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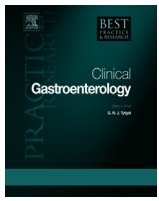

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Use of probiotics and prebiotics in infant feeding

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A B S T R A C T

Gut colonization by beneficial bacteria in early life is necessary for establishing the gut mucosal barrier, maturation of the immune system and preventing infections with enteric pathogens. Mode of delivery, prematurity, breastfeeding, and use of antibiotics are some of many factors that have been described to influence early life colonization. Dysbiosis, the absence of normal colonization, is associated with many disease conditions. Pre- and probiotics are commonly used as supplementation in infant formula, such as prebiotic oligosaccharides for stimulation of *Bifidobacterium* growth aiming to mimic the high levels of these commensal bacteria in the gut of breastfed infants. Studies suggest that probiotic supplementation may be beneficial in prevention and management of disease (e.g., reducing the risk of necrotizing enterocolitis in preterm infants and treatment of acute gastroenteritis in children). Although these studies show promising beneficial effects, the long-term risks or health benefits of pre- and probiotic supplementation are not clear.

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Background

The human microbiota

Humans have more than 10^{14} symbiotic organisms in the distal small intestine and colon, and 10–100 times more bacterial cells than body cells. The human gastrointestinal tract is mainly a bacterial ecosystem, but also contains eukaryotic viruses, bacterial viruses (bacteriophages), fungi and archaea [1]. Each individual has a unique composition of bacterial species, but the various body habitats, e.g. saliva, skin, and gut have some specific bacteria which will be found among all individuals, in varying abundance [2].

Until recently, knowledge of the bacteria that reside in the various human body habitats was limited to those species that could be cultured in the laboratory. New high-throughput sequencing techniques have offered insight into the vast abundance of bacterial species inhabiting the gut, identifying species previously unrecognized. The majority of phylotypes belong to two divisions (superkingdoms) of bacteria – the Bacteriodetes and Firmicutes. The remaining phylotypes are distributed among the Protobacteria, Verrucomicrobia, Fusobacteria, Cyanobacteria, Spirochates and VandinBE97 [3,4].

The microbiota has many roles in its symbiotic relations with the host. Metabolic functions such as fermentation of indigestible fibers resulting in the production of short chain fatty acids (SCFA), trophic activity such as stimulation of angiogenesis, effect on intestinal motility by maintaining motor and sensory functions, and immune activity of resistance to pathogen colonization and improving mucosal barrier function [5].

With the exception of few specific pathogens, the gut microbiota are considered to have an important role in maintaining health. Changes to the diversity, structure or function of the gut microbiota (dysbiosis) have been shown to be associated with disease conditions, although the causality between the gut microbiota and disease has not been established in most conditions.

Colonization of microbiota in early life

Colonization evolves continuously after birth [2,6], and by the end of the first year of life, the infant gut is dominated by bacteria from the phyla Bacteroidetes and Firmicutes. It was thought that the microbiota resembles adult-like composition by the age of three [7]. However, recent studies reveal changes to the healthy infant gut continue after the age of three, and even at the age of five the gut microbiota is still distinguishable from that of adults in composition and in diversity [7,8]. The order in which the various bacteria colonize the infant gut is influenced by several factors, including mode of delivery, prematurity, breastfeeding and antibiotic use. Genetics were previously believed to contribute to bacterial composition, but recent studies of twins suggest that overall heritability of the microbiome is low [9] confirming the importance of environmental influence. Mode of delivery determines which type of bacteria will be the first to colonize the gut. The gut of vaginally delivered infants is influenced by bacteria encountered in the maternal vaginal tract, whereas the gut of infants born by Cesarean section is influenced by the first bacteria encountered outside the mother's womb. Vaginally delivered newborns typically have gut bacteria composition with *Lactobacillus*, *Bacteriodes*, *Bidfidobacterium*, *Prevotella*, *Escherichia*, and *Streptococcus* spp, whereas Cesarean delivered infants typically have a reduced proportion of *Bifidobacterium* or *Bacteroides* and rather a microbiome representative of the maternal skin microbiota including *Staphyloccus* [6,10,11].

Diet influences gut colonization [12], and introducing breast milk as the first source of oral feeding is important for the establishment of health-promoting bacteria [13]. Several constituents in breast milk (non-metabolized oligosaccharides, lysosome, lactoferrin, antibodies, and cytokines) alter the intestinal milieu to stimulate an increase in *Bacteroides*, *Bifidobacterium*, and *Lactobacillus* spp. These bacteria have important specific effects on neonatal immune function. *Bifidobacteria infantis* can activate B cells to mature into secretory-(s)-IgA-producing plasma cells, which coat the intestinal surface and help protect against pathogen penetration. *Bacteroides fragillis* and Clostridia species can interact with the Toll-like-receptor (TLR)-2 on dendritic cells and preferentially create a milieu that allows naïve T-helper cells (T_h0) to differentiate into T_{reg} and T_h sub-class cells which influence the immunological response. Thus,