0021-7557/11/87-04/292
Jornal de Pediatria

Probiotics and prebiotics in prevention and treatment of diseases in infants and children

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Abstract

Objective: To evaluate the impact of probiotics and prebiotics on the health of children.

Sources: MEDLINE and LILACS were searched for relevant English and French-language articles.

Summary of the findings: Human milk is rich in prebiotic oligosaccharides and may contain some probiotics. No data suggest that addition of probiotics to infant formula may be harmful, but evidence of its efficacy is insufficient for its recommendation. Since data suggest that addition of specific prebiotic oligosaccharides may reduce infections and atopy in healthy infants, their addition to infant formula seems reasonable. Long-term health benefits of pro- and prebiotics on the developing immune system remain to be proven. Selected probiotics reduce the duration of infectious diarrhea by 1 day, but evidence in prevention is lacking, except in antibiotic-associated diarrhea. Some specific probiotics prevent necrotizing enterocolitis, and other microorganisms may be beneficial in *Helicobacter pylori* gastritis and in infantile colic. Evidence is insufficient to recommend probiotics in prevention and treatment of atopic dermatitis. The use of probiotics in constipation, irritable bowel syndrome, inflammatory bowel disease, and extra-intestinal infections requires more studies.

Conclusions: Duration of administration, microbial dosage, and species used need further validation for both pro- and prebiotics. Unjustified health claims are a major threat for the pro- and prebiotic concept.

J Pediatr (Rio J). 2011;87(4):292-300: Gastrointestinal flora, intestinal microbiota, oligosaccharide, prebiotic, probiotic.

Introduction

Exclusive breastfeeding during at least the first 4 months of life is the preferred infant feeding method. Since this is not possible to achieve in all infants, artificial formula feeding is an alternative, that is, a second infant feeding choice. Exclusive breastfeeding, and not the composition of mother's milk, should be considered as the gold standard or the reference. Therefore, the goal of any alternative feeding method should be to mimic the effects of mother's milk on the baby as closely as possible. There are many immunological components in mother's milk, but prebiotic oligosaccharides and the recently discovered probiotics are among the most important. Although the literature comparing the effects of breast milk to those of artificial feeding is limited, all studies show a health benefit to breastfeeding. Breast- and formula-fed infants differ in physical growth and cognitive, emotional and social development. Health-care cost of formula-fed

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No conflicts of interest declared concerning the publication of this article.

Suggested citation: Vandenplas Y, Veereman-Wauters G, De Greef E, Peeters S, Casteels A, Mahler T, et al. Probiotics and prebiotics in prevention and treatment of diseases in infants and children. J Pediatr (Rio J). 2011;87(4):292-300.

Manuscript submitted Feb 02 2011, accepted for publication Mar 16 2011.

doi:10.2223/JPED.2103

babies is much higher than that of breastfed babies.[1] Pediatric diseases for which the Agency for Healthcare Research and Quality reported risk ratios that favor breastfeeding are: necrotizing enterocolitis (NEC), otitis media, gastroenteritis, lower respiratory tract infection, atopic dermatitis, sudden infant death syndrome, asthma, leukemia, type 1 diabetes *mellitus*, and childhood obesity.[1] The first few years of life are a vulnerable period, during which the child's immature immune system is still developing and maturing. A child with frequent episodes of infection will not fully benefit from this window of opportunity and will not develop its full potential.

Mother's milk and artificial feeding

The composition of mother's milk is a very dynamic process and changes according to the region where the mother lives, the duration of breastfeeding, the moment of the day, and even during one feeding. It will never be possible to mimic this dynamic process. The macro- and micronutrient composition of cow's milk differs substantially from the composition of mother's milk. The amounts and quality of proteins, carbohydrates, and lipids differ. Besides that, one of the most striking differences is the significant amount of prebiotic oligosaccharides in mother's milk (the third most important component, after carbohydrates and lipids), and the virtual absence of these oligosaccharides in animal milk.[2,3] The amount and quality of oligosaccharides in mother's milk is a dynamic process, as happens with all the other constituents. More than 130 different oligosaccharides have been identified in breast milk.[4]

