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REVIEW ARTICLE

The role of probiotics and prebiotics in pediatric practice

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Abstract

Objective: To review the effects of probiotics and prebiotics in clinical pediatric practice.

Sources: MEDLINE was searched, especially for articles that addressed their practical application, in the form of reviews, clinical trials and meta-analyses. Articles that had already been analyzed by the authors were also included.

Summary of the findings: Scientific literature on probiotics and prebiotics has remarkably increased in the last 10 years. Their mechanisms of action have been experimentally investigated. Studies indicate that probiotics can act by competing with pathogens, modifying the intestinal environment by reduction in pH, as a result of fermentation products, interacting and modulating local and systemic inflammatory and immune response, among others. Clinical trials and meta-analyses show that probiotics seem to contribute towards the prevention of acute diarrhea and of antibiotic-associated diarrhea, in addition to shortening the duration of acute diarrhea. However, the data are inconsistent and there are no studies confirming their efficacy in terms of cost-benefit ratio. Preliminary studies show that probiotics in early life can reduce the occurrence of atopic dermatitis. The addition of prebiotics to infant formulas is associated with the change in the profile of the intestinal microbiota compared to infants fed milk formulas without prebiotics.

Conclusions: Evidence indicates that new studies should be carried out about probiotics, prebiotics and symbiotics. The specific clinical effects that each probiotic or prebiotic may cause must be considered.

J Pediatr (Rio J). 2006;82(5 Suppl):S189-97: Prebiotics, probiotics, symbiotics, lactobacillus, bifidobacteria, diarrhea.

Introduction

Modern society, in industrialized countries, has a different disease profile today than it used to have decades ago, when infectious diseases prevailed. Now, there has been a progressive increase in the occurrence of allergic, autoimmune and chronic inflammatory diseases. The same has occurred in developing countries, where this process may currently coexist with infectious diseases.¹

This phenomenon, according to some evidence, seems to result from changes in the western society, such as the reduced contact of children with microorganisms, attained by better hygiene and vaccination conditions and by changes in eating habits which, together, determine changes to the intestinal microbiota (intestinal flora).¹ This process is part of the so-called "hygiene hypothesis." Information about the importance of the intestinal flora as

an active mechanism for the control of infectious processes and for the modulation of immune response has encouraged the search for treatment and prevention measures against diseases based on the maintenance of the ideal intestinal flora.¹ A way to achieve this effect is the observation of the characteristics of the normal intestinal flora and of several attempts to restructure it, either by introducing microorganisms that provide health benefits, or substances that help their growth.¹

Historically, fermented milks have been used by humans for over 10,000 years.² This is one of the oldest methods for food preservation. With regard to their benefits to human health, Metchnikoff's observations, made in the early 20th century, are noteworthy, since he related the consumption of fermented milk to the longer longevity of Bulgarian peasants. In the 1930s, Shirota, in Japan, isolated a lactobacillus species that has been used in the production of a fermented milk, commercialized for several decades, also in Brazil. Both lactobacilli and bifidobacteria were initially identified by Moro and Tissier, respectively, in the stools of infants fed human milk, at the turn of the 19th century.²⁻⁴

The use of the term probiotic for living organisms dates back to 1989, when they were regarded as a supplement

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of living microorganisms that bring a health benefit by improving the balance of the intestinal microbiota.³ In 2002, this concept was corroborated in a meeting of experts held by the Food and Agriculture Organization (FAO) and by the World Health Organization (WHO).⁵

On the other hand, prebiotics are defined as substances which, when ingested, are not digested and taken up by the small intestine, and that selectively stimulate a bacterium or group of bacteria (e.g.: bifidobacteria) when they reach the colon, bringing health benefits to the host.³ Symbiotics are defined as products that contain both prebiotics and probiotics.³

The number of articles about probiotics and prebiotics indexed in MEDLINE between 1996 and 2005 has significantly increased. Table 1 shows the number of published articles that contained the words probiotic(s) and prebiotic(s). The annual increase in the number of articles denotes the growing scientific interest they have aroused to the health science literature. When we add the keyword "randomized clinical trial" to the search, as publication type, the number of articles falls drastically, corresponding to 8.4% (232/2748) of articles on probiotics and to 4.7% (37/784) of those on prebiotics. When the word "meta-analysis" is used for the search, as publication type, the number of publications is extremely low. Given that randomized clinical trials represent the studies that assess the efficacy of a given intervention, we may see that there exists scant evidence regarding the use of probiotics and prebiotics before a strong and definitive position can be taken about their efficacy.

