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Early-Life Gut Microbiome—The Importance of Maternal and Infant Factors in Its Establishment

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Abstract

The early-life microbiome is gaining appreciation as a major influencer in human development and long-term health. Multiple factors are known to influence the initial colonization, development, and function of the neonatal gut microbiome. In addition, alterations in early-life gut microbial composition is associated with several chronic health conditions such as obesity, asthma, and allergies. In this review, we focus on both maternal and infant factors known to influence early-life gut colonization. Also reviewed is the important role of infant feeding, including evidence-based strategies for maternal and infant supplementation with the goal to protect and/or restore the infant gut microbiome. (*Nutr Clin Pract.* 2020;35:386–405)

Keywords

asthma; developmental disabilities; gastrointestinal microbiome; human milk; infant formula; microbiota; obesity; pediatrics; prebiotics

Introduction

With its dynamic composition and function, the gut microbiome plays a key role in health and disease.[1] The first 3 years of life are crucial to the early establishment of the gut microbiome, which continues to develop throughout childhood into adolescence.[2,3] During early life, the gut microbial composition rapidly changes, largely because of the infant's diet transitioning from milk to solid foods.[4-6] As initial intestinal colonization coincides with the development of the gut immune system, gut microbial disturbances during this crucial period can potentially lead to adverse health outcomes later in life.[1] In the past decade, research has focused on early gut microbial colonization, acquisition, maturation, and factors that may affect these processes. Illustrated in Figure 1 are multiple modifiable and nonmodifiable factors known to influence early infant gut colonization. This review aims to summarize the process of early colonization, discussing prenatal and postnatal determinant factors associated with neonatal health outcomes, as well as how maternal or infant supplementation with prebiotics and/or probiotics may target and protect the neonatal gut microbiome.

The Infant Gut Microbiome

Throughout the first few years of life, the complexity of the neonatal gut microbiome shifts from being dominated by bifidobacteria and *Lactobacillus* to becoming enriched in *Bacteroides* and Firmicutes, like that of an adult.[7] This coincides with increased functionality of the microbiome, with a gain in genes relevant for plant polysaccharide metabolism, which primes the infant microbiome even before solid foods are presented.[8] Following the introduction of solid foods, a sustained shift in gut microbial composition and diversity occurs, with an increase in Bacteroidetes. Short-chain fatty acids (SCFAs), generated by the fermentation of dietary fermentable fibers by the gut microbiota, increase with the

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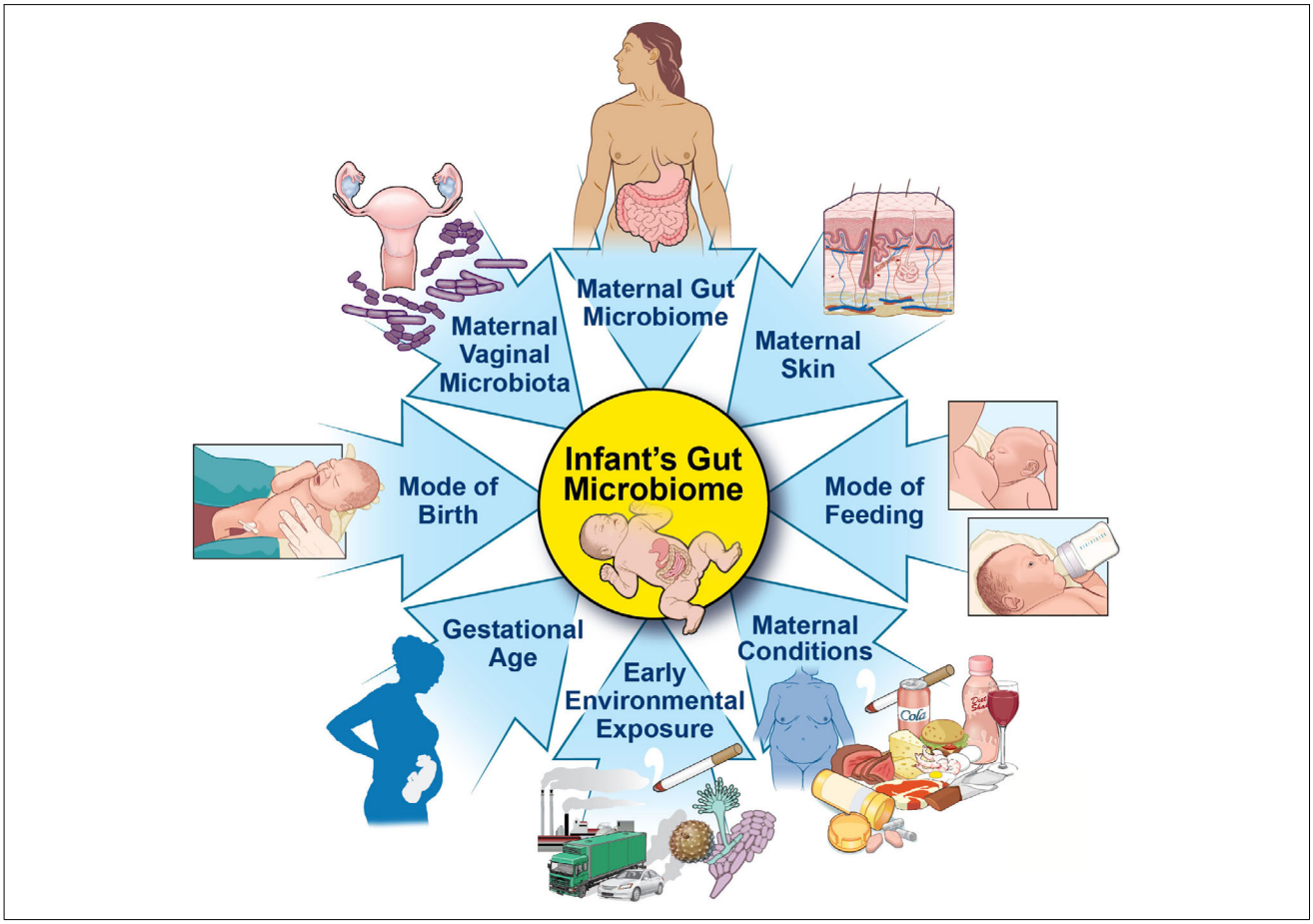

Figure 1. Known factors influencing the development of the infant microbiota. Several factors play a role in shaping of the bacterial seeding in infants early in life. Gut microbial composition initiates from the gestational period, being influenced by gestational age, mode of delivery, and mode of feeding. Maternal conditions such as maternal body weight, diet, and risky lifestyle during gestation and lactation and other factors such as genetics, maternal vaginal, and skin microbes also influence the microbial composition of the infant. Early-life factors such as antibiotics and environmental exposure influence the trajectory of the developing microbiota.

introduction of solid foods, along with the expression of genes relevant for carbohydrate metabolism, vitamin biosynthesis, and xenobiotic degradation.[8] Characterizing the metagenomic profiles between pediatric and adult microbiomes, Hollister et al found children were enriched with genes that may support ongoing development, such as those for de novo folate synthesis and amino acid metabolism, whereas adults were enriched with genes involved with pathways for oxidative phosphorylation, lipopolysaccharide biosynthesis, flagellar assembly, and steroid hormone biosynthesis.[9] Although they reported a 35%–46% taxonomic similarity between gut microbe communities in children, there was a >90% similarity in the genes categorized in the same groups and pathways detected from different organisms.[9] This suggests that the functional capacity of microbes is more highly conserved than microbial composition in the pediatric gut microbiome.

