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Systematic Review of the Effect of Enteral Feeding on Gut Microbiota in Preterm Infants

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Keywords
donor human milk
feeding
formula
long-chain polyunsaturated fatty acids
microbiome
mother's own milk
prebiotics
probiotics
systematic review

ABSTRACT

Objective: To examine the effect of feeding type on microbial patterns among preterm infants and to identify feeding factors that promote the colonization of beneficial bacteria.

Data Sources: PubMed, Cochrane Database of Systematic Reviews, Scopus, and the Cummulative Index of Nursing and Allied Health Literature were thoroughly searched for articles published between January 2000 and January 2017, using the keywords *gut microbiome, gut microbiota, enteral microbiome, enteral microbiota, premature infant, preterm infant, extremely low birth weight infant, ELBW infant, very low birth weight infant, feeding, breast milk, breastfeeding, formula, prebiotic, probiotic,* and *long chain polyunsaturated fatty acid.*

Study Selection: Primary studies written in English and focused on the association between enteral feeding and gut microbiome patterns of preterm infants were included in the review.

Data Extraction: We independently reviewed the selected articles and extracted information using predefined data extraction criteria including study design, study participants, type of feeding, type and frequency of biospecimen (e.g., feces, gastric aspirate) collection, microbiological analysis method, and major results.

Data Synthesis: In 4 of the 18 studies included in the review, researchers described the effects of milk products (mothers' own milk, donor human milk, and formula). In 5 studies, the effects of prebiotics were assessed, and in 9 studies, the effects of probiotics on the gut microbiome were described. Mothers' own breast milk feeding influenced the compositional structure of preterm infants' gut microbial community and increased diversity of gut microbiota compared with donor human milk and formula feeding. The results of the use of prebiotics and probiotics varied among studies; however, the majority of the researchers reported positive bifidogenic effects on the development of beneficial bacteria.

Conclusion: Mothers' own milk is considered the best form of nutrition for preterm infants and the gut microbial community. Variation in fatty acid composition across infant feeding types can affect microbial composition. The evidence for supplementation of prebiotics and probiotics to promote the gut microbial community structure is compelling; however, additional research is needed in this area.

JOGNN, ■, ■–■; 2017. https://doi.org/10.1016/j.jogn.2017.08.009

Accepted August 2017

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The authors report no conflict of interest or relevant financial relationships.

Human gut microbiota refers to all microorganisms that reside in the digestive tracts of humans, including bacteria, viruses, fungi, and other microbes in which bacteria comprise most of the flora (Guarner & Malagelada, 2003). The microbiome refers to the genomic elements of the whole microbiota (D'Argenio & Salvatore, 2015). The gut microbial community benefits humans in many different ways, including the fermentation of indigestible dietary fiber into short-chain fatty acids (SCFAs), and provides essential chemical compounds such as hormones, essential fatty acids, and vitamins to maintain proper function of the human body. Gut microbiota also have important roles in the modification of host immune function and inflammatory responses to resist pathogenic organisms and in the regulation of the development of the gut defense systems (Boleij & Tjalsma, 2012; Quigley, 2013; Round & Mazmanian, 2009).

Our knowledge of bacteria communities continues to broaden along with culture-independent molecular techniques used to detect an expansive

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microbial world. Measures commonly used to evaluate gut microbiome include microbial alpha-diversity (α-diversity), beta-diversity (β-diversity), abundance, and incidence of individual species (Lozupone & Knight, 2008; Morgan & Huttenhower, 2012). The α-diversity is an estimate of the richness and evenness of the bacterial species in a community (Morgan & Huttenhower, 2012). In most circumstances, a greater α-diversity is indicative of a healthier and more mature microbiome pattern, and it is often quantified with the Simpson Diversity Index and the Shannon Diversity Index in human gut microbiome studies. The β-diversity is a measure of the number or the presence/absence of species shared among microbial communities and evaluates the extent to which two or more communities differ among each other (Lozupone & Knight, 2008). β-Diversity is also used to evaluate the changes of gut microbial community over time, for example, changes caused by environmental or disease status, and can be quantified with the Bray-Curtis Dissimilarity Index (Kapiki et al., 2007).