The available literature shows that there is a logical theoretical basis for the mechanism of action of prebiotics and probiotics. Moreover, some clinical trials have confirmed their efficacy. There is a large potential for the use of prebiotics and probiotics in several fields of human health, including infections, allergies, inflammations and neoplasms.⁶ However, it is very unlikely that a single probiotic may have health benefits on such a wide range of pathological processes.⁶

Scientifically speaking, probiotics and prebiotics are incontestably a fascinating field of investigation and research. They have the digestive tube, more specifically the intestinal microbiota, as the place for their action, considering also that the gastrointestinal tract can be the site where several immune and inflammatory processes commence. It should be borne in mind that probiotics can potentially cause systemic effects, i.e., their effects can go beyond the gastrointestinal tract.

Thus, the composition of the intestinal microbiota and the effects of prebiotics and probiotics on the development and maintenance of the intestinal microbiota regarded as "healthy" are key to understanding the action of probiotics and prebiotics. The major probiotics include the following:^{7,8} *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus reuteri*, *Lactobacillus rhamnosus*, *Lactobacillus paracasei*, *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium lactis*, *Bifidobacterium longum*, *Bifidobacterium adolescentis*, *Saccharomyces boulardii*, and *Propionibacterium freudenreichii*.

Table 1 - Number of articles indexed in MEDLINE between 1996 and 2005, using the keywords probiotic or probiotics and prebiotic or prebiotics

	Probiotic			Prebiotic		
	Total	Randomized controlled trial	Meta-analysis	Total	Randomized controlled trial	Meta-analysis
1996	30	3	0	24	0	0
1997	51	8	0	43	0	0
1998	118	4	0	54	0	0
1999	162	9	0	54	1	0
2000	197	18	1	35	1	0
2001	291	16	0	84	2	0
2002	404	30	4	116	4	0
2003	422	33	0	102	4	0
2004	508	45	0	128	6	0
2005	565	66	4	144	19	1
Total	2,748	232	9	784	37	1

In the present article, we are going to briefly address the following topics: 1. intestinal microbiota; 2. definition of probiotics; 3. mechanisms of action of probiotics; 4. probiotics and diarrhea; 5. probiotics and allergy; 6. safe use of probiotics; 7. prebiotics in pediatrics and 8. final remarks.

Source of data

To obtain the information included in the topics mentioned above, we searched MEDLINE for articles, especially clinical trials and meta-analyses and review articles related to pediatrics. Articles that had been previously analyzed by the authors were also used. Therefore, we may say that the selected articles constituted a convenience sample. A systematic review was not carried out due to the vast extension of the topic addressed in this article.

Intestinal microbiota

The intestine of a fetus is sterile. The digestive tube of an infant born by vaginal delivery is initially colonized by the vaginal and fecal flora of his/her mother. On the other hand, infants born by C-section are colonized by environmental bacteria. In addition to the type of delivery, the type of feeding, natural or artificial breastfeeding, is very important in determining the intestinal microbiota of an infant. Natural breastfeeding provides an intestinal microbiota predominantly (> 90%) constituted of bifidobacteria and lactobacilli. In infants who are artificially breastfed, these bacteria correspond to 40 to 60% of the microbiota, where clostridia, staphylococci and bacteroides are also found.^{1,3,7,8}

In the digestive tube, there are marked differences in the amount and in the species that make up the intestinal microbiota. The stomach is practically sterile (except in case of *Helicobacter pylori* infection). The proximal small intestine contains up to 10⁴ bacteria/mL, most of them from the oropharynx and also those that survived the effect of gastric acidity. In the colon, however, the amount of bacteria is much larger, nearly 10¹² bacteria per gram of feces.

