Chapter 13

Probiotics in Pediatrics – Properties, Mechanisms of Action, and Indications

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1. Introduction

Probiotics have been the topic of many studies over the past 20 years. Metchnikoff and Tissier (Metchnikoff 1907, Tissier, 1906) were the first to make scientific suggestions concerning the probiotic use of bacteria. They suggested that these bacteria could be administered to patients with diarrhea to help restore a healthy gut flora. Fuller (1989) in order to point out the microbial nature of probiotics redefined the word as "A live microbial feed supplement which beneficially affects the host animal by improving its intestinal balance. " The most recent but probably not the last definition is "live microorganisms, which when consumed in adequate amounts, confer a health effect on the host"(Guarner and Schaafsma,1998). In the last 20 years however, research in the probiotic area has progressed considerably and significant advances have been made in selection and characterization of specific probiotic cultures. Most of the studies aim to investigate the physiological and functional properties of various probiotic strains, the mechanisms of action and the indications for human use and health benefits.

Probiotic bacteria are a subset of specific organisms, which, when ingested, transiently occupy the gastrointestinal tract and lead to documented health benefits. Lactic-acid-producing bacteria (LAB), particularly members of the genus Lactobacilli, Bifidobacteria, non pathogenic gram positive bacteria and non bacterial microorganisms (for example certain yeasts, such as Saccharomyces boulardii) have been used as probiotic agents. [1] The use of specific probiotic bacteria has been shown to enhance host defense mechanisms. [2] Prebiotics are non-digestable food ingredients that beneficially affect the host by stimulating the growth and/or activity of a limited number of bacterial species in the colon. Compounds most commonly studied for their prebiotic nature are non-digestable carbohydrates. In particular, oligosaccharides are considered the main units among prebiotics, which include fructooligosaccharides (FOS), inulin, lactulose and galactooligosaccharides (GOS). Synbiotics

are a combination of probiotics and prebiotics and it is the synergy between these two substances that becomes known as synbiotics.

Several clinical benefits have been reported as a result of interaction between host and becteria ,such as for treatment and prevention of viral diarrhea [3] and reducing the risk of necrotizing enterocolitis (NEC), mitigating antibiotic associated diarrhea ,and modulating host immune response (such as in allergic disease).

2. Properties

Intestinal microflora is composed of both well-established resident microbes and those ingested orally which transiently occupy the gastrointestinal (GI) tract. Probiotics are generally defined as non pathogenic organisms in food supply (ingested microbes) that are capable of conferring a health benefit to the host by modifying gut microbial ecology.

Probiotics are live microorganisms which when ingested in adequate amounts confer a health effect on the host by enhancing host defense mechanisms. Several clinical benefits have been reported with various specific microbes in pediatric populations. It is increasingly clear that these benefits to the host are mostly mediated by the profound effect that intestinal microflora (microbiota) have on gut barrier function and host immune response. The most frequently used probiotic agents are the lactic acid producing bacteria, such as Lactobacilli and Bifidobacteria, non pathogenic strains of Gram positive bacteria, such as Streptococcus, E. Coli and non bacterial microorganisms, such as Saccharomyces Bulardii

There are several generally accepted characteristics that define probiotic bacteria. [4-6]

- They are microbial organisms
- They remain viable and stable after culture manipulation, and storage before consumption
- They survive gastric, biliary, and pancreatic digestion.
- They are able to induce a host response once they enter the intestinal microbial ecosystem (by adhering to gut epithelium or other mechanisms) and they yield a functional and clinical benefit to the host when consumed.
- It has been suggested that probiotic bacteria should be of “human origin” and that they should “colonize” the intestine. [5,6]

Probiotics can be found in certain foods, such as yogurts, fruit juices and soy beverages. They are also found in supplements that come in liquid, capsule and powdered forms. It is believed that a concentration of 10 live microorganisms per gram or ml of product is required in order to exert a health benefit on the host.