Abundance and incidence are used to evaluate individual bacterial species. Abundance of a bacteria species refers to the number of individual species found in a community, whereas incidence is a measure of the frequency of each bacterial species found in communities. In general, greater abundance of beneficial microbiota, for example, *Bifidobacterium* and *Lactobacillus,* is more desirable, whereas pathogenic bacteria, including *Escherichia coli* (*E. coli*), *Enterobacter, Citrobacter, Proteus, Klebsiella*, and *Candida,* are less desirable in the promotion of gut health among preterm infants.

The alteration or imbalance of microbiota, also called dysbiosis or dysbacteriosis, can disrupt human wellness, particularly among vulnerable infants born prematurely (<37 weeks gestational age). Dysbacteriosis has been associated with increased risk of colic (Kianifar et al., 2014) and necrotizing enterocolitis in preterm infants (Thomas, 2016; Warner et al., 2016) and can lead to immune disorders (e.g., inflammatory bowel disease; Burcelin, 2016; Jiang et al., 2015; Marteau, 2009), diabetes (Rozanova, Voevodin, Stenina, & Kushnareva, 2002), obesity (Menni et al., 2017; Turnbaugh et al., 2009), and cancer (Loo et al., 2017; Yamamoto & Matsumoto, 2016; Zhu, Gao, Wu, & Qin, 2013) later in life. Preterm infants, especially very-low-birth-weight infants, are susceptible to an imbalanced gut microbial community as the result of gut immaturity (Groer et al., 2014). Other environmental factors that influence the development of a normal gut symbiosis in preterm infants may include perinatal/postnatal use of medication (i.e., intensive use of antibiotics), host genetic factors, mode of delivery, NICU environments, stressful early-life events, mother–infant contacts, feeding compositional differences, and practices during the perinatal period (Cong et al., 2016).

Total fat in infant feedings comprises 40% of calories ingested. Evidence from human and animal investigations suggests that dietary fatty acid composition probably plays a role in gut microbiota development and composition (Balfegó et al., 2016; Ghosh, Molcan, DeCoffe, Dai, & Gibson, 2013; Noriega, Sanchez-Gonzalez, Salyakina, & Coffman, 2016; Pu, Khazanehei, Jones, & Khafipour, 2016). Given this potential, it is important to consider that fatty acid composition and bioavailability differ among feedings provided to preterm infants on the basis of the type of feeding they are provided. Although the percentage of total calories from fat is similar between human milk and infant formula, the composition of specific fatty acids can vary widely on the basis of maternal factors (i.e., maternal diet, stage of lactation) or compositional differences between formula type provided (i.e., standard preterm, elemental; Robinson & Caplan, 2015). These compositional differences affect percentage and form of saturated, monounsaturated, and long-chain polyunsaturated fatty acids provided to infants, with implications for microbiota development and associated health outcomes.

Prebiotics are the nondigestible food ingredients that stimulate the growth and/or activity of beneficial bacterial species (e.g., *Bifidobacteria*) and thereby potentially improve the health of the host (Gibson & Roberfroid, 1995). Human alimentary enzymes are not able to digest most complex carbohydrates and plant polysaccharides. Instead, these polysaccharides are metabolized by microbes that generate SCFAs, including acetate, propionate, and butyrate (Holscher, 2017). Oligosaccharides, well known as beneficial prebiotics for preterm infants, are contained in human milk (human milk oligosaccharides, HMOs), which has been shown to facilitate the growth of *Bifidobacteria* and *Lactobacillus* (Dai & Walker, 1999). With regard to oligosaccharides, it is important to highlight that oligosaccharides are naturally abundant in human milk and are

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