Among the colonizing commensal gut bacteria in early life, *Bifidobacterium* dominate the gut microbiome in a healthy infant.[10] Bifidobacteria and lactobacilli contribute to both natural and acquired immune responses in healthy newborns. Studies report an association between lower levels of fecal bifidobacteria in early life with a greater risk of noncommunicable diseases (eg, atopic disease and obesity) later in life.[11,12] Bifidobacteria presence is minor in the human adult gut microbiota,[13] indicating that *Bifidobacterium* seem specific to early life. Various factors influence *Bifidobacterium* abundance in the infant gut, including geographical location, with reduced numbers in infants from developed nations[14]; mode of delivery[15]; method of first feeding[16,17]; and intra-postpartum antibiotic usage.[18]

Early Colonization in Healthy Newborns

The establishment of the gut microbiota is integral in maintaining intestinal homeostasis in the newborn, a time that is critical for immunological and physiological development.[19]

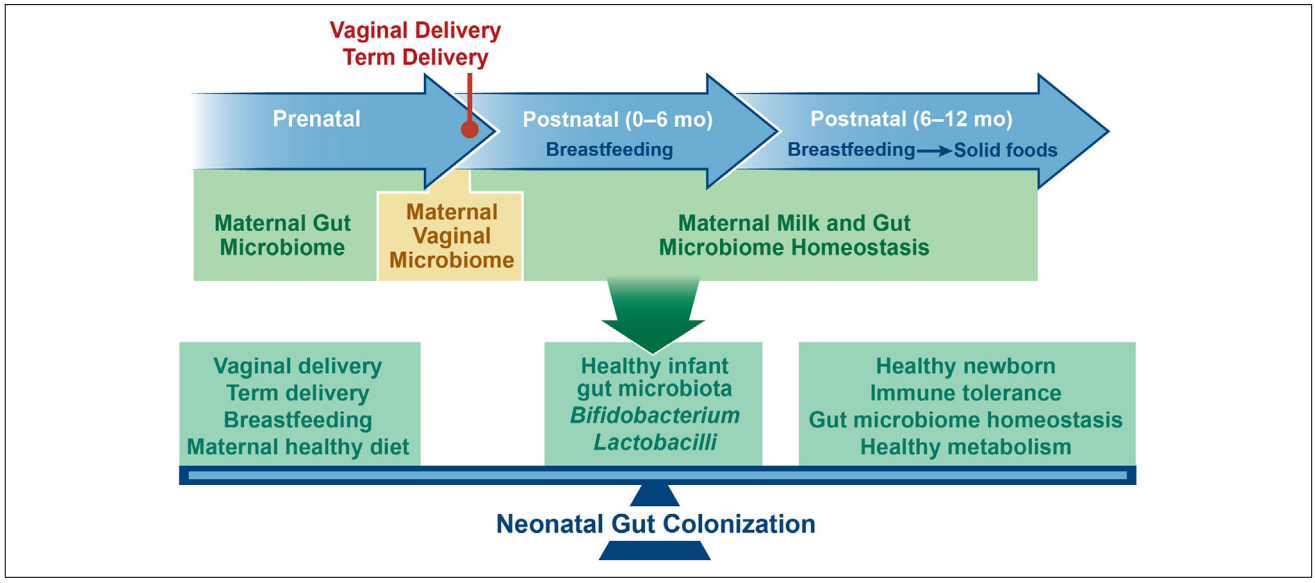

Figure 2. Maternal and early-life factors and healthy-type neonatal microbiome. Neonatal gut bacterial colonization is affected by maternal gut microbiome during gestation and lactation. Thus, healthy-type infant gut microbiomes are related to the healthy maternal gut, vaginal, and milk microbiome transferred during gestation, vaginal delivery, and breastfeeding.

The gut microbiota assists with essential nutrient synthesis and absorption,[20,21] generates SCFAs that serve as an energy source for colonocytes,[22-24] maintains the intestinal mucosal barrier and protects against pathogenic bacteria and endotoxin translocation, stimulates immune-system maturation,[25] provides anti-inflammatory signals to the host,[26] and influences infant growth.[23,24] Disruption in the gut microbiota (ie, gut dysbiosis) has been linked to necrotizing enterocolitis, as well as some chronic diseases, including obesity, diabetes, inflammatory bowel disease, cancer, allergies, asthma,[1] and neurological diseases associated with the gut-brain axis.[27]

In Utero Colonization

Contrary to prior belief, the intrauterine environment is not sterile.[28] Nonpathogenic bacteria is detected in the placenta, umbilical cord,[29,30] and the meconium of the healthy newborns, independent of birth mode of delivery,[28] and its composition is associated with the gestational age. *Lactobacillus* and *Bifidobacterium* DNA have been detected in infants delivered vaginally and by cesarean section (C-section), highlighting bacterial translocation from maternal gut to placenta.[29] Interestingly, with a healthy pregnancy, the intrauterine bacteria appears to be similar to that of the mother's oral cavity.[31] However, intrauterine infection has been reported to be associated with a leaky gut, confirmed by finding maternal gut microbes in the amniotic fluid of women with premature membrane rupture.[32] This suggests microbial translocation from a maternal leaky gut to the uterus and placenta. Animal experiments with maternal provision of bacteria orally found the same bacteria in the placenta[33] and meconium of the pups delivered by sterile C-section.[28] These data demonstrate mother-to-fetus transmission of bacteria during gestation. The placenta has been also shown to contain SCFA and their receptors,[34] indicating a potential role of microbial by-product interactions during gestational development. Taken together, these findings suggest that initial small-scale colonization occurs prior to birth. Potential mechanisms regarding the maternal-to-fetus microbiome interactions and delivery outcomes remain to be elucidated.

Although increases in gut microbial density and diversity are suggested to be biologically determined,[14] a range of various factors influence the development of a healthy infant microbiota, as illustrated in Figure 2. There is a common universal pattern of early colonization of the infant's gut in vaginally born healthy children.[14] Aerobic and facultative bacteria dominate the newborn's gut, and in an age-dependent process, a reduction in oxygen enables anaerobic bacterial growth,[35] a process that is independent of diet.[14] Gestational age affects infant gut bacterial composition. In a preterm infant, delayed intestinal bacterial colonization[36] and an immature gastrointestinal tract might increase susceptibility to infection.[37] Geographical differences appear to influence infant gut colonization. The merged data published globally provide an overall view of geographical differences in the gut microbial composition of infants. In a study reported by Korpela and de Vos, after adjusting for age, an American cohort had a relatively high abundance of *Bacteroides* spp and enterobacteria, with significantly low levels of *Bifidobacterium* subsp during the

first 6 months of life.[14] However, data from African, Asian, and Central European cohorts show high abundances of bifidobacteria and lack of Clostridia during the first year of life, implying a slow maturation pattern in the gut microbiota in children from these regions. Geographical differences in both maternal and infant dietary practices may influence early gut colonization.[14]

Infant Mode of Delivery

Infant mode of delivery influences early-life gut microbial composition.[38,39] Infants delivered vaginally are colonized with bacteria present in the maternal vagina,[38,40] whereas those delivered by C-section are colonized with bacteria similar to maternal skin and oral cavity.[41,42] Compared with vaginally delivered infants, C-section–delivered infants are reported to have decreased α diversity,[43] with a delayed and reduced colonization of *Bacteroides* persisting over time[45] or being undetectable, indifferent to breastfeeding.[6] Interestingly, a greater abundance of *Clostridium difficile*,[44,45] bacilli, and enterobacteria are reported with C-section delivery.[14]

Gut microbial differences associated with infant mode of delivery may disappear over time.[41] However, more importantly, early-life variances may be related to the incidence of noncommunicable chronic diseases that appear later in life.[1] C-section–delivered infants are reportedly at a greater risk of developing asthma, obesity, and type 1 diabetes.[46] A recent animal study reported a link between immune-system malfunction, microbial alterations, and increased appetite in a mouse model.[47] This study showed mice with a genetically impaired innate immune system exhibited significant alterations in their gut microbial composition, which was correlated with hyperphagia, and clinical features of metabolic syndrome (eg, hyperlipidemia, hypertension, insulin resistance, and increased adiposity). Alterations in immune system development and function as a result of gut colonization differences between delivery modes demonstrated in humans[48] may partially explain C-section–associated incidence of noncommunicable diseases later in life.[49] Conversely, a recent study conducted by Ahlqvist et al revealed no significant clinical association between C-section and developing obesity later in life in young adult men.[50] Further longitudinal studies considering more maternal factors as well as gut microbiome differences during development are warranted to show the association between mode of delivery and obesity later in life.