Once established, around the 18th to 24th month of life, an individual's microbiota tends to be stable throughout the lifetime. It includes 400 to 1,000 bacterial species, of which 30 to 40 prevail. Approximately 97% of the species are anaerobic and 3% are facultative anaerobic. An intestinal microbiota with large participation of bifidobacteria and lactobacilli is regarded as healthy.^{1,3,7}

In individuals with an already established microbiota, the influence of probiotics is usually restricted to the period in which they are used. Thus, in order for these

individuals to keep the desired change in their intestinal microbiota, they should ingest these microorganisms continually and indefinitely.¹

In children, especially when the intention is to use probiotics for the prevention of certain diseases, the intervention should be made during the establishment of the infant's intestinal microbiota, so that they become part of the host's definitive microbiota.^{1,9} The particularities of the microbiota of an exclusively breastfed infant are probably related to the advantages of natural breastfeeding over artificial breastfeeding, such as the lower risk for allergic diseases.

Table 2 shows the basic composition of human intestinal microbiota.

Probiotics in pediatrics

Although the use of probiotics has been widespread in the general population, only a few health benefits have been actually confirmed by well-designed trials, which allow for definitive conclusions.⁸ The definition of probiotics is problematic to begin with. It should be properly understood so that the effects of probiotics on human health can be better determined.

Definition

The term probiotics was initially introduced in medical literature by Lilly & Stillwell in 1965.¹⁰ Although many definitions have already been proposed, we currently use the one suggested by the meeting of FAO/WHO experts, held in 2002: "probiotics are living organisms, which when administered in adequate amounts, confer a health benefit on the host."⁵ According to this definition, we note that two aspects are underscored: organisms must be living and in adequate amounts. These two aspects exclude several products referred to as probiotics.

The current definition has been criticized by some. New studies indicate that bacterial products and even bacterial DNA can exert benefits on health in specific situations. New research into this matter should be undertaken and, as scientific evidence is provided, the current definition can then be adapted.

Some criteria are used for the definition of a microorganism as probiotic:¹¹

- human origin;
- nonpathogenic;
- resistance to processing;
- stability to acid and biliary secretion;
- adherence to the epithelial cell;
- capacity to persist in the gastrointestinal tract;
- capacity to influence local metabolic activity.

Table 2 - Bacterial microbiota (flora) in human digestive tube

Predominant genera of bacteria (colony-forming units /mL or /g)		
Stomach and duodenum 10 ¹ - 10 ³	Jejunum and ileum 10 ⁴ - 10 ⁸	Colon 10 ¹⁰ - 10 ¹²
Lactobacilli	Lactobacilli	Bacteroides
Streptococci	Enterobacteria	Bifidobacteria
Yeasts	Streptococci	Streptococci
	Bacteroides	Fusobacteria
	Bifidobacteria	Enterobacteria
	Fusobacteria	Clostridium
		Veilonella
		Lactobacilli
		Proteus
		Staphylococci
		Pseudomonas
		Yeasts
		Protozoa

Adapted from Holzapfel et al.⁹

The major bacterial microorganisms regarded as probiotic are those of the genera *Lactobacillus* and *Bifidobacterium*, in addition to *Escherichia*, *Enterococcus* and *Bacillus*. The fungus *Saccaromyces boulardii* has also been considered to be probiotic. Other microorganisms frequently added to infant feeding, such as *Lactobacillus bulgaricus* and *Streptococcus thermophilus* are not regarded as probiotic, since they do not meet the criteria mentioned above. Despite this restriction, many researchers regard them as probiotic, since they confer benefits on human health.⁸

With regard to the adequate amounts for health benefits, a dose of 5 billion colony-forming units a day (5x10⁹ CFU/day) has been recommended, for at least 5 days. Although this is the recommended dose, studies assessing therapeutic effects recommend variable doses from 10⁶ to 10⁹ CFU.¹²

Mode of action

The precise mechanisms of action of probiotics have not yet been fully established.^{1,3,8,13} According to its own definition, a probiotic should be viable at the time of consumption. After ingestion, it should keep its viability after coming in contact with gastric acid and bile salts. In addition to overcoming this chemical barrier, probiotics should adhere to the intestinal surface where they perform

their functions, competing with pathogenic agents and modulating the host's inflammatory and immune responses. It should be highlighted that probiotics do not multiply quickly, and so they are not permanent colonizers of the digestive tube.¹³

Probiotic microorganisms positively change the intestinal flora, inhibit the growth of pathogenic bacteria, promote adequate digestion, stimulate the local immune function and increase resistance to infection.