Gastrointestinal flora

The relevance of the composition and of the function of the gastrointestinal (GI) tract flora has been neglected for long. The GI flora, or GI microbiota, of an adult consists of more than 1,000 species.[5] Microbiota refers to a population of microscopic organisms that inhabit a bodily organ or portion of a person's body.[6] Human microbiome refers to the unique entire population of microorganisms, and their complete genetic elements, which inhabit one's body.[6] Adults have one trillion bacteria in the gut, that is, 10 to 100 times more bacteria than their own human cells. However, at birth, the GI tract is sterile. The presence of bacteria in the gut is mandatory for the development of different functions of the GI tract. If animals live in a sterile environment, adequate peristalsis does not develop. In other words, in the absence of an intestinal flora, the motor function of the gut is impaired. Bacteria are needed for the development of the gut-associated lymphoid tissue. It is often overlooked that the gut contains 60-70% of all the immune cells that a human being possesses.[7]

Because of the differences in composition between human milk and standard infant formula, there is broad consensus now that GI flora composition differs substantially in breast- and formula-fed infants,[8] although there is also literature concluding that breast- and bottle-fed babies have similar counts of bifidobacteria.[9-12]

Although bifidobacteria are the most prevalent bacteria found in the GI flora of both feeding groups, the amount is significantly higher in breastfed than in formula-fed infants.[8] As early as in 1906, Tissier noted that significant stool colonization with bifidobacteria was protective against the likelihood of the development of diarrhea. The amount of *Escherichia coli* and bacteroids is significantly higher in formula-fed than in breastfed infants. Formula-fed infants have a more adult-type flora. After weaning (introduction of solids), the flora becomes more complex in both breast- and formula-fed infants.

Bifidobacteria are the most important constituent of the dominant active flora.[8] Lactobacilli are part of the sub-dominant flora and are under control by the dominant flora. Dietary and environmental changes constitute the transient flora, which is exogenous and does not colonize the GI tract. Lactobacilli and bifidobacteria inhibit the growth of exogenous and/or harmful bacteria, stimulate immune functions, aid in the digestion and/or absorption of food ingredients and minerals, and contribute to the synthesis of vitamins.

Infant's gestational age at birth, mode of delivery (vaginal birth vs. cesarean section), and diet seem to have significant effects on the intestinal microbiota.[6,13] When infants are born by cesarean section, they do not swallow the mother's vaginal and intestinal flora. Mode of delivery, sterile foods, decreased consumption of naturally fermented food, increased hygiene measures, urban life, increased use of antibiotics, and many other factors decrease the exposure of the GI mucosa to microbes, which results in an altered intestinal microbiota.[13]

How can the dietary intake change the intestinal flora?

The composition of intestinal microflora does not change significantly after infancy. The composition of fecal flora in older children and adults is less variable and not as dependent on diet. However, during infancy, diet is a major player in the development of the intestinal microbiota. The abundant presence of prebiotic oligosaccharides in breast milk and their virtual absence in cow's milk are major determinants to explain the differences in intestinal microbiota in infants. The quality and amount of peptides[14] and lactose[15] are bifidogenic factors as well. During the first days or weeks of life, lactase is not yet fully developed.[16] Therefore, undigested lactose reaches the colon, where it is fermented and has a bifidogenic effect.

The prebiotic concept means that non-digestible food ingredients are added to the dietary intake to beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon that can improve the health of the host. Prebiotics evade digestion in the small intestine and must be selectively fermented in the colon. Prebiotics are usually in the form of oligosaccharides, which may occur naturally but can also be added as dietary supplements to foods, beverages, and infant formula. Although dietary nucleotides do not fit the exact definition of a prebiotic, they are prebiotic-like agents, and have immunomodulating and direct intestinal biological properties.[17]