Infant Feeding Methods

Maternal milk. Among the factors affecting early colonization, mode of infant feeding is of high importance. Mother's own milk is considered the gold standard for infant nutrition, as it meets the infant's nutrition requirements during early life.[51,52] Maternal milk contains all the nutrients and vitamins required for optimal infant development, including complex protein, fat, and carbohydrate.[53] Additionally, maternal milk contains a myriad of biologically active molecules that are critical and protective in early life[54] (Table 1).

Table 1. Bioactive Molecules in Maternal Milk.[54,218,219]

Oligosaccharides
Microbes
Immunoglobulin A
Antimicrobial peptides (lactoferrin, lysozyme, lactadherin, mucin)
Antioxidants
Stem cells
Glycoconjugates

Table 2. Microbes Identified in Human Milk.[61,62]

Staphylococci
Streptococci
Corynebacteria
Propionibacteria
Lactobacillus spp
Bifidobacterium spp

Maternal milk—Commensal microbes. Recent studies support that human milk is not sterile and is a primary and continuous source of colonizing bacteria to the infant's gut.[55,56] Mother-to-child transmission studies, with and without culture consideration, support that bacterial transfer from mother to infant occurs via breast milk.[56-59] This was demonstrated by the presence of the same bacterial strain identified in mother's milk and their breastfed infant's stool.[60] Pannaraj et al also showed that maternal transfer of bacteria via breast milk has a greater impact on the newborn's early colonization compared with areolar skin.[56] Although the bacterial composition of human milk is low, with <3-log colony-forming units (CFU)/mL, it is physiologically important.[61,62] Following birth, breast milk microbiota is a main factor that drives the acquisition and evolution of the gut microbiota in early life. Breast milk contributes significantly to the metabolism, development of gut integrity, and maturation of the immune and neuroendocrine systems.[63-67]

Breast milk contains a rich microbiota composed of viable skin and non-skin gram-positive bacteria (Table 2). Streptococci (*mitis* and *salivarius* groups) and coagulase-negative staphylococci are among the dominant bacteria in both human milk[59,68-70] and the feces of breastfed infants.[71-73] These microbes are potentially able to compete with the establishment of undesired pathogens (eg,

Staphylococcus aureus) in the infant gut.[74,75] Similar pathogen exclusion is noted through fermentation of the antimicrobial compound glycerol monolaurate found in breast milk.[76] *Propionibacterium acnes* can prevent the growth of *S aureus*.[77] *Bifidobacterium* and *Lactobacillus* spp in breast milk are noted to activate immunoglobulin A (IgA)–producing plasma cells in the neonatal gut.[61] It has been hypothesized that *Bifidobacterium* control inflammation through mucosal host-microbe crosstalk.[78] An association was shown between low levels of intestinal *Bifidobacterium* microbiota during infancy and an increased risk of atopy later in life.[79-81] The original source of breast milk microbiota is unclear.[53] The entero-mammary pathway is one hypothesis that proposes a selective colonization of the mammary gland by cells of the immune system.[62] The similarity between the bacterial composition of maternal stool and breast milk supports this concept.[82-84] Clinical studies demonstrating ingested probiotic strains were identified in maternal breast milk further support this hypothesis.[85,86] More information about the origin of milk microbes can be found in this review by Moossavi et al.[87]

The composition of human milk, including the structure of microbial community,[53] produced by a healthy woman is personalized. Each mother's own milk provides specific requirements for their infant according to gestational age, lactation stage, environmental exposures, geographical location,[88-90] and daily breastfeeding practices.[55,91] Gestational age has been reported to influence the concentrations of *Bifidobacterium* spp in maternal breast milk, with lower levels in preterm deliveries. However, the entire range of the microbial groups detected in breast milk are similar with both term and preterm deliveries.[61] Therefore, maternal milk is the preferred mode of feeding for all infants, both term and preterm.[51,92-94]

Maternal milk microbiota and infant mode of delivery. Infants born by C-section had increased total bacteria counts, particularly *Streptococcus* spp,[95] and reduced levels of *Bifidobacterium* spp[61] that persisted for up to 6 months after lactation.[88] A higher abundance of *Staphylococcus* reported in the gut bacteria of infants delivered by C-section has been speculated to contribute to a higher incidence in methicillin-resistant *S aureus* skin infections compared with that in infants delivered vaginally.[96] It has been suggested that maternal milk dysbiosis could exacerbate C-section delivery–induced infant gut dysbiosis.[97] Interestingly, breast milk dysbiosis was only observed in mothers who underwent an elective C-section; the breast milk microbiota in mothers who underwent an emergency C-section was comparable to that of mothers who delivered vaginally. Therefore, breast milk microbial alterations might be attributed to the physiological stress and/or hormonal changes that occur with labor or an emergency C-section.[88] Vaginal delivery might induce intestinal permeability and enhance the bacterial translocation from the gut to the mammary gland and breast milk.[97] A review by Neu et al found most infants delivered by C-section were not breastfed.[46] Therefore, in addition to a no-physiological initial colonization during childbirth, the absence of early nutrition support for the infant microbiome due to delayed lactation, breast milk dysbiosis, or the lack of breastfeeding might contribute to a long-lasting dysbiosis in C-section–delivered infants. Further research investigating whether modulation of maternal breast milk microbiota could affect the infant's gut microbiome and their health in elective C-section–delivered infants, mimicking that of mothers who delivered vaginally, is warranted.

Maternal milk—Prebiotics. Human milk contains human milk oligosaccharides (HMOs), a type of prebiotic. As an energy source for commensal gut microbes,[52] HMO fermentation stimulates the growth of bifidobacteria, *Lactobacillus*, and *Bacteroides* within the infant gastrointestinal tract.[52] Furthermore, the abundance of specific bacterial taxa in human milk, such as *Staphylococcus* species, might increase the levels of microbial by-products (eg, SCFAs) by fermenting HMOs.[53] HMOs have also been shown to prevent neonatal diarrhea and respiratory tract infections.[98] How maternal conditions influence HMOs in breast milk, microbial by-products, gut microbiome composition, and health outcomes is discussed later.

