA to both bind pathogens and promote mucosal colonisation of the intestine with some protective species may influence protection against NEC.

Epidermal growth factor (EGF) is also present in high levels in breastmilk and amniotic fluid and may protect against NEC in part by inhibition of Toll-like receptor 4 (TLR4).³³ Infants who develop NEC, have increased TLR4 activity which leads to increased enterocyte apoptosis and reduced enterocyte proliferation and migration that in turn lead to breakdown of the intestinal epithelium and barrier integrity.³³

9 | HUMAN MILK OLIGOSACCHARIDES IN PRETERM INFANTS

Recent studies have shown that HMOs improve survival and reduce NEC in a neonatal rat model.³⁴ Similar to sIgA, they block attachment of potential pathogens such as *Streptococcus pneumoniae* and *Campylobacter jejuni* to the intestinal epithelial surface by behaving as adhesion decoy receptors, owing to the similarity of their glycosylated regions to epithelial cell surface receptors. Rodent studies suggest that HMOs have benefits in protection against NEC with a seminal study by Autran et al (2018) showing that a single specific HMO, disialyllacto-N-tetraose, was associated with lower NEC risk in human milk-fed infants,²⁴ although this requires confirmation in a larger cohort.

10 | THE GUT MICROBIOME IN PRETERM INFANTS

Gut microbiota in preterm babies is substantially different to that of term babies, largely due to the NICU environment and medical

interventions including caesarean section, antibiotics and feeding practices. As such, preterm infants demonstrate reduced gut microbiota diversity, stability and presence of bacteria associated with health (eg, *Bifidobacterium*), and increases in potential pathogens such as Enterobacteriaceae and Proteobacteria.³⁵ These changes are most pronounced in those infants who develop NEC and LOS³⁶ with changes seen between those who do and do not develop NEC, and with similar changes also seen in the same infant in the days immediately preceding NEC diagnosis.³⁷ This combined with studies that show lower rates of NEC and LOS in infants receiving probiotic supplementation, underpin the importance of the microbiome to health in this population.

11 | CLINICAL RELEVANCE AND MODIFICATION OF THE MICROBIOME

Understanding the gut and breastmilk microbiome and their interactions with the developing immune system is key to developing therapeutic approaches to modify the microbiome with a view to improving the health of the preterm infant and reducing the risk of NEC and LOS.

To date, there have been limited therapeutic options to treat or prevent NEC despite numerous interventional trials. Indeed, aside from use of breastmilk, the potential benefit of probiotics and introduction of standardised feeding guidelines, no other specific beneficial interventions have been conclusively identified. It has been hypothesised that several of the individual components of breastmilk could be administered to reduce risk or severity as summarised in Table 1.

The use of probiotics to promote a more beneficial microbiome and potentially reduce NEC remains controversial despite 44 trials including 22 000 infants and extensive meta-analysis.³⁸ Reductions in NEC were not seen in a large UK trial,³⁹ but a different probiotic was found to significantly reduce NEC in a large Australia and New Zealand trial,⁴⁰ suggesting precise strains and cross-contamination in the NICU might be important. Overall, meta-analysis has shown a benefit in administration of probiotics for the prevention of NEC⁴¹ with overall risk reduction of 0.57 (CI 0.47-0.7) and some units have adopted their routine use. Underpinning mechanistic microbiome work in probiotic studies is rare, but Abdulkadir et al (2016) showed that supplementation with probiotics resulted in modification of the microbiome leading to long-term colonisation of the gut with *Bifidobacterium*.⁴² This was replicated by a sub-analysis of the ProPremis randomised control trial which showed probiotic supplementation (with *Bifidobacterium longum* subsp. *infantis*, *Bifidobacterium animalis* subsp. *lactis* BB-12 and *Streptococcus thermophilus*) resulted in increased abundance of *Bifidobacterium* spp in the gut microbiota of very preterm infants.⁴³

The supplementation of human milk (either mothers' own or pooled donor) with generic or specific HMOs could have potential important therapeutic use as summarised below (Table 2).²⁸

TABLE 1 Current interventions that reduce NEC or LOS likely to involve modulation of the microbiome