Change in intraluminal pH

Lactobacilli and bifidobacteria help maintain a healthy balance of the intestinal flora by producing organic compounds from fermentation, with formation of lactic acid, hydrogen peroxide and acetic acid, which increase acidity in the intestine, thus inhibiting the proliferation of bacteria with potential damage to the intestinal epithelium.³

Production of substances with antimicrobial activity

Bacteria regarded as probiotic also produce substances known as bacteriocins, metabolically active proteins, which help destroy undesirable microorganisms. Several bacteriocins have already been described, including a low-molecular weight substance, reuterin, produced by *L.*

reuteri. Both lactobacilli and bifidobacteria are able to produce these elements.³ Also interesting is that *Lactobacillus rhamnosus GG*, in addition to producing bacteriocins, also produces a biosurfactant, which helps its own survival.

Competition for nutrients

This action is extremely important due to the fact that the availability of nutrients is a limiting factor for bacterial growth. One of the limiting factors for bacterial growth in the intestinal lumen is the availability of nutrients. Competition is fiercer in the distal colon, where there is a smaller amount of food residues, compared to the proximal colon and small intestine. Therefore, the increase in the number of lactobacilli and bifidobacteria would not allow the proliferation of pathogenic bacteria.¹⁻³

Competition for intestinal receptors for adherence

One of the factors responsible for the action of pathogenic bacteria in the gastrointestinal tract refers to their capacity to adhere to specific receptors found in the intestinal mucosa. One of the actions attributed to probiotics, mainly to lactobacilli, is their capacity to adhere to these receptors, not being eliminated by peristalsis and preventing pathogenic bacteria such as *Salmonella typhimurium*, *Yersinia enterocolitica* and *Escherichia coli* from producing their enteropathogenic effect.¹⁻³ For instance, *Lactobacillus plantarum* synthesizes adhesins for intestinal receptors that contain mannose. Therefore, they compete with *Escherichia coli*, which needs to bind to intestinal cells through these receptors in order to exert its pathogenic activity.¹³

Immunomodulatory effect

The intestine is the largest lymphoid organ in the human body and is an important setting for immune reactions, including the presence of antibodies, such as secretory immunoglobulin A and several immunocompetent cells dispersed in the lamina propria and epithelium or organized into well-defined structures, which play a key role in antigenic presentation and development of immune response to microorganisms and dietary proteins.

The immune effects of probiotics that have been observed include increase in gamma-interferon in patients with cow's milk allergy and atopic dermatitis, probably due to the deviation of immune response to a TH1 profile.¹⁴ Thus, the presence of these agents in the gastrointestinal tract can help with the development of a tolerogenic response.

CD34⁺ hematopoietic precursor cells have been detected in large numbers in the peripheral blood of atopic patients. A study showed a reduction in these cells, in addition to clinical resolution of symptoms in these patients, after the use of probiotics.¹⁵

Recovery of intestinal permeability

Some lactobacilli may have some effect on the expression of the mucin gene, stimulating the production of mucus in the intestinal mucosa and contributing to the efficiency of the barrier function of the intestinal mucosa.¹⁶

Gastrointestinal tract protein synthesis

Both lactobacilli and bifidobacteria are capable to induce the synthesis of proteins with allergenic potential in the gastrointestinal tract. This process can contribute to the reduction of protein allergenicity, minimizing the risk for food allergy.

Use of probiotics in clinical practice

Probiotics have been used in several interesting situations in pediatric practice, but here, only those of great importance and with potential use in clinical practice will be discussed.

Probiotics and diarrhea

In Brazil and in other regions around the world, infant mortality due to acute and persistent infectious diarrhea, malnutrition, and dehydration among children younger than 5 years has decreased in the last decades. This can be ascribed to the wider availability of treated water, longer duration of natural breastfeeding, widespread use of oral rehydration therapy, better information and availability of special formulas for the feeding of malnourished infants with severe diarrhea, among other factors. However, since the beginning of the last century, there has been some interest in using probiotics for the prevention and treatment of diarrhea. In the current context, probiotics aimed for this purpose should be regarded as "adjuvant" measures widely accepted as efficient in the control and treatment of diarrhea and its consequences.

The role of probiotics in the prevention and treatment of diarrhea can be analyzed according to three perspectives:

- treatment of acute diarrhea;
- prevention of diarrhea;
- prevention of antibiotic-associated diarrhea.