Donor human milk. Donor human milk is viewed as superior to infant formula for seriously ill infants, when maternal milk is unavailable or insufficient for appropriate infant growth.[51,99-101] Donor human milk supports infant growth and development, including neurodevelopment, and protects against various diseases, including necrotizing enterocolitis.[102,103] Milk donated to a milk bank is provided to fragile, hospitalized infants. Using questionnaires, human milk donors undergo screening regarding their lifestyle, disease, and risk factors, as well as microbiological screening (eg, HTLV-I and HTLV-II, syphilis, hepatitis B and C, human T-lymphotropic virus 2, human papillomavirus, herpes simplex virus types 1 and 2, *Chlamydia trachomatis*, *Neisseria gonorrheae*, or *Trichomonas vaginalis*), and the donated milk undergoes prepasteurization and/or postpasteurization microbiological analysis.[104] As recommended by the American College of Pediatricians and the Centers for Disease Control, to further assure microbiological safety, donor human milk is pasteurized (56–62 °C for 30 minutes) to destroy all non–spore-forming microbes that may contaminate the milk via poor hygiene, from the extraction devices during collection, or maternal transfer.[105,106] Although pasteurization destroys the microbes in the donor milk, the biologically active components of the human milk (Table 1) are preserved.[61] An approach to increase the bacterial richness of pasteurized donor milk is by

personalization. This includes adding 10% of the infant's maternal milk and incubating it for 4 hours to increase the levels of some bacteria that were naturally found in the maternal milk.[68] Collecting the milk by breast pump can increase the bacterial count of milk compared with that expressed manually.[107] Maternal milk can be frozen at −20 °C for approximately 6 weeks without any adverse effects on breast milk quality and bacteria abundance.[107]

Infant formula. Significant compositional distinction is found between the gut microbiota of breastfed infants and formula-fed infants. Earlier studies found that the gut of a breastfed infant was rich in gram-positive bacteria, acidophilic "*Bacillus bifidus*" (*Bifidobacterium*).[109] In the first month of life, bifidobacteria and staphylococci predominate in the intestine of breastfed infants, whereas enterococci, Coliform, and clostridia are rich in formula-fed infants.[72] Grönlund et al (2007) reported that the concentration of *Bifidobacterium* spp in breastfed infants can increase up to 60%–90% of the total fecal microbiota.[110] An enriched population of bifidobacteria competes with other species in the infant gut and produces nutrients vital for early development, including sialic acid. Sialic acid (*N*-acetyl-neuraminic acid) is an essential nutrient for optimal brain development and cognition.[111,112] Ruhaak et al (2014) found the presence of sialylated oligosaccharides in the blood of infants that might have originated from the hydrolysis of HMO.[113] The gut microbiota in early life is composed of predominantly *Lactobacillus*, *Staphylococcus*, *Megasphaera*, and Actinobacteria in breastfed infants, whereas Clostridiales and Proteobacteria are more abundant in formula-fed infants. Formula feeding was also shown to enrich *Atopobium* and *Bacteroides* but reduce *Bifidobacterium*.[114] Feeding infants with formula reduced total gut bacterial numbers but increased gut microbial diversity compared with breastfeeding. Lower gut microbial diversity in breastfed infants is attributed to the unique HMO contained in breast milk, which may serve only a limited number of gut microbes.[115] Breastfeeding was also shown to influence the oral bacteria in infants.

These data suggest that the prebiotics and probiotics in breast milk may play a role in supporting infant health. Taken together, these data support the notion that adding these components to infant formula might be an approach to improve health outcomes in formula-fed newborns that do not have access to human milk.

Maternal and Early-Life Factors Influencing Maternal Milk Composition, Early Colonization, and Neonatal Health Outcomes

Multiple factors are associated with maternal milk HMO and microbiota and with infant gut microbiota (see Figure 1).[116] However, in some cases, there is no explanation for microbial changes in the infant gut, particularly the reduction in levels of *Bifidobacterium*.[116] This highlights the potential role of other factors, like maternal chronic conditions or risky lifestyle, that may influence the maternal gut microbiota, maternal milk, and early infant gut colonization (Figure 3).

Maternal Obesity

Infant birth weight can vary between those born from overweight vs normal–body-weight mothers, and this transference of maternal phenotype corresponds to the transfer of the newborn's gut microbiota.[117] Intergenerational transmission of the obesogenic microbes hypothesis has been supported by several studies.[118,119] Obesity is characterized with an imbalance in the Firmicutes-to-Bacteroidetes ratio in the gut.[120,121] Birth cohort studies reveal that infants born from overweight or obese mothers were abundantly colonized with the bacterial genera belonging to the phyla Firmicutes, especially of the Lachnospiraceae family, and had a greater risk of becoming overweight by 1–3 years of age.[119] Experimental data in obese mice support that Lachnospiraceae may contribute to the development of obesity[122] and adipocyte inflammation[123] and promote diabetes.[124] *Bacteroides* colonization of the infant gut is associated with reduced growth in early life.[125] Some studies have reported elevated levels of *Bacteroides* in the stool from both obese mothers[126] and infants whose mothers were overweight or obese.[118] However, Santacruz et al reported reduced numbers of *Bacteroides*, belonging to the phylum Bacteroidetes, in overweight compared with normal-weight women.[117] More studies are required to explain discrepancies in these data and their significance.

Levels of *Staphylococcus*,[117] Enterobacteriaceae, and *Escherichia coli* have been reported to be elevated in overweight compared with normal-weight pregnant women.[117] Animal experiments suggest that higher levels of gram-negative bacteria in the gut are a result of endotoxemia and inflammation induced by obesity.[127] Excessive gestational weight gain, defined as >11.5 kg in overweight and >16 kg in normal-weight women, was associated with an expansion of *Bacteroides*,[126] Enterobacteriaceae, and *E coli* and a reduction in *Bifidobacterium* and *Akkermansia muciniphila*.[117] Thus, these data suggest that maternal gut microbiota might be a factor contributing to weight gain during pregnancy beyond the maternal nutrition.[128] Moreover, a significant reduction in the community of bacteria involved in metabolic signaling and energy regulation, including *Enterococcus*, *Acinetobacter*, *Pseudomonas*, and *Hydrogenophilus*, have been found in infants born to overweight or obese mothers.[118] Infant gut dysbiosis associated with maternal obesity has been shown to increase gut permeability and directly initiate pathways of nonalcoholic fatty liver disease.[129]