Probiotics have a wide range of beneficial effects and numerous indications of use in pediatric populations, such as:

- Acute diarrhea
- Antibiotic-Associated Diarrhea
- Allergy prevention
- Necrotizing enterocolitis

3. Mechanisms of action

The intestine of the newborn is essentially sterile. During the birthing process and during the first days of life, the gut is inoculated with bacteria. In the first two days of life, an infant's intestinal tract is rapidly colonized with bacteria consisting mainly of Enterobacteria. In most breastfed infants, the Bifidobacteria counts increase rapidly to constitute 80-90% of the total flora. Formula-fed infants, on the other hand, tent to have a flora that is more complex, consisting mostly of coliforms and Bacteroides with significantly lower prevalence of Bifidobacteria. [7] Although the composition of the microflora varies among individuals, the composition within each individual remains stable over prolonged periods. [8] A normal microbial flora is necessary for the development of gut associated lymphoid tissue (GALT). The gut luminal microbes are responsible for mucosal immune system development in healthy infants. Signaling through specific receptors, particularly toll-like receptors, intestinal bacteria affect epithelium cell function, which determines T-cell differentiation and antibody responses to T-cell-dependent antigens, regulating immune gut response for IgA responses to luminal antigens. [9] Resident bacteria, particularly Lactobacilli and Bifidobacteria, can exert antimicrobial activities influencing both local and systemic immunity. [10]

Intestinal bacteria have a major effect on enhancing secretory immune function. Among the more consistently found effects of specific Bifidobacteria and Lactobacilli in pediatric populations is the effect on humoral immunity, particularly on secretory IgA(s IgA) and other immunoglobulins. An increase in IgA-, IgM-,and IgG-secreting cells in circulation ,as well as fecal IgA concentrations ,has been reported. During the neonatal period, s IgA in the stool of formula-fed infants is essentially undetectable. [11, 12] Bifidobacteria and Lactobacillus given orally have been shown to influence s IgA in a number of animal trials [13] Infant studies that investigated the effects of specific Lactobacilli and Bifidobacteria supplementation on stimulating the mucosal immune response have reported similar positive results. Breast milk contains significant levels of sIgA that are transferred to the infant. Bifidobacteria, which predominate in breast-fed infants, have shown to stimulate the synthesis and secretion of IgA. Recent reports indicate similar IgA increases in premature infants receiving B lactis. [14] sIgA, the most important and predominant immunoglobulin in mucosal surfaces, provides protection against antigens, potential pathogens, toxins, and virulence factors. [15]

The resident Bifidobacteria and Lactobacilli in the gut can offer resistance to colonization by other potentially pathogenic microbes, thereby functioning as part of the gut defense barrier. They have also been associated with the secretion of substrates that have antimicrobial properties [16] and the secretion of mucins via activation of MUC2 and MUC3 genes, part of the intestinal barrier that can inhibit adherence of pathogenic bacteria. [17]

An increasing number of clinical trials have documented effects of ingestion of specific probiotic bacteria on gut barrier function and immunity. For example in both animal and human models, ingestion of L casei, L bulgaricus, and L acidophilus has been shown to activate production of macrophages and enhance phagocytosis. [8] Serum sCD14, a marker

of immunologic maturation in the neonate, was significantly greater than placebo in infants provided probiotics. Additionally, decreased gut permeability with Lactobacilli [18] , and recently in premature infants receiving Bifidobacteria [19] , is another mechanism by which probiotics may function.

Some probiotic bacteria have been shown to exert beneficial effects on pro- and anti-inflammatory cytokine secretion [8]. Decreases in fecal 1 antitrypsin, urinary protein eosinophil X, tumor necrosis factor (TNF)-α [20,21] have been reported as a result of down-regulation of the inflammatory immune response by probiotic agents.