Among many possible prebiotic oligosaccharides, galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS) are the best known. GOS are short-chain oligosaccharides, resulting in fermentation in the cecum and right colon, are side products of lactose hydrolysis, and show lower incidence of side effects such as gas production and bloating. FOS are long-chain oligosaccharides, resulting in fermentation over the entire colon, and are derived from natural carbohydrates present in many plants like artichoke, leek, chicory, wheat, and banana. A mixture of FOS and GOS promotes the growth of healthy bacteria, and brings the GI flora composition of formula-fed infants close to that of breastfed infants.[18-20] A specific FOS/GOS mixture has also been shown to increase fecal IgA secretion.[20]

Another possibility is to add probiotics, living microorganisms, to the food, or to administer them as food supplements or even medications. Probiotics are non-pathogenic live microorganisms that resist normal digestion to reach the colon alive, and which, when consumed in adequate amounts, have a positive effect on the health of the host. Probiotic microorganisms are typically members of the genera *Lactobacillus*, *Bifidobacterium*, and *Streptococcus.* However, yeast such as *Saccharomyces boulardii* is also a probiotic microorganism. A postbiotic is a metabolic by-product generated by a probiotic microorganism that influences the host's biological functions.[21]

Prebiotics change the intestinal flora of the host; probiotics, in turn, are specific strains of micro-organisms added as supplements, and belong to the transient flora. The healthy balance of the gut flora is constantly challenged by many elements, such as environmental factors (for example, age and stress), diseases (for example, infectious gastroenteritis), medications (for example, antibiotics and antacids), and many other factors. As with antibiotics, the use and efficacy of pro- and prebiotics need evidence-based medicine support.

Prevention with pre- and probiotics

The longer an infant is breastfed and the longer breastfeeding is exclusive, the better the protection from infectious diseases such as gastroenteritis will be. Promotion of exclusive breastfeeding has to be maximally endorsed. During recent years, the composition of the second choice infant feeding, cow's milk-based formula, was adapted to better mimic the immune development of breastfed infants. To recreate the benefits of breastfeeding, probiotics and/or prebiotic oligosaccharides have been added to infant formula. The study from Weizman et al. illustrates the specificity of the strains used for this purpose: *Lactobacillus reuteri* resulted in a greater health benefit than *Bifidobacterium* BB12.[22] Compared to the *B.* BB12 group, the *L. reuteri* group had a reduction in number of health care contacts, absent days from day care, febrile episodes, diarrheal episodes, and antibiotic prescriptions, and a reduction in the duration of diarrhea as well.[22] Three large randomized controlled trials (RCTs) provide evidence of a modest effect, statistically significant but of questionable clinical importance, of some probiotic strains (*Lactobacillus casei* GG, *L. reuteri*, and *Bifidobacterium lactis*) on the prevention of community-acquired diarrhea.[23] Results of RCTs later published have indicated that there is modest benefit to administer probiotics to prevent acute GI tract infections in healthy infants and children.[6] With a number needed to treat between 7 and 15 for gastroenteritis, and of 30 for respiratory tract infections, *L. casei* GG reduces nosocomial infections.[24-26] Most of the studies were conducted in childcare centers. The strains of probiotics used include *L. casei* GG, *Streptococcus thermophilus*, *B. lactis*, and *L. reuteri* mixed with milk or infant formula, or given as an oral supplement.[6] However, to date, the available data do not support routine use of probiotics to prevent nosocomial diarrhea in childcare centers.[6] In comparison to placebo, daily dietary probiotic supplementation with either a single strain (*Lactobacillus acidophilus* NCFM) or two strains (*L. acidophilus* NCFM in combination with *Bifidobacterium animalis* subspecies *lactis* Bi-07) for 6 months reduces fever, rhinorrhea, cough, antibiotic prescription incidence, and the number of missed school days attributable to illness in children 3 to 5 years of age.[27] Saran et al. showed that feeding fermented milk to Indian infants over a period of 6 months resulted in a significantly better weight gain and a 50% reduction of infectious diarrhea.[28] *Bifidobacterium lactis* HN019 and GOS fortified milk resulted in a better iron status, although both groups were fed isocaloric diets with the same iron content as a control formula.[29] In a double-blind, prospective, randomized trial in 3,758 children aged 1-5 years living in an urban slum community in Kolkata (India), the health benefit of the daily intake of a probiotic drink with *Lactobacillus casei* strain Shirota or a nutrient drink during 12 weeks, with a follow-up of another 12 weeks without intake of any study product, was tested. The results showed a 14% decrease in episodes of diarrhea.[30]