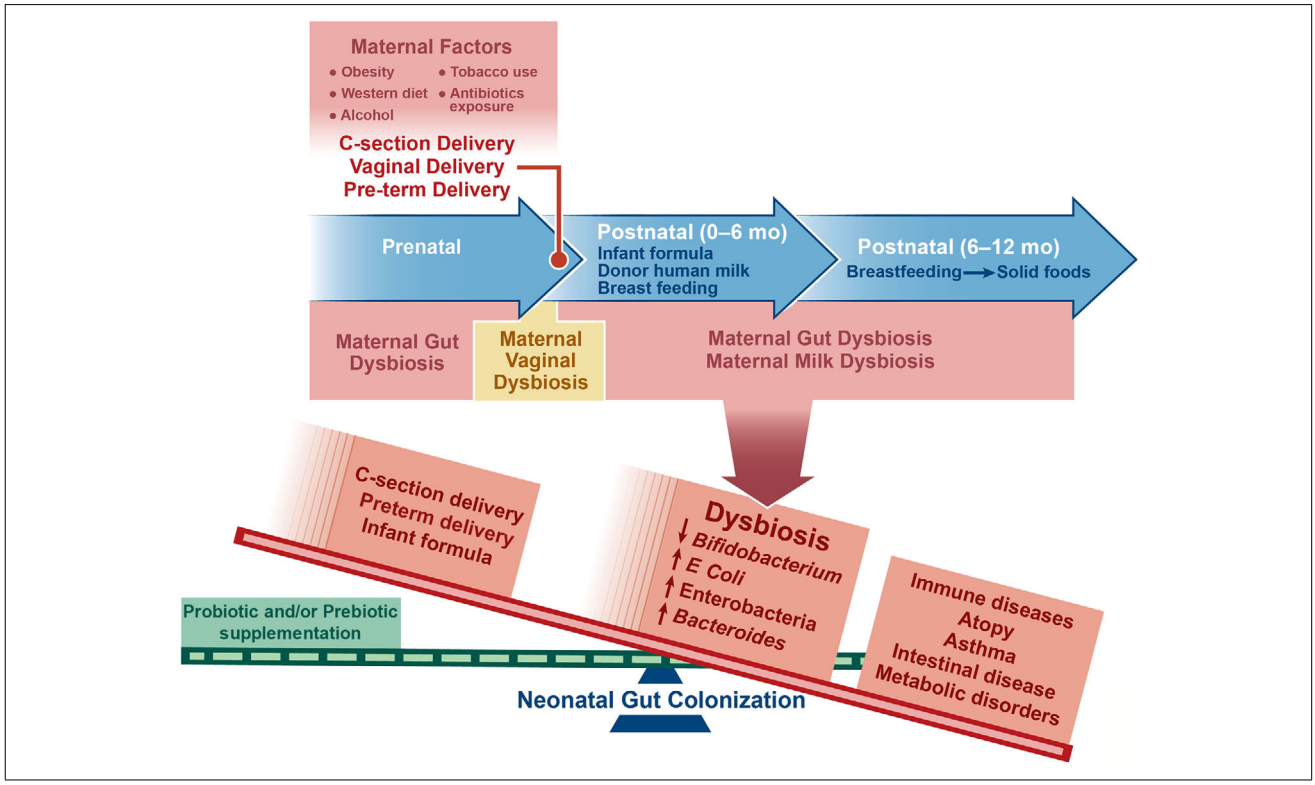

Figure 3. Maternal and early-life factors and dysbiosis in neonatal gut microbiome. Maternal gut and milk dysbiosis induced by maternal conditions, such as maternal Western diet, obesity, alcohol, and tobacco use, can be vertically transmitted to offspring. Cesarean section (C-section), preterm delivery, and infant formula are other factors for imbalanced infant gut bacterial community, especially *Bifidobacterium*. The potential role of selective supplement with prebiotics and probiotics in both mothers and infants makes them a good therapeutic strategy for infants at the risk of gut dysbiosis.

Maternal obesity–induced infant gut dysbiosis has been reported to be more evident before 9 and 18 months[130] and to differ by mode of delivery. In a study by Mueller et al, vertical transmission of higher levels of *Bacteroides* was observed in overweight pregnant women to their newborns during vaginal delivery. Reduced levels of *Bacteroides* was detected in the meconium soon after birth in infants delivered by C-section.[118] C-section–delivered infants from overweight mothers are at higher risk of becoming overweight later in life than infants born vaginally to overweight or obese mothers.[119]

Maternal weight status also might affect maternal milk composition.[131,132] Recent data associating the milk metabolome with both maternal and infant obesity suggest that obesity-related differences in human milk composition might contribute to early childhood obesity.[133] Cabrera-Rubio et al detected higher total bacterial counts, expansion of *Staphylococcus* and *Lactobacillus*, and reduced levels of *Bifidobacterium* in the milk of obese compared with normal-weight women during the first 6 months of lactation.[88] They suggested that the alterations in the microbial composition of breast milk from an obese mother might be an additional mechanism explaining the intensified obesity risk in infants born to obese and overweight mothers. Limited studies have investigated the role of maternal or infant probiotic supplementation on the breast milk as a means to mitigate the obesity-related alterations.

Maternal Diet

Maternal diet has been shown to be linked to infant gut microbiota. Population-based human longitudinal cohort data showed that a maternal high-fat diet altered early bacterial colonization independent of maternal obesity.[134] In association with a maternal high-fat diet, the neonatal meconium microbiome varied with a significant relative depletion in *Bacteroides* immediately post partum, which persisted until 6 weeks of age.[134] Data from animal experiments also showed that a high-fat diet during gestation and postweaning period caused significant gut dysbiosis early in life.[135] This highlights the important role of a maternal high-fat diet rather than just maternal obesity per se in shaping the gut microbiota early in life.[135] Maternal high-fat diet during gestation and lactation might also increase the susceptibility to immune-mediated diseases and some metabolic consequences for the offspring, partially through

alteration in responses to microbes.[136] A study conducted by Val-Laillet et al demonstrated significant programming effects of a maternal Western diet during gestation and lactation on microbiota fermentation activity in sows. This resulted in a significant drop in fecal SCFA levels in both sows and their piglets that persisted even after weaning.[137] Thus, these data suggest maternal dietary factors modulate both bacterial composition and their fermentation activity in the neonatal gut.

Limited data are available regarding the effects of other factors of a Western diet on maternal-infant gut dysbiosis, such as the influence of high sugar, sodium, and animal proteins. A combination of a high-fat/high-sugar diet led to gut dysbiosis in mice[138]; and dietary intake of refined sugars modulate the gut microbial composition to that of an inflammatory-type microbiota.[139] Since maternal milk microbiota is hypothesized to originate from maternal gut microbiota, the gut dysbiosis associated with the maternal diet might be transferred to maternal milk and further exacerbate dysbiosis seen in the early gut microbiome in breastfed infants. However, further studies are warranted to address the knowledge gaps regarding the role of maternal Western diet and breast milk microbiota. In contrast, the Mediterranean diet, which is enriched in fruits, vegetables, unsaturated fats, nuts, legumes, and whole grains, has been linked to improvements in the diversity and richness of the gut microbiota. This alteration in the gut microbiota might be associated with a large number of health benefits, including the prevention of metabolic diseases and cognitive disorders.[140] However, research investigating potential beneficial effects of a maternal Mediterranean diet during gestation and lactation on the infant's gut microbiota is lacking.

Maternal and Infant Antibiotic Exposure

Antibiotic exposure during gestation or in infant early life can have short-term and long-term influences on the developing infant gut microbiome.[141] The antibiotic-induced perturbation in gut microbiota of pregnant germ-free mice was transmittable to their offspring's gut. Although not directly exposed to the antibiotic, the mouse pups had alterations in their gut bacterial composition, which persisted for 21 weeks and made them more susceptible to developing colitis.[142] Persistence in maternal antibiotic-induced gut dysbiosis was also associated with alterations in T cells' functions in mouse pups.[143] Because microbial colonization in early life coincides with key neurodevelopment periods, it is suggested that antibiotic-induced perturbation in the infant gut microbiota might be linked to disruption in the gut-brain axis and potentially related to neurodevelopmental disorders, such as autism.[144]

Exposure to antibiotics is common in early life, with the average US child receiving 3 courses of antibiotics by 2 years of age.[145] Antibiotic provision in the first year of life is associated with increased body weight[146] and incidence of inflammatory bowel disease[147] and allergies.[148,149] These relationships in antibiotic-treated infants are presumed to be attributed to the antibiotics causing alterations in microbiota assembly during early life.[122] Antibiotic exposure throughout early life reduced the levels of Lachnospiraceae spp and other Clostridiales within infant's gut microbiota. Lachnospiraceae is known to produce butyrate and other SCFA[150] that regulate host immunity[151,152] and control body weight.[153]

Maternal treatment with antibiotics can also affect the breast milk microbiome. Intrapartum antibiotic exposure independently affects breast milk microbiota composition 1 month after delivery[97] and perturbs infant gut colonization.[154] *Bifidobacterium* has been reported to be uniquely detectable in the breast milk of mothers who did not receive antibiotics compared with those that did.[97]

Maternal treatment with antibiotics during lactation reduced breast milk microbial community, including lactobacilli and bifidobacteria, and caused overgrowth of mastitis-inducing opportunistic bacteria[155,156] associated with lower bacterial diversity in breast milk.[157,158] Many mothers cease breastfeeding early because of painful mastitis. Combined reduction in breast milk microbial diversity with early cessation of breastfeeding might lead to low intestinal diversity in the first weeks of life, which is associated with necrotizing enterocolitis.[159] Recent studies have shown that some lactobacilli strains isolated from human milk have been applied topically to treat or prevent mastitis,[160,161] suggesting their potential involvement in mammary homeostasis.