It is being recognized that host-microbe interactions have an effect on atopic disease. Alterations in the balance of intestinal microflora, particularly in immune and inflammatory-related diseases coupled with significant reduction in the oral ingestion and exposure to a microbe that has led to postulation of the "hygiene hypothesis". This theory suggests that a lower exposure in early childhood to bacterial and other antigens in industrialized societies has led to inadequate development and maturation of immune responses and appears responsible for the increased prevalence of asthma and allergies due to inadequate defensive and immune-modulating gut immune diseases. [22, 23, 24] Infants are born with a predominance of Th2 (T helper 2) lymphocyte activity ,which predisposes them to an exaggerated response to allergens ,with increased IgE production. Exposure to intestinal bacteria ,on the other hand ,stimulates Th1 (T helper 1) activity (which primarily reacts defensively to bacterial stimuli as part of the protective immune response). As a consequence ,intestinal microbes (resident and ingested)can redirect immune balance from a Th2-predominant response to a balanced Th1/Th2 response ,decreasing the changes for a potential exaggerated allergic response. Finally, TReg (regulatory) cells release cytokines such as transforming growth factor β(TGF-β) ,which can inhibit Th1 or Th2 overexpression and also play a role in adequate balancing the host response to bacterial food antigens ,and their activity seems to be increased by luminal microbes [25,26,27,28] Some Bifidobacteria and Lactobacilli given orally may enhance the production of a balanced T-helper-cell response [29,30] and stimulate production of interleukin (IL)-10, and TGF-β [21,31,32] both of which have a role in the development of immunologic tolerance to antigens and can decrease allergic type immune responses.

Bifidobacteria supplementation in premature infants has been shown to positively modify the microflora of the intestines. [33] Beneficial increases in stool, short-chain fatty acids, reductions in stool pH, and decreases in fecal ammonia and indoles [34, 35] and concentrations of Bacteroides and E. Coli have been documented [36, 37] with Bifidobacteria supplementation. Specific probiotic bacteria positively affect the ratio of favorable to unfavorable in the gut luminal environment. Lactobacilli and Bifidobacteria when ingested they are not part of the resident microflora of the host, and their counts typically decrease or disappear once ingestion stops. Specific Lactobacilli and Bifidobacteria, when ingested, can modify the composition of intestinal microbial ecology. They are not typically pathogenic and seem beneficial in fostering host immune development and response. These ingested organisms have the potential of further supporting gut barrier function and appropriate host immune system development and immune response.

In summary effects have been documented supported by a large body of evidence from in vitro and animal studies. These include effects on innate (nonspecific immune defense) and adaptive immunity (responses that require exposure to pathogens or antigens that the immune system recognizes and "remembers"). Adequate adaptive responses are important for host defense, as well as to develop immune tolerance, which decreases chances for abnormal immune hyperreactivity or inflammation. The following effects on innate and adaptive immunity have been reported:

Effects on innate immunity

- Compete with and inhibit growth of potential pathogens
- Promote mucin production
- Decrease gut permeability
- Enhance natural killer cell activity, macrophage stimulation, and phagocytosis

Effects on adaptive immunity

- Increase total and specific s IgA in serum and intestinal lumen
- Increase IgA-, IgG-, and IgM- secreting cells
- Modulate inflammatory gut immune responses [5]

4. Indications

Clinical benefits with specific probiotic bacteria by enhancing defense mechanisms, as well as by modulating host immune response include prevention and treatment of acute infectious diarrhea and antibiotic-associated diarrhea, modulating allergic immune response, prevention of NEC and treating constipation.

4.1. Acute infectious diarrhea

The clinical outcome with the use of probiotic bacteria in order to treat or prevent acute diarrheal diseases has been supported by a large and growing body of evidence. The larger number of trials documents therapeutic use of probiotics as supplements early in the course of the disease. The rationale of using probiotics to treat and prevent diarrheal diseases is based on the assumption that they modify the composition of colonic microflora and act against enteric pathogens. The majority of studies have included various species of Lactobacilli, and by far the most used has been L rhamnosus (GG). This specific strain has shown efficacy when given as a supplement early in the course of rotaviral diarrhea. The most consistent effect reported is a reduction in duration of illness (0, 5 to 1, 5 days). While for the individual infant the effect may be modest, the effect on the population may be significant. [38]

A reduction in incidence of acute diarrheal disease has been reported by another body of literature. Several studies have documented a reduction in incidence or severity of acute diarrhea with Bifidobacteria mainly B. lactis [39, 40] and with Lactobacilli, mainly L rhamnosus (GG) [41, 42] though protection is not always significant. [43] Both L rhamnosus