In the prevention of antibiotic-associated diarrhea (AAD), meta-analyses of published results of RCTs provide evidence for efficacy of a number of probiotic strains, such

as *S. boulardii*.[31-35] Approximately one in seven cases of AAD was prevented by the use of a probiotic.[31] According to a recent review, administration of lactobacilli reduces AAD in adults, but not in children.[32] A Cochrane review from 2007 concluded that there was not enough evidence to recommend probiotics to prevent AAD, because there was no statistical benefit, according to the intention-to-treat analysis.[36]

A limited number of data suggest that probiotics reduce the incidence of atopic dermatitis. This effect is long-lasting, resulting in a reduced incidence of atopic dermatitis even at the age of 7, with an intervention that started during pregnancy and stopped at 6 months of age.[37] The evidence in prevention of atopic disease is limited to selected strains.[38,39] As concluded in a review by Prescott & Björkstén and in the 2007 Cochrane review, despite the encouraging results of some studies, there is insufficient evidence to recommend the routine supplementation of probiotics to either pregnant women or infants to prevent atopic diseases in childhood.[40,41] Van der Aa et al. reviewed seven RCTs on prevention of atopic dermatitis (and 12 on treatment), and found that the results of these trials are conflicting.[42] The authors conclude that there is not enough evidence to support the use of pro-, pre- or synbiotics for prevention or treatment of atopic dermatitis in children.[42] Explanations for varied study results include host factors such as genetic susceptibility, environmental factors such as geographic region and diet, and study variables such as probiotic strains and doses used.[40,43]

Different probiotics strains reduce the risk for NEC.[44] Although the first papers on probiotics strains reducing the incidence of NEC date only from about 12 year ago,[45] literature on this topic has recently exploded. The old and newest data report that administration of lactobacilli and bifidobacteria reduces the incidence of NEC, especially in hospital units with a high incidence of this condition.[45,46] However, as the number of studies increase, negative data (with *L.* GG) are published as well.[47] The number needed to treat to prevent one case of NEC is over 20.[48,49] Improved intestinal motility may be one of the mechanisms of action of NEC prevention.[45] In newborns and infants, *L. reuteri* has recently been shown to improve gastric emptying and reduce regurgitation.[50,51]

It is estimated that approximately 40-70% of children and adult patients suffering from inflammatory bowel disease routinely use alternative medicines, including probiotics, as adjunctive or replacement therapy for prescribed medications.[52] Although the experimental basis to expect clinical efficacy of probiotics in inflammatory bowel disease is rather convincing, clinical evidence for the benefit of probiotics is currently not convincing in Crohn's disease, either in adults or in children.[53] In ulcerative colitis, several probiotic products, especially VSL#3 (a high-concentration mixture of seven strains), have been found effective as adjuvant therapy, both in inducing and maintaining remission.[53] Recent literature suggested a reduction in relapse of ulcerative colitis with VSL#3 in children.[54]

There is some evidence that some lactobacilli prevent recurrent urinary tract infection in women. However, data in children are lacking. The same is true for recurrent vulvovaginitis. There are also some reports on probiotics in otitis media and asthma.

Most of the information regarding prebiotic oligosaccharides results from studies with specific FOS/GOS mixtures. These oligosaccharides lead to a GI flora development close to the flora in breastfed infants. Stool consistency and frequency are similar in breast- and formula-fed infants if prebiotic oligosaccharides were added to the formula. Neutral and acidic oligosaccharides in preterm infants reduce serious infections in this high-risk population.[55] Moro et al. showed that a prebiotic mixture results in a decrease in atopic dermatitis, and could relate this finding to the number of bifidobacteria[56]. In a similar study, a reduction of infections not only during the 6-month intervention period, but persisting up to the age of 2 years, was demonstrated.[57,58] Another group confirmed these data in a similar study with a follow-up to the age of 12 months.[59] Higher levels of secretory IgA in the feces are measured in relation to the presence of FOS/GOS in formula.[60] However, immune parameters are not different at week 8 and 26 in infants fed with breast milk or formula, with or without GOS/FOS prebiotics.[61]