The role of probiotics in the treatment of acute diarrhea was analyzed in a meta-analysis published in 2001,¹⁷

including seven double-blind, placebo-controlled, randomized clinical trials, in which 416 patients were assessed. *Lactobacillus rhamnosus* GG was used in three of seven studies, *Lactobacillus reuteri* in two, *Saccharomyces boulardii* in one and *Lactobacillus acidophilus* in one study. The final result of the assessment showed that patients treated with probiotics were 2.5 times less likely to have diarrhea for more than 3 days after intervention than those who received placebo. With regard to the duration of diarrhea immediately after intervention, patients treated with probiotics showed, on average, duration of diarrhea 18.2 hours shorter than the controls. Considering only younger children with rotavirus infection, this value corresponded to 24.8 hours, i.e., diarrhea lasted, on average, approximately one less day.

After 2001, clinical trials were published, which assessed the efficiency of probiotics in the treatment of acute diarrhea in children. In Denmark, 69 children aged 6 and 36 months hospitalized due to acute diarrhea were investigated.¹⁸ Although hospitalized, none of the patients was dehydrated. Rotavirus was identified in 66.7% of patients. The intervention group received *Lactobacillus reuteri* and *Lactobacillus rhamnosus* whereas the control group received placebo (both for 5 days). Duration of diarrhea immediately after intervention amounted to 81.5 ± 37.3 hours in the intervention group and to 101.1 ± 47.6 hours in the control group. However, no statistical significance was observed ($p = 0.07$). On the other hand, when only the patients included in the study with previous duration of diarrhea less than 60 hours were considered, the mean duration of diarrhea in 10 children who received probiotics was lower ($p = 0.03$) than in 18 (79.6 ± 44.0 hours) who received placebo (129.7 ± 23.4 hours). The authors concluded that the effect of probiotics was more pronounced when they were used in the initial phase of the diarrheic process.¹⁸

In Brazil, a study including 124 children was carried out to assess the effect of *Lactobacillus* GG on the reduction of fecal losses in children with severe acute diarrhea associated with dehydration (moderate or severe in over 90% of patients).¹⁹ The mean duration of diarrhea right after the intervention was similar ($p = 0.59$), 38.3 ± 3.8 and 39.1 ± 4.6 hours, respectively, in the groups that received probiotic and placebo. In addition, fecal losses varied considerably in both groups, with similar medians ($p = 0.81$), 67.7 and 56.1 mL/kg, respectively, in the probiotic and placebo groups.¹⁹

A study conducted in Bangladesh assessed the effect of *Lactobacillus paracasei* in 230 male infants aged 6 to 24 months and with diarrhea for less than 2 days. The study showed that the use of probiotics was associated with a statistically significant reduction in the following parameters of patients with nonrotavirus diarrhea: cumulative fecal loss, number of bowel movements, intake of oral

rehydration solution and proportion of children whose diarrhea resolved on the sixth day of intervention. On the other hand, no favorable effect was observed in infants with rotavirus diarrhea.²⁰

The role of probiotics in the prevention of diarrhea was assessed by studies carried out with hospitalized infants or in the community. Saavedra, in 1994, published the results of a study that included 54 hospitalized infants aged 5 to 24 months followed up for 17 months.²¹ The infants fed milk formula containing probiotics (*B. bifidus* and *S. thermophilus*) had a lower incidence of diarrhea (7.0%) than those in the control group (31%).²¹ However, a study conducted in the outskirts of a Peruvian town, using *Lactobacillus* GG or placebo in 204 infants, did not reveal any reduction in the duration of diarrheal episodes, but showed some advantage for infants who were not naturally breastfed.²² The use of probiotics in the prevention of "acute diarrhea" was assessed in a meta-analysis published in 2006.²³ Nevertheless, only nine out of 28 studies included in the meta-analysis referred to infectious diarrhea (the remaining articles were about antibiotic-associated diarrhea and traveler's diarrhea). The articles on presumably infectious diarrhea showed a statistically significant reduction (34%) in the risk for diarrhea.²³