Intervention	Possible mechanisms of action	Level of evidence ^a
Maternal breastmilk	Multiple mechanisms involving macro- and micronutrients, functional components and milk-associated microbes.	LOE 1a: Multiple studies, trials and meta-analysis. Recommended by several professional organisations. ²²
Oropharyngeal colostrum	Immunological impacts on oropharyngeal lymphoid tissue and direct modulation of oral microbes.	LOE 2a: Cochrane systematic review concluded low-quality data showed no difference, should be validated in larger studies. ⁴⁴
Donor human milk	Exposure to functional components not present in formula milk; avoidance of bovine antigens.	LOE 1a: Meta-analysis. Recommended by several professional organisations. ³⁰
Multi-strain probiotics	Alter balance of microbiome in favour of non-pathogenic bacteria.	LOE 1a: Meta-analysis. Recommended by ESPGHAN position statement. ⁴¹
Preventative administration of enteral antibiotics	Reduces aberrant gut colonisation in an immunocompromised host.	LOE 1a: Meta-analysis does not recommend routine use. ⁴⁵
Reduce empiric antibiotic use	Antibiotics alter normal postnatal gut colonisation.	LOE 3b: Retrospective case-control studies suggested a reduction in prolonged empiric antibiotics without proven blood culture data increased risk of NEC, not widely validated.
Human milk-based fortifier	Reduce exposure to bovine milk products.	LOE 2b: One RCT (127infants) did not show reduction in NEC. ⁴⁶ More data needed.
Bovine lactoferrin	Breakdown products have antimicrobial properties.	LOE 1a: Largest RCT showed no reduction in NEC, combined with meta-analysis showed no benefit but a significant reduction in fungal sepsis (with a trend towards reduction in all LOS). ¹¹ Not proven to be effective when used routinely.
Oral immunoglobulin	Increase IgG/ IgA available in gut to bind bacteria and modify microbiome.	LOE 1a: Cochrane database review showed no reduction in NEC with IgG/IgA-IgG combination. ⁴⁷ Not proven to be effective.
Growth factors	EGF has been shown to protect rat pups against NEC-like injury. Administration of amniotic fluid to mouse models reduced severity of NEC due to activation of EGF receptor. ³³	LOE 5: Requires more validation in human infants.
	Erythropoietin protective against NEC in a rat model. ⁴⁸	LOE 5: Requires validation in human infants.
	G-CSF supports clonal maturation of neutrophils. ⁴⁹	LOE 5: Small pilot study: no progression of mild NEC in preterm infants who received recombinant G-CSF, needs replicated.
Cytokines	Enteral TGF- β can protect mouse pups against NEC-like injury as it suppresses cytokine production by macrophages. ⁵⁰	LOE 5: Requires replication in human infants.

Abbreviations: LOS, late-onset sepsis; NEC, necrotising enterocolitis.

^aLevel of evidence determined as per Oxford Centre for Evidence-based Medicine Levels of Evidence 2011.⁵¹

TABLE 2 Potential future interventions that might reduce NEC/LOS that act via the microbiome

Intervention	Possible mechanisms	Available evidence
Prebiotics, for example fructose, galactose, lactulose, inulin. HMOs	Promote growth and metabolic activity of subspecies of microbes such as <i>Bifidobacterium</i> spp. Provide nutrients to brain.	Rat models show specific HMO patterns associated with reduced rate of NEC, ³⁴ replicated in seminal study in human infants. ²⁴ Requires replication in larger setting.
Synbiotics (a combination of prebiotic and probiotic) for example inulin and a probiotic	Combined mode of action of prebiotics and probiotics resulting in a significantly increased growth of potentially beneficial bacteria.	Little data.
Postbiotics (supplementation with bacterial metabolites derived from probiotic microbes)	Hypothesised to reduce risk of sepsis related to giving live organisms whilst still conferring beneficial effects.	Recent small RCT compared infants formula-fed standard formula or <i>Lactobacillus paracasei</i> fermented formula and found increased sIgA in the fermented formula group and associated reduced microbial diversity. Requires replication in larger studies. ⁵²

12 | CONCLUSIONS

The benefits of breastmilk are apparent not only in the preterm population to reduce risk of NEC and sepsis, but also in the longer term to reduce obesity, improve cardiovascular outcomes, reduce risk of immune-mediated illness and potentially result in improved cognitive outcomes. Some of these benefits may be mediated by the key role that breastmilk has in modification of the gut microbiome. The extent of the benefits conferred by alternative feeds when mother's own milk is not available, including donor human breastmilk or supplemented bovine formula, is yet to be determined.

Overall, the benefits of immunomodulatory components in breastmilk are key to understanding the potential modifiable factors, with a view to therapeutic and clinical implications.

CONFLICT OF INTEREST

CJS declares performing consultancy for Astarte Medical and honoraria from Danone Early Life Nutrition. NDE declares institutional research funding from Prolacta Biosciences and Danone Early Life Nutrition, and honoraria from Danone Early Life Nutrition, and Nestle Nutrition Institute. The other authors declare that they have no competing interests.

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