In a community-based RCT, children 1-3 years of age were randomly allocated to receive either control milk (n = 312) or the same milk fortified with 2.4 g/day of a prebiotic oligosaccharides and $1.9x10^7$ colony forming unit/day of *B. lactis* HN019 (n = 312).[62] Biweekly household surveillance was conducted to gather information on compliance to trial plan and morbidity. Overall, there was no effect of the prebiotic and probiotic on diarrhea (6% reduction, 95% confidence interval [95%CI] -1 to 12%, p = 0.08). The incidence of dysentery episodes was reduced by 21% (95%CI 0-38%, p = 0.05), while the incidence of pneumonia and severe acute lower respiratory infection was reduced by 24 (95%CI 0-42%, p = 0.05) and 35% (95%CI 0-58%, p = 0.05), respectively. Compared to children in the control group, children in the intervention group had 16 (95%CI 5-26%, p = 0.004) and 5% (95%CI 0-10%, p = 0.05) reduction in days with severe illness and high fever, respectively.[62] The authors concluded that milk can be a good medium for delivery of pre- and probiotics.[62]

Treatment with pre- and probiotics

Most of the evidence is provided by studies evaluating the efficacy of probiotics in the treatment of acute and chronic infectious gastroenteritis. While some studies with probiotics in acute gastroenteritis are negative, a significant number

of them show a shortening of the duration of diarrhea by approximately 24 hours.[23] A 24-hour shortening in the length of hospitalization was also reported.[63] The probiotic yeast *S. boulardii* was shown to be more effective than fermented food.[64] *Lactobacillus rhamnosus* GG is associated with reduced diarrheal duration and severity.[65,66] However, recent studies with this lactobacillus reported no dose-efficacy or were negative.[67-69] Several meta-analyses[70-72] and a Cochrane review[73] concluded that, in the treatment of acute infectious diarrhea in children, probiotics reduce the number of diarrheal stools and the duration of the diarrhea by approximately 1 day. Probiotic efficacy was also demonstrated in infections with *Giardia lamblia* and amebiasis.[74,75] Seven studies on *S. boulardii* were included in one meta-analysis.[76] The Iberic-Latin American guideline for acute gastroenteritis management in infants and preschoolers recommends racecadotril, zinc, smectite, *L.* GG or *S. boulardii*.[77] The European Society of Paediatric Gastroenterology, Hepatology and Nutrition concluded that the use of specific probiotics in the treatment of acute gastroenteritis may be indicated in some situations.[78] The benefit is strain-dependent.[6]

There have been no published RCTs of children that have investigated the effect of probiotics for treatment of AAD. However, recently published data suggest some efficacy in treatment as well.[79]

A number of studies evaluated the efficacy of probiotics as add-on treatment in the eradication of *Helicobacter pylori*.[80,81] While some studies are negative, the majority of the data shows a reduced incidence of adverse effects of the eradication therapy. Moreover, a number of studies showed that probiotics, even when administered as a dairy product, result in an additional eradication rate of about 10%.[80] As a consequence, the use of such probiotic strains in eradication-resistant cases should be further evaluated.[80,81]