Other Prenatal Factors

Research is just beginning to investigate other maternal exposures on maternal and infant microbiomes. Maternal allergies may impact the microbiome in breast milk. A study by Grönlund et al noted that significantly depleted levels of *Bifidobacterium* in the breast milk of mothers with allergies were associated with the *Bifidobacterium* counts in their infants' feces.[110]

Labrecque et al investigated the effects of alcohol and artificial sweeteners on the gut microbiome during pregnancy in mice. They found that low to moderate levels of ethanol exposure in combination with artificial sweeteners reduced *Clostridium* and *Bacillus* and increased *Eubacterium* levels in the gut microbiota of pregnant mice compared with nonpregnant and control mice.[162]

Prenatal and postnatal exposure to environmental smoke increased gut bacterial richness in infants, particularly the Firmicutes phylum, at 3 months of age and was associated with a higher risk of overweight and obesity at 1–3 years of age.[163] Moreover, maternal smoking increased the

abundance of *Bacteroides* and *Staphylococcus* at 6 months of age; and early-life exposure to environmental smoke increased the levels of *Ruminococcus* and *Akkermansia* in infant gut microbiota.[163] Air pollution is also associated with immune, neurological, and metabolic disturbances during development that potentially can result in atopic disease, obesity, and autism. Although it is hypothesized that air pollution–associated diseases are related to disruptions in the neonatal gut microbial composition, in particular depletion of the phyla Firmicutes, further studies are needed to validate this theory.[164]

Jašarevi et al (2017) showed in mice that maternal stress in the first week of pregnancy caused lasting disruption in fecal microbial diversity, community, and composition in the vaginal microbiota during gestation and after birth.[165] Maternal stress-induced vaginal microbial disruption highlights the possibility for transmitting vaginal dysbiosis to offspring during birth. Results from rodent and primate models also support the link between prenatal stress and offspring intestinal microbiota.[165-167] In a cohort study conducted by Zijlmans et al (2015), the microbiota composition in vaginally born infants was associated with maternal prenatal stress, reported by mothers and evaluated by basal maternal salivary cortisol levels.[168] In this study, prenatal stress–exposed infant guts harbor significantly higher relative levels of proteobacterial groups related to pathogens and lower relative levels of *Lactobacillus* and *Bifidobacterium*. This alteration in the microbial pattern of maternal stress–exposed infants during pregnancy was associated with infant gastrointestinal symptoms and allergic reactions as reported by their mothers.[168]

Gestational diabetes mellitus (GDM) is associated with altered gut microbiota in pregnant women,[169] including *Bifidobacterium* spp.[170] Moreover, it has been shown that this GDM-related dysbiosis can be vertically transmitted to the offspring.[171] Wang et al (2018) evaluated the microbial communities of oral, intestinal, and vaginal samples of pregnant women with GDM and oral, pharyngeal, meconium, and amniotic fluid samples of neonates, the majority of whom were delivered via C-section. They found GDM-associated dysbiosis with maternal and neonatal gut bacteria at birth, as well as an association between the abundance of several predominant bacteria and values of oral glucose tolerance tests.[171]

Medical interventions such as chemotherapy reportedly impact the breast milk microbiome. A single case study found breast milk samples collected from a lactating woman undergoing a course of chemotherapy for Hodgkin's lymphoma contained reduced levels of genera *Bifidobacterium*, *Eubacterium*, *Staphylococcus*, and *Cloacibacterium* and expanded levels of *Acinetobacter*, Xanthomonadaceae, and *Stenotrophomonas*.[172] *Eubacterium* is a butyrate-producing bacteria[173] that plays a critical role in infant health.[174] Further larger cohort studies are warranted to examine the chemotherapy-associated changes to lactating mothers and the consequences for the microbiome and long-term health of infants.

All these studies highlight the importance of early-life microbiome formation and its relationship to maternal factors, which offers a therapeutic approach by maternal intervention, therefore modulating initial microbial colonization to diminish the risk of adverse health outcomes.

Maternal and Early-Life Prebiotic and Probiotic Supplementation

Prebiotics

Prebiotics are complex polysaccharides that escape digestion by the host and, upon reaching the distal gut, are fermented by and support the growth of commensal microbes.[175] Whereas human milk is rich in prebiotics (HMO), bovine milk also contains oligosaccharides, some of which are structurally similar to HMOs. Simeoni et al (2016) conducted a randomized, double-blinded study comparing an infant formula with or without added bovine milk–derived oligosaccharides, containing galacto-oligosaccharides and 3′- and 6′-sialyllactose, and the probiotic *Bifidobacterium animalis* subsp *lactis* strain CNCM I-3446 on tolerability and the ability to affect the gut microbiome. Breastfed infants served as a reference group.[176] Compared with the nonsupplemented formula, the supplemented formula was well tolerated and supported similar growth in newborns followed for 12 weeks. The supplemented formula stimulated a marked shift in endogenous *Bifidobacterium* (*B longum*, *B breve*, *B bifidum*, *B pseudocatenulatum*) and increased *B lactis* in the infant stool by 100-fold.[176] Adding various types of prebiotics (eg, fructo-oligosaccharides and galacto-oligosaccharides) to infant formula has also been shown to stimulate the growth of bifidobacteria and lactobacilli in the infant's gut to levels detected in breastfed infants.[177] By inducing a fecal microbiota that closely resembles the microbiota of breastfed infants,[178] prebiotic supplementation in infants may improve gut mucosal barrier, prevent enteric pathogen infection and bacterial translocation,[179,180] and ultimately support infant growth.[181] Both maternal and infant prebiotic supplementation have been reported in allergy prevention.[182]

Probiotics

A probiotic is defined as "a live micro-organism which, when administered in adequate amounts, confers a health benefit on the host."[183] Intervention with probiotics as a means to maintain a healthy gut ecosystem in early life has gained popularity over the past 2 decades. In attempts to mimic the composition of human milk, the design of some infant formulas includes the addition of probiotics.

Bifidobacterium and *Lactobacillus* species have been isolated from a healthy infant gut and added to the GRAS (generally recognized as safe) list by the Food and Drug Administration. *Bifidobacterium* and *Lactobacillus* are the species added to infant formulations. However, compared with breast milk, probiotic-supplemented infant formula contains a notably higher concentration of a limited number of probiotic strains.[61] Isolated from a healthy infant intestine, *B longum* subsp *infantis* (*B infantis*), *B longum* subsp *longum* (*B longum*), *B bifidum*, and *B breve* have a large repertoire of genes for the utilization of HMOs.[184] Important to note is that not all probiotics are equally safe, and the effects demonstrated from one strain cannot be extrapolated to another strain, even if they belong to the same species.[185]

Adding bifidobacteria strains to infant formula, from birth to 12 months, does not seem to compensate for differences in microbiota composition observed between breastfeeding and formula feeding in early life in full-term infants.[186] Moreover, bifidobacterial colonization in infant gut was not stable over time, because of competition within the ecosystem.[186] However, recent data in preterm infants showed that compared with *B animalis* subsp *lactis* supplement, *B infantis* significantly increased the fecal bifidobacteria in formula-fed preterm infants.[187] This might be because among bifidobacterial strains, *B infantis* is the only one that has the ability to consume HMOs because of its specific genome sequence.[188] Supplementation with *Lactobacillus rhamnosus GG* (LGG) into an extensively high casein-based commercially available formula, in infants at high risk for allergic manifestation associated with IgE-mediated cow's milk allergy, reduced the incidence of other allergy manifestations and improved the development of oral tolerance to cow's milk allergy.[189] This supplementation was more effective in combination with extensively high casein-based than with whey-based formula.[190] The beneficial effect of LGG might be attributed to the alterations in strain-level bacterial community structure expanding butyrate-producing bacterial strains in food allergic infants.[191]

Probiotic provision can also reach the infant if provided to the mother during gestation and lactation or if added separately to breast milk or infant formula. This section summarizes major studies involving maternal-to-infant microbial transfer via maternal provision of prebiotics and probiotics during gestation or lactation or via supplementation of infant formula and other vehicles (see Table 3). Information pertaining to commercially available products can be found in Table 4.