(GG) and L reuteri (during treatment) [44] and B lactis (used prophylactically) [45] have documented reduced rotaviral shedding. Thirty-four randomized clinical trials reviewed by a meta-analysis evaluated the efficacy of probiotics in the prevention of acute diarrhea. Probiotics significantly reduced the risk of diarrhea developing in infants and children by 57%. The protective effect did not significantly vary among the probiotic strains used, including B lactis, L rhamnosus GG, L acidophilus, S bouladrii, and other agents used alone or in combination with 2 or more strains. [46] Decreased hospitalization [47] and reduced duration of hospitalization were also confirmed. All studies suggested that the effect occurs on both the manifestations of the disease and on the course of the infection. There has been no study so far documenting an increase in diarrheal disease with probiotic use. These findings suggest that specific probiotics may be used in a long-term and prophylactic manner, particularly in infancy.

Several mechanisms have been proposed in order to explain the efficacy of probiotics in preventing or treating acute diarrhea. It has been shown that probiotics stimulate or modify nonspecific and specific immune responses to pathogens. Probiotics have been shown to enhance mucosal immune defenses and protect structural and functional damage promoted by enteric pathogens in the brush border of enterocytes, probably by interfering with the cross-talk between the pathogen and host cells. [48] It has been shown that L rhamnosus (GG) and Lactobacillus plantarum 299v inhibit, in a dose-dependent manner, the binding of E.coli to intestinal-derived epithelial cells grown in tissue culture by stimulation of synthesis and secretion of mucins. [49] Certain probiotics increase the number of circulating lymphocytes [50] and lymphocyte proliferation [51,] stimulate phagocytosis, increase specific antibody responses to rotavirus vaccine strain [52] , and increase cytokine secretion, including interferon-γ. [51] L rhamnosus GG and Lactobacillus acidophilus have been shown to produce antimicrobial substances against some gram-positive and gram-negative pathogens. [53, 54] Other mechanisms proposed by which probiotics might exert their activity against pathogens are competition for nutrients required for growth of pathogens [55,56] ,competitive inhibition of adhesion of pathogens [57-60] ,and modification of toxins and toxin receptors. [61,62]

4.2. Antibiotic-associated diarrhea

Antibiotic-associated diarrhea (AAD) is defined as an acute inflammation of the intestinal mucosa caused by the administration of a broad spectrum of antibiotics. The single bacterial agent most commonly associated with AAD is Clostiridium difficile. However, when the normal fecal gram-negative organisms are absent, overgrowth by staphylococci, yeasts and fungi has been implicated. [63] In fact, most episodes of AAD in childhood are not due to C. difficile. [64] The rationale for the use of probiotics in AAD is based on the assumption that the key factor in the pathogenesis of AAD is a disturbance in normal intestinal flora.

Several probiotic bacteria have proved to be beneficial in reducing the risk of antibiotic-associated diarrhea in infants and children. [65-67] Six randomized controlled trials that collectively assessed 766 children for the efficacy of probiotics in the prevention of AAD

indicated that concomitant treatment with probiotics, compared with placebo reduced the risk of diarrhea from 28, 5% to 11, 9%. [67] Beneficial effects were strongest for B lactis and S thermophilus given in infant formula and L rhamnosus (GG) as a supplement.

In conclusion, Randomized Controlled Trials (RCTs) in children have provided so far evidence of a moderate beneficial effect of L rhamnosus (GG), B. lactis, S. thermophilus and S. boulardii in preventing AAD. No data on efficacy of other probiotic strains are available in children. Based on the previously reported evidence probiotics have been shown capable of providing reasonable protection against the development of AAD. Their use is probably warranted whenever the physician feels that preventing this usually self-limited complication is important.

4.3. Nosocomial diarrhea

Nosocomial diarrhea refers to any diarrhea contracted in a health care institution and is more commonly caused by enteric pathogens especially rotavirus. [68] The reported incidence ranges from 4, 5 to 22, 6 episodes per 100 admissions. It may prolong hospital stays and increase medical costs. Although hand washing is the essential infection control measure, other cost-effective approaches to prevent nosocomial diarrhea are being evaluated.