Probiotics have been clinically tested in many other indications such as colic, constipation, and atopic dermatitis. A number of studies provided limited evidence for a beneficial effect of different probiotics in the management of allergic diseases (atopic eczema and allergic rhinitis).[37,39] A 2008 Cochrane review concluded that probiotics have not yet been proven to be effective in the treatment of atopic dermatitis.[82] A RCT concluded that synbiotics (*Bifidobacterium breve* M-16V and a GOS/FOS mixture) did not reduce atopic dermatitis.[83] In theory, probiotics may be beneficial in the treatment of inflammatory bowel disease. A recent Cochrane review indicated that there is no proven benefit for maintaining remission by administering probiotics to adults or children with Crohn's disease.[84] Nor are probiotics recommended in ulcerative colitis at this time, although there is more evidence of benefit for this disease. There is no evidence to recommend the routine use of probiotics in children with constipation or irritable bowel syndrome. One open and one double-blind study, from the same group, reported an efficacy of over 90% of *L. reuteri* in colicky breastfed infants.[85,86] In the open trial, success rate of the probiotic was 95% compared to a 93% failure rate of simethicone treatment.[86] In the double-blind trial, crying time decreased by 90% in the probiotic group, while the decrease was 70% in the control group, which did not receive any intervention.[85] Responders, defined as patients that presented a decrease of crying time by more than 50%, were 96% in the intervention group and 71% in the control group.[86] On the basis of limited information, probiotics may be of benefit in treatment of colic in exclusively breastfed infants, but more studies are needed before this attitude can be recommended.[6]

Choice of probiotic strains, as well as timing of the intervention, are important variables.[37] Fecal colonization has been shown to be dose-dependent.[87] Only very few data have been published regarding dose-efficacy of probiotic strains. Recently, a study with *L.* GG did not report a dose-effect relationship.[69] A dose-related efficacy has been demonstrated for *L. reuteri*.[88] Indirect evidence for a dose-efficacy relationship for *S. boulardii* is shown by the negative results in the trial by Lewis et al., in which a low dose (250 mg/day) was used to prevent AAD.[90] If probiotics are used as medication, a medication-like approach should be stronger developed. In this situation, dose-response studies are required,[90] especially because there is literature suggesting that small doses can be more effective than higher ones.[91] Equally, clinical studies with the product in its commercial presentation and dosage are mandatory, since certain *in vitro* effects are seen only at small bacterial doses,[92] and high doses may produce opposite effects to those obtained at small doses.[93] A few studies suggest that administration of probiotics (*Lactobacillus rhamnosus* 19070-2, *Lactobacillus reuteri* DSM 12246, and *S. boulardii*) may have beneficial effects in certain conditions, but data are too limited to make recommendations.[94-96] There is even less evidence regarding the optimal duration of treatment; to the knowledge of the authors, there are no studies comparing the outcome for several durations of probiotic administration.

Gastrointestinal flora and immune function

The intestinal flora is a major determinant of the development of the intestinal mucosal defense system. It is thought that the occurrence of many diseases, both intestinal and non-intestinal, can be related to dysregulation or interference in the early development of the intestinal mucosal defense system.[6] These diseases can be atopic or autoimmune. Although genetic predisposition is the major determining factor, GI flora plays an important role. Breakdown products from the diet, such as nucleotics and oligosaccharides, and intestinal bacteria give orientation

to the development of mature T lymphocytes, which are needed for the development of the acquired and innate immune system.[97] T-lymphocyte recognition of specific oligosaccharides bound to intestinal pathogens plays an important role in preventing GI illness.[6] Therefore, the early intestinal microbial development of an infant is considered to be a pivotal factor for later health. Probiotic bacteria, postbiotic bacterial by-products, and dietary prebiotics may exert positive effects on the development of the mucosal immune system.[6] As a consequence, contact with "non-beneficial" microorganisms and antimicrobial agents during the neonatal period may result in immune dysregulation in susceptible individuals, and may be related to some diseases.[6] There is evidence that human milk contains mononuclear cells that traffic intestinally derived bacterial components from the mother to her infant.[6,98] Mother's milk contains bacterial components derived from the mother's intestinal flora. This process is termed "bacterial imprinting."[6,99]

Cost, safety and adverse effects

Cost of pre- and probiotics should be considered as well. Since probiotics shorten the duration of infectious diarrhea by about 24 hours, the patient should decide if the cost of a probiotic compensates for 24 hours less of diarrhea. However, if the few data showing a 24-hour decrease in the duration of hospitalization are confirmed, probiotics offer a socio-economic benefit to the society in case of hospitalization.[100]