Maternal Probiotic Supplementation

Maternal supplementation with LGG (2×10^9 CFU/d) during late pregnancy (30–36 weeks) showed colonization with LGG in the infant's gut that was stable for up to 24 months in some cases. However, the role of breastfeeding on the colonization proficiency of LGG was not reported.[193] In contrast, LGG administration (1.8×10^{10} CFU/d), from 36 weeks of gestation until delivery, enhanced the intestinal colonization of *Bifidobacterium* species but not LGG in breastfed infants.[194] Interestingly, the transfer of LGG from mother to infant has been reported to establish more diversity in *Bifidobacterium* in the infants' gut.[195] Administration of LGG during gestation and then into their infants for 6 months with a maternal family history of atopic disease reduced the occurrence of atopic eczema by half in supplemented infants compared with a placebo group.[80] Therefore, it seems that factors such as the choice of probiotic strain and duration of supplementation affect the beneficial effects of maternal probiotic supplementation. Maternal dietary supplementation with the *Lactobacillus* strains during lactation lead to the isolation of such strains in maternal milk.[28,195] Furthermore, probiotic supplementation only during gestation resulted in the appearance of the bacteria in the fecal samples of their breastfed neonates, even in those born by C-section and no exposure to the vaginal microbiome.[192] This highlights the important role of breast milk in the transfer of microbes to the infants.

Maternal Prebiotic Supplementation

In the study conducted by Paul et al,[196] it has been shown that maternal prebiotic supplementation with oligofructose, in the context of diet-induced obesity, increased circulating concentrations of satiety hormones and the relative abundance of *Bifidobacterium* spp in gut. These alterations were accompanied by reduced gestational weight gain and a significant prevention in increased adiposity in both dams and offspring at weaning, potentially impacting their lifelong obesity risk.[196]

Term-Infant Supplementation With Probiotics

Provision of a *B longum* subsp *infantis* CECT7210–supplemented infant formula for 3 months was reported to be safe and well tolerated and to significantly reduce the prevalence of diarrhea and constipation in healthy infants.[197] Exogenous administration of selected bifidobacterial strains, alone or in combination with lactic acid bacteria, decreased the incidence of a variety of gastrointestinal or allergic conditions associated with delayed bifidobacterial colonization and/or a depleted bifidobacterial population in the infant's gut.[198] Data from in vitro studies reveal that *B infantis* stimulates anti-inflammatory and inhibits proinflammatory cytokines in intestinal cells.[199] Animal experiments show that *B infantis* mitigates inflammation[200] and prevents intestinal barrier dysfunction in a mouse model of necrotizing enterocolitis.[201] In breastfed infants, supplementation with $1.8–2.8 \times 10^{10}$ CFU *B longum* subsp *infantis* EVC001 daily for 21 days, starting at day 7 after

Table 3. Prebiotic and Probiotic Supplementation in Infants Through Mothers During Gestation or via Breast Milk, Formula, and Other Vehicles.

Reference	Prebiotic and probiotic supplement	Vehicle	Study population	Timing of exposure	Duration	Timing of assessment	Variables measured	Outcomes
(Guest and Fuller, 2019)[190]	Probiotic: LGG	eHWF vs eHCF	Children with cow's milk allergy	4.2–5.4 months of age	24 months	28.2–29.4 months of age	Allergic manifestation (eczema, urticaria, asthma, and rhinoconjunctivitis) and tolerance acquisition to the cow's milk	LGG was more effective than eHWF in managing the symptoms of cow's milk protein allergy and had a greater potential to prevent the occurrence of other allergic manifestations
(Berni Canani et al, 2017)[189]	Probiotic: LGG	eHCF	n = 110 test vs n = 110 control, children with cow's milk allergy	1–12 months of age, median age of 5 months	36 months of age	12, 24, 36 months of age	Allergic manifestation (eczema, urticaria, asthma, and rhinoconjunctivitis) and tolerance acquisition to the cow's milk	LGG supplementation reduced relative risk for the occurrence of at least 1 allergic manifestation by 49% in eHCF-fed children compared with controls
(Berni Canani et al, 2016)[191]	Probiotic: LGG, 4.5×10^7 to 8.5×10^7 CFU/g of powder	eHCF	n = 12 LGG-fed vs n = 7 no-*LGG*-fed children with cow's milk allergy n = 20 control, healthy children	1–12 months of age, average age of 4 months	6 months	After 6 months	Fecal microbial composition and diversity, tolerance acquisition to the cow's milk	LGG promoted tolerance in infants with cow's milk allergy associated with higher levels of butyrate and butyrate-producing bacteria in eHCF-fed children compared with controls
(Bazanella et al, 2017)[186]	*B bifidum*, *B breve*, *B longum, B longum* subsp *infantis,* 10^7 CFU/g of powder	Standard whey-based formula	n = 48 test vs n = 49 placebo, healthy infants, n = 9, control exclusively breastfed infants for a period of 12 months	After birth	12 months	1, 12, and 24 months	Fecal microbial composition and diversity	*Bifidobacterium* strains modulate occurrence of specific bacteria with no changes in microbial diversity or bifidobacterial sequence at month 1, indicating that probiotic supplement likely failed to compensate for differences in microbiota composition observed between breastfeeding and formula feeding. Although *Bifidobacterium* strains were colonized at 12 months, they were not detectable at 24 months of age, suggesting a nonsustainable colonization.

(*continued*)

Table 3. (continued)

Reference	Prebiotic and probiotic supplement	Vehicle	Study population	Timing of exposure	Duration	Timing of assessment	Variables measured	Outcomes
(Escribano et al, 2018)[197]	Probiotic: *B longum* subsp *infantis* CECT7210 (*B infantis* IM1), 10^7 CFU/g of powder	Infant formula	n = 93 test vs n = 97 control, standard formula-fed healthy term infants	<3 months of age	3 months	1, 2, and 3 months	Diarrhea, growth, gastrointestinal symptoms, fecal microbiota, and bifidobacteria	CECT7210-supplemented formula was safe and well tolerated; increased the level of *B infantis* in probiotic group, leading to reduced diarrheal episodes; and was associated with lower constipation prevalence
(Karav et al, 2018)[202]	Probiotic: *B longum* subsp *infantis* (*B infantis*) EVC001 1.8×10^{10} CFU/d	Lactose/ breast milk	n = 9 test vs n = 10 control, healthy breastfed infants	7 days old	21 days	29 days of age	Structure of colonic Mucin, fecal microbiota	EVC001 significantly increased *B infantis* and significantly reduced the fecal levels of *Bacteroides* in test vs control infants; there was increased colonic mucin–derived O-glycans in control relative to *B infantis*–colonized infants;, EVC001 use diminished colonic glycan degradation
(Frese et al, 2017)[203]	Probiotic: *B longum* subsp *infantis* (*B infantis*) EVC001 1.8×10^{10} CFU/d	Lactose/ breast milk	n = 34 test vs n = 32 control, healthy breastfed infants	7 days old	20 days	During the first 60 postnatal days	Fecal microbiota, fecal biochemistry	EVC001 use increased *B infantis* in fecal microbiota in test group that persisted 30 days after EVC001 exposure; lowered levels of fecal gram-negative Proteobacteria and Bacteroidetes, endotoxin, milk oligosaccharides, and fecal pH; and increased levels of fecal acetate and lactate vs control group, indicating higher consumption of HMO by EVC001
(Casaburi et al, 2019)[204]	Probiotic: *B longum* subsp *infantis* (*B infantis*) EVC001 1.8×10^{10} CFU/d	Lactose/ breast milk	n = 29 test vs n = 31 control, healthy breastfed infants	7 days old	21 days		Fecal gut microbiota and antibiotic-resistant genes of bacteria	Lower fecal levels of antibiotic-resistant bacteria

CFU, colony-forming units; eHCF, extensively hydrolyzed casein formula; eHWF, extensively hydrolyzed whey formula; HMO, human milk oligosaccharide; LGG, *L rhamnosus GG*.