In the literature, there is a larger number of studies on the prevention of antibiotic-associated diarrhea. A pioneering study in this field was carried out by Vanderhoof et al.²⁴ The authors assessed 188 children who had received antibiotics for the treatment of respiratory infections combined with *Lactobacillus* GG or placebo. There was a statistically significant reduction in the occurrence of diarrhea in the probiotic group (relative risk = 0.28 with a 95%CI between 0.13 and 0.62). A Brazilian study, carried out by Correa et al., assessed the effect of a milk formula with (*Bifidobacterium lactis* and *Streptococcus thermophilus*) or without probiotics, in the prevention of antibiotic-associated diarrhea in 157 children aged 6 to 36 months who had received antibiotic therapy against respiratory disorders.²⁵ The percentage of children who developed diarrhea on the subsequent 30 days after the implementation of antibiotic therapy corresponded to 16.3% in the group that received the milk formula with probiotics, and to 31.2% in the control group, with a statistically significant reduction. The prevention of antibiotic-associated diarrhea with the use of probiotics was assessed in four meta-analyses, two of them published in 2002^{26,27} and the other ones in June²³ and August 2006.²⁸ Those published in 2002 showed a relative risk of 0.37 and 0.40, with similar 95%CI, with the upper confidence limit less than 1.0. Therefore, both showed that the use of probiotics reduced the risk of antibiotic-associated diarrhea by approximately 2.5 times.^{26,27} In the studies published in 2006, which included a larger number of clinical trials, these values were confirmed

(0.43 with a confidence interval of 0.20 and 0.75 and 0.48 with a confidence interval of 0.35 and 0.65).^{23,28} In one of these meta-analyses, which assessed six clinical trials carried out exclusively with children, the intention-to-treat principle was also evaluated.²⁸ In this evaluation, there was no advantage in the use of probiotics for the prevention of diarrhea (relative risk = 1.0 with a confidence interval of 0.62 and 1.61). Considering the subgroup of four studies in which more than 5 billion colony-forming units a day of probiotic (*Lactobacillus* GG, *Saccharomyces boulardii* or *L. sporogens*) were given, there was stronger evidence of protection, characterized by lower relative risk and narrower confidence intervals.²⁸

Probiotics and allergic diseases

Changes in the lifestyle of the population, especially in the western world, with better hygiene conditions, also reduced early contact with microorganisms, which may have produced a reduction in the TH1 response to the detriment of immune TH2 response, characteristic of allergic processes.²⁹ A proof of that is that children from families that adopt an anthroposophic lifestyle, with restricted use of antibiotics and vaccines and an organic diet, show lower incidence of allergic processes, in addition to having an intestinal microbiota rich in lactobacilli and bifidobacteria.³⁰ Most studies on the use of probiotics have assessed patients with atopic eczema. Majamaa & Isolauri assessed children with atopic eczema and cow's milk allergy and found health benefits with the use of *L. rhamnosus* GG.³¹ Another study carried out in Finland compared whether the use of one probiotic, four probiotics or placebo had an additional effect on conventional treatment of atopic dermatitis in infants.³² Topical treatment included hydrocortisone and moisturizer, and cow's milk and derivatives were withdrawn from the diet, being replaced by protein hydrolysate. It was a double-blind, randomized trial that assessed 230 infants. The group that received only one probiotic had an advantage over the other two groups when an IgE-mediated mechanism was identified. Surprisingly, the use of four probiotics yielded similar results to those obtained with the placebo.

As far as respiratory allergy is concerned, two double-blind, randomized controlled trials assessed the effects of using lactobacilli in allergic patients.^{33,34} One of the studies assessed the use of *Lactobacillus acidophilus* in adults with moderate asthma and showed reduction in the number of eosinophils and increase in gamma-interferon, but without any changes in clinical parameters.³³ Another study assessed adolescents with pollen allergy and used *Lactobacillus rhamnosus* GG without finding any health benefits.³⁴

With regard to the role of probiotics in the prevention of early atopic disease, a study assessed the use of

Lactobacillus GG in pregnant women at the end of their gestational period and in the first months of life of those infants who had family history of atopic disease.⁹ At the age of 2 years, the proportion of infants with atopic dermatitis was lower among those who had received *Lactobacillus* GG than among those who received placebo; however, the increase in IgE levels, of specific immunoglobulins and of positive skin puncture test results was similar in both groups.⁹ The same infants who participated in this study were reassessed at the age of 4 years and the protective effect against atopic dermatitis persisted.³⁵