Probiotics are generally regarded as safe, and side effects in ambulatory care are seldom. Large-scale epidemiological studies in countries where probiotic use is endemic demonstrate low rates of systemic infection in adults, between 0.05 and 0.40%.[101] *Saccharomyces fungemia* secondary to use of the probiotic has been described in critically ill patients who were receiving nutrition enterally or with a central venous catheter.[102] Before use of a probiotic is considered in hospitalized patients, careful assessment of the risk-benefit ratio must be made.[102] To ensure patient safety, probiotics should be properly handled during administration.[102]

Regarding probiotics, strain specificity is important. Until a few years ago, probiotics were discussed primarily in the context of alternative medicine, but they are now entering mainstream medical practice.[103] As a consequence, probiotics are more frequently used in critically ill patients. The use of probiotics in cancer patients is an area of ongoing intensive research. In adult critically ill patients, probiotic administration and intestinal decontamination seem to have a similar preventive effect on infection and mortality.[104] A multispecies probiotic preparation did not reduce the risk of infectious complications and was associated with an increased risk of mortality in patients with a predicted high risk for severe acute pancreatitis.[105] This study illustrates that probiotic administration is not free of adverse events *per se*. *Bifidobacterium animalis*, a traditional probiotic species that is tested in experimental colitis in a GF IL-10-/- mice model, is capable to induce marked duodenal and mild colonic inflammation, and also TH1/TH17 immune responses.[106] This suggests a potential pathogenic role for this commensal bacterial species in a susceptible host.[103] Although reduction of allergic sensitization has been shown with several probiotic strains, an increased incidence of sensitization has been shown as well.[107] There are reports of trials that had to be stopped because of the high incidence of GI side effects and even of heat-killed microorganisms.[108] There are indications that certain *in vitro* effects are seen only at low bacterial doses,[92] and that high doses may produce opposite effects to those obtained at low doses.[93]

Conclusion

Western medicine has only recently discovered that intestinal microbiota is a major determinant of the well-being of the host. Exclusive human milk is the preferred feeding for infants until 4 to 6 months of age. Human milk is rich in oligosaccharides, which are part of its prebiotic components. Human milk may also contain some naturally occurring probiotic bacteria. There are no data to suggest that addition of probiotics to infant formula may be harmful to healthy term infants. On the other hand, evidence of clinical efficacy for addition of probiotics is insufficient to actively recommend the routine use of these formulas. Specific prebiotics are capable of reducing common infections and atopy in otherwise healthy children. Addition of specific oligosaccharides to infant formula seems reasonable. Long-term health benefits of pro- or prebiotics providing evidence of beneficial effects on the developing immune system beyond early infancy remain to be proven.

There is some evidence that manipulation of the intestinal microbiota with food and food supplements containing pre- and probiotics contributes to a possible health benefit if the initial flora was abnormal. There is evidence in otherwise healthy infants and children to support the use of selected probiotics early in the course of infectious diarrhea, because of a reduction of its duration by 1 day. However, there is no evidence to support the routine use of probiotics to prevent infectious diarrhea. There is some evidence for using selected probiotics in the prevention of AAD, but not in its treatment. Evidence is insufficient to recommend probiotic administration in the prevention and treatment of atopic dermatitis. There is some evidence that specific probiotics prevent NEC. There may be some benefit for administration of selected probiotics as add-on treatment of *Helicobacter pylori* gastritis and in infantile colic, but further studies are necessary. The benefit of probiotics for treating

conditions such as constipation, irritable bowel syndrome, inflammatory bowel disease (although data are slightly better for ulcerative colitis than for Crohn's disease), and extra-intestinal infections requires more RCTs.

Although probiotics can be helpful in specific disorders, they have been broadly prescribed for disorders without clear evidence to support their use. Probiotic effects are target specific. Optimal duration of administration, preferred microbial dosage, and species used need further validation for both pro and prebiotics. The major threat for the concept of allocating a major role to the manipulation of the intestinal microbiota on health is the commercialization of products claiming health benefits that have insufficiently been validated. The effect of probiotic microorganisms vary with factors such as age, health, gender, diet, residence, and environment. The consequence of this variation is that results from studies in children/aged subjects, in sick people, or people from the Third World cannot be transferred without further examination to adults, healthy people or people from industrialized countries, respectively.[6]

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