Table 4. Select Commercially Available Prebiotic and Probiotic Options for Infants.

Product	Probiotic	Prebiotic	Vehicles
EVC001, Evolve Biosystems, Inc	Activated *B infantis*	-	Breast milk/lactose
Good Start Supreme Natural Cultures Infant Formula (0–12 months)	*B lactis* cultures	-	Infant formula
FlorastorBaby	*Saccharomyces boulardii*	-	Lactose
Culturelle Probiotic Baby Calm + Comfort	LGG	-	Rice bran oil
Natren Probiotics Life Start Powder	*B infantis*, super strain NLS	-	Lactose
Gerber Good Start Gentlepro (HMO) Powder Infant Formula (up to 12 months)	*B lactis* cultures	2′-Fucosyllactose human milk oligosaccharide	Infant formula
Gerber Good Start Gentlepro (age groupings 6–12 months)	*B lactis* cultures	2′-Fucosyllactose human milk oligosaccharide	Infant formula
Gerber Good Start Soothe (HMO), Non-GMO Powder Infant Formula	-	2′-Fucosyllactose human milk oligosaccharide	Infant formula

HMO, human milk oligosaccharide; LGG, *L rhamnosus GG*.

birth, was safe and well tolerated up until at least 1 month after the supplementation period. There was no difference between 2 groups regarding the mode of delivery, and the safety and tolerability end points considered were flatulence, bloody stool, body temperature, gastrointestinal symptoms, use of antibiotics or gas-relieving medications, infant colic, jaundice, number of illnesses, sick doctor visits, or diagnoses of eczema.[188] Using the same study design, a marked increase in the relative abundance of *B longum* subsp *infantis* occurred and was accompanied with a significant depletion of mucolytic taxa, including *Bacteroides*, compared with control infants. These alterations were associated with the relative abundance of colonic mucin–derived O-glycans in the total glycan pool, which was higher among the control group. As a result, infant colonization with *Bifidobacterium* stimulated by EVC001 might prevent colonic glycan degradation, required for maintaining gut barrier function.[202] In another study with a similar design conducted by Frese et al (2017), *B infantis* enrichment of fecal samples in EVC001-exposed infants remained stable 40 days beyond the supplementation period (20 days). Moreover, probiotic-supplemented infants had lower colonization with gram-negative Proteobacteria and Bacteroidetes in their feces that was consistent with lower levels of fecal endotoxin compared with that of control group. In the EVC001-supplemented breastfed infants, HMO fermentation increased, as shown by significantly increased levels of fecal acetate and lactate, lower fecal pH, and negligible concentrations of fecal HMOs.[203] In a study by Casaburi et al (2019) with the same design (infants supplemented with EVC00), changes to the gut microbiome were associated with lower levels of antibiotic-resistant genes of bacteria compared with control infants, suggesting that EVC001 supplementation might reduce the incidence of antibiotic-resistant infections in breastfed infants.[204]

Bacteria isolated from breast milk are also good sources for a probiotic supplement. In particular, breast milk lactobacilli strains have been shown to have potent antibacterial activities that result in a higher protection against infection in a mouse model. Increased expression of intestinal mucins observed in these breast milk–isolated bacteria might be another mechanisms by which they inhibit the infection of pathogenic microorganisms.[205]

Preterm Infant Supplementation With Probiotics

The rationale for supplementing preterm infants with probiotics is to support the initial colonization of the neonatal intestine that is abruptly disrupted with premature birth. A recent review containing clinical trials and case studies that evaluated several probiotics (eg, *Bacillus*, *Bifidobacterium*, *Lactobacillus*, *Saccharomyces*, and probiotic mixtures) provided to premature infants with low or very low birth weight found that a probiotic mixture and *Bifidobacterium* reduced the risk of necrotizing enterocolitis.[206]

Probiotic supplements have been shown to be safe, as well as to significantly reduce the risk of necrotizing enterocolitis, decrease the time required for enteral feeding tolerance, and diminish the mortality risk in preterm infants.[207-214] Moreover, probiotic supplementation in premature infants has been reported to improve the intestinal barrier, enhance the production of IgA and anti-inflammatory cytokines, increase the diversity and functionality of the gut microbiota,

and reduce pathological bacterial translocation.[214] Although rare, there have been reports of fungal infection due to probiotic contamination,[215] and pharmaceutical standards need to take into account how probiotics are produced and maintained.[211] There are challenges with successful probiotic supplementation in preterm infants. Because most low-birth-weight infants are exposed to antibiotics early in life, some were resistant to probiotic colonization; thus, prolonged probiotic therapy well beyond the period of antibiotic exposure might be required.[216]

Other strategies to protect against necrotizing enterocolitis is with oropharyngeal application with mother's own milk to the preterm infant. Small studies support improved immune effects in infants that received 0.2 mL of their own mother's colostrum oropharyngeally every 2 hours for 48 hours compared with controls. Supplemented infants had elevated urinary lactoferrin level and achieved full enteral feedings 10 days earlier than controls.[217] Moreover, it has been suggested that the donor milk can be individualized by their own maternal milk, as mentioned earlier. The development of human milk–like minimal or synthetic microbiotas is also a novel approach for premature population protecting them against necrotizing enterocolitis and sepsis to increase the preterm viability at lower gestational age.[61]

Conclusion and Future Directions

Here, we summarize the current understanding of the initial colonization and development of the early-life gut microbiome. Our review of maternal and environmental factors impacting gut dysbiosis points to the need to be attentive to these factors during gestation. The gut microbiome is an important factor in human growth and development and assists in establishing immune responses, supporting that a balanced gut microbiome is crucial for optimal health. Emerging data demonstrating the importance of early-life gut microbiome development as a protective factor against gut dysbiosis–related diseases later in life support the rationale for targeted therapies to restore early-life gut microbiome.

Therefore, modifying infant early colonization or correcting early-life gut dysbiosis might be a potential strategy to support infant health later in life, which is highlighted in evidence-based interventions.

As this field is evolving with new technological advances, future investigations into strategies to modify maternal and infant factors that contribute to early-life gut dysbiosis are needed. There is a gap in the literature regarding the influence of paternal gut dysbiosis with their offspring gut microbiome. With the rise in chronic health conditions that are now known to be associated with gut dysbiosis, understanding the impact of maternal-to-infant transfer of dysbiotic microbes is imperative to avoid perpetuating this epidemic to future generations.

Statement of Authorship

F. R. Kapourchali and G. A. M. Cresci equally contributed to the conception and design of the research; F. R. Kapourchali and G. A. M. Cresci contributed to acquisition, analysis, or interpretation of the data; all authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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