Two RCTs evaluated the use of L rhamnosus G [69, 70] on nosocomial diarrhea prevention. The first study showed that L rhamnosus G administered orally twice daily significantly reduced the risk of diarrhea compared with placebo (6, 7% vs 33, 3%; p=0,002) [69]. The second RCT evaluating L rhamnosus G in the prevention of diarrhea involved 220 children. L rhamnosus (GG) was administered orally once daily and did not prevent nosocomial rotavirus infections compared with placebo (25, 4% vs 30, 2%; p=0, 4). However, the rate of symptomatic rotavirus enteritis was lower in children receiving L rhamnosus (GG) compared with placebo (13% vs 21%; p=0, 13). [70]

The available data do not provide strong evidence for the routine use of L rhamnosus (GG) to prevent nosocomial rotavirus diarrhea in infants and toddlers.

Two other RCTs evaluated the efficacy of B. bifidum and S. thermophilus in preventing nosocomial diarrhea. The first study showed that the administration of standard infant formula supplemented with B. bifidum and S. thermophilus reduced the prevalence of nosocomial diarrhea compared with placebo. The risk of rotavirus gastroenteritis was significantly lower in those receiving probiotic-supplemented formula [71]. The second RCT showed that infants living in residential care settings, although they differ from hospital settings are also at increased risk for diarrheal illnesses, and the mode of acquiring diarrhea is similar. The infants received milk formula supplemented with viable B. lactis strain Bb12. It was shown that the previous intervention did not reduce the prevalence of diarrhea compared to placebo. [72]

In conclusion there is conflicting evidence on the efficacy of L rhamnosus (GG) provided by 2 RCTs in preventing nosocomial diarrhea. One small RCT suggests a benefit of B. bifidum

and S. thermophilus in sick infants admitted to the hospital, but no such benefit has been identified in healthy children in residential care settings. The already mentioned studies suggest that there is currently not enough evidence to recommend the routine use of probiotics to prevent nosocomial diarrhea. There is a need for large and well-designed RCTs.

4.4. Allergy

The rationale for using probiotics in prevention and treatment of allergic disorders is based on the concept that appropriate microbial stimuli are required for normal early immunological development. Microbial-gut interactions can improve the integrity of the gut barrier by decreasing intestinal permeability, reducing both adherence of potential antigens and their systemic effect, and by modulating GALT immune response toward antigen tolerance. The intestinal microflora interacts with the mucosal immune system. It has been found that different strains of commercial bacteria vary in the cytokine response they generate. The Th1/Th2 imbalance is crucial to the clinical expression of allergy. Probiotic bacteria can produce significant antiallergenic effects by intricate interactions inducing Th1 cytokines, such as interferon-γ [73] , T-regulatory cytokines, such as IL-10 and TGF-β [74] , and mucosal immunoglobulin A production [75].

Three species of Lactobacillus were shown to modulate the phenotype and functions of human myeloid dendritic cells (DCs). Lactobacillus-exposed myeloid DCs up-regulated HLA-DR, CD83, CD40, CD80, and CD86, and secreted high levels of IL-12 and IL-18, but not IL-10. [76]

Infants with atopic dermatitis who received hydrolyzed whey formula supplemented with L rhamnosus (GG) showed greater clinical improvement than those who received the hydrolyzed formula alone. They also excreted less TNF-α and α-1-antitrypsin in their stool suggesting that the probiotics decreased gut inflammation. [77] Atopic infants treated with extensively hydrolyzed whey-based formula with L rhamnosus (GG) or B lactis showed greater improvement in severity of skin manifestations than with hydrolysate formula alone. The probiotic-supplemented group also demonstrated a reduction in serum soluble CD4 (a marker of T-cell activation) and an increase in serum TGF-β1 involved in suppressing the inflammatory response via IgE production and oral tolerance induction. [21] These studies suggest that regular probiotic supplementation may stabilize intestinal barrier function and play a role in modulating allergic responses leading to a decreased severity of atopic symptoms, particularly atopic dermatitis associated with cow's milk protein [21,29,78].