Experimental studies have been carried out on the effect of probiotics in animal models, suggesting that the use of probiotics may help with the induction of oral tolerance, preventing the TH2 response. So far, it is necessary to better assess the effects of probiotics for the control and/or prevention of allergic disease, since experimental studies suggest that specific strains of probiotics may act upon the intestinal mucosa with potential modulation of the allergic response.³⁶

Safe use of probiotics

This is a crucial issue – evaluating the potential use of probiotics in pediatric patients. Studies have shown that the use of probiotics in healthy individuals does not increase the risk of bacterial diseases. Even in immunosuppressed patients, this risk is seemingly low, although 89 cases of bacteremia induced by lactobacilli have been reported, usually associated with previous severe comorbidities.³⁷

Conclusion

Only some strains of probiotics have been included in studies with rigorous scientific methodology. The findings of these studies might probably not be applied to other strains, since the effects may be strain-specific. New information is necessary about the mechanism of action of probiotics so that their therapeutic potential can be explored. Currently, the most thriving use of probiotics concerns diarrheas and, although some studies show improvement of atopic eczema, these data need to be corroborated. Further studies are necessary to confirm the efficacy and safety of probiotics in the pediatric population.

Prebiotics in pediatrics

According to the data shown in Table 1, the number of articles related to prebiotics is quite smaller than the publications on probiotics.

Prebiotic is an indigestible nutrient that confers benefits on the host by selectively stimulating one bacterium or a group of bacteria in the colon with probiotic properties.³ Prebiotics include: fructo-oligosaccharides, inulin, gluco-oligosaccharides, galacto-oligosaccharides, isomalto-oligosaccharides, xylo-oligosaccharides, among others.^{1,3} Lactitol, lactulose and lactose not absorbed by the small intestine may have a prebiotic effect on the colon.¹

The first prebiotic is found in breastmilk.⁷ Oligosaccharides are one of the most abundant nutrients in human milk. The bifidogenic effect of human milk, known since the 1920s, was related to human milk oligosaccharides in the 1950s.⁷ However, the composition of human milk oligosaccharides is not the same for all breastfeeding mothers. Thus, because of the qualitative and quantitative variability of human milk oligosaccharides, there may be differences in the infant's intestinal microbiota.⁷

In this context, the addition of prebiotics to infant formulas allows offering a kind of food whose composition is close to that of human milk carbohydrates. Clinical trials have shown that formulas with prebiotics increase the amount of bifidobacteria and lactobacilli in the microbiota of infants, compared to those who are formula-fed. However, a fixed formulation of prebiotics is unlikely to mimic the peculiarities observed in the composition of human milk. For this reason, also considering the other advantages of human milk, natural exclusive breastfeeding must be continually encouraged.³⁸

Some ongoing studies have attempted to relate prebiotics to immune mechanisms. Some properties related to protection against infections, increase in intestinal calcium absorption, among others, have been described as characteristics of prebiotics in experimental studies.

Final remarks

There is a wide range of other clinical conditions which were not mentioned in the present article, for which the possible use of probiotics and prebiotics is contemplated. Among these conditions, we have: inflammatory intestinal disease, post-colectomy pouchitis due to ulcerative colitis, lactose intolerance, necrotizing enterocolitis, vulvovaginitis and intestinal constipation. In this article, our aim was to explore the definition of probiotics in common pediatric practice situations.

Prebiotics, probiotics and symbiotics will certainly be the target of many studies in forthcoming years. The wide array of preventive and therapeutic possibilities is reason for enthusiasm; however, for each desired effect, there will probably be a single or a given group of probiotics. This

specificity can be exemplified by a study carried out with adults suffering from irritable bowel syndrome.³⁹ The patients were placed in three groups that received: 1) *Lactobacillus salivarium*, 2) *Bifidobacterium infantis* or 3) placebo. The only group with clinical improvement attributed to the use of probiotics was the one that received *Bifidobacterium infantis*. This group also normalized the interleukin (IL) 10/IL-12 ratio, unlike the groups that received *Lactobacillus salivarium* and placebo. Therefore, besides clinical improvement, there was also a change in the profile of inflammatory markers in this group of patients with a disease that is regarded as predominantly functional. In other words, the prescription of any probiotics does not guarantee that a favorable effect will be obtained for all aspects of human health. In this regard, it is necessary that the current definition of probiotics be further developed so as to allow choosing a probiotic for each clinical situation of prevention and treatment.

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