A marked anti-inflammatory effect was produced by bifidobacteria with an IL-10 induction by dendritic cells and consequent inhibition of Th1 activation with decreased interferon-γ production [79]. In atopic infants supplemented with B lactis a decrease of Bacteroides and E coli in the stool was shown. Most interestingly, serum IgE correlated with E coli counts, and in highly sensitized infants correlated with Bacteroides counts. Thus, certain probiotics seem to influence the gut's allergen-stimulated inflammatory response and provide a barrier

effect against antigens that might otherwise ultimately lead to systemic allergic symptoms such as eczema. [37]

Proliferation and growth of beneficial bacteria in the digestive system is being promoted with the use of prebiotics. Prebiotics are generally considered to be safe and they are naturally present in several kinds of food. A food ingredient must fulfill the following criteria to be considered a prebiotic: it should be hydrolyzed or absorbed in the upper part of the gastrointestinal tract, it has to be a selective substrate for beneficial bacteria in the colon for example bifidobacteria, and it must be able to alter the intestinal microflora towards a healthier composition [80].

In regards to the immunomodulatory effect of prebiotics, the proposed mechanisms of action are the following: They are thought to stimulate the activity of lactic acid bacteria, such as lactobacilli and bifidobacteria, which have immunomodulatory qualities. A second mechanism of action is that fermentation of prebiotics by lactic acid bacteria enhances Short Chain Fatty Acids (SCFA) that they act as energy substrate for colonocytes. It has been shown that SCFA stimulate Interferon-γ and IL-10 production. [81-84]

The immunomodulatory effect of prebiotics on the prevention of atopic dermatitis has been evaluated by several studies. A study by Moro et al showed that a mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age [85]. A study by van der Aa et al determined the effect of Bifidobacterium breve M-16V combined with a prebiotic oligosaccharide mixture (synbiotic) on atopic markers. The synbiotic mixture had no detectable effect on plasma levels of the analysed atopic disease markers in vivo [86]. Another study by de Kivit S, et al investigated the effect of prebiotic galacto- and fructo-oligosaccharides (scGOS/lcFOS) in combination with Bifidobacterium breve M-16V (GF/Bb) on atopy. The study showed that dietary supplementation with GF/Bb enhances serum galectin-9 levels, which associates with the prevention of the allergic symptoms. [87]

In conclusion, although theoretically pro-, pre and synbiotics are promising candidates to prevent or treat AD, results of the clinical trials performed so far are not conclusive. Prevention trials show promising but heterogenic results. Therefore at this moment there is not enough evidence to support the use of pro-, pre-, or synbiotics for prevention of AD in clinical practice. Results of treatment trials are not very convincing, however pro- or synbiotics could possibly play a role in the treatment of IgE-associated AD, which should be elucidated in future prospective trials.

4.5. Necrotizing enterocololitis

Microflora establishment and composition in premature infants is a major determinant in the pathophysiology of NEC. The premature infant is exposed to a variety of factors that negatively affect their possibilities of attaining an appropriate colonization. These factors include increasing exposure to potential delayed colonization, colonization with “neonatal intensive care unit environmental microbes”, use of antibiotics, lack of exposure to maternal flora and breast milk.

Mechanisms by which probiotics could prevent NEC include increase in favorable type microflora with reduced colonization by pathogens, increased intestinal barrier to translocation of bacteria into the bloodstream, modification of the host response to microbial products by sensitization and immunization, and enhanced tolerance and advancement of enteral nutrition [88-91.]

Several RCTs have assessed the efficacy of probiotics in preventing NEC. In a preospective, double-blind study premature infants (n=585) were randomized to receive standard milk formula supplemented with L rhamnosus G, or placebo. The group supplemented with L rhamnosus GG was found to have lower incidence of urinary tract infections and lower, but not statistically significant, incidence of NEC [92]. Two other trials have shown various degrees of reduction in relative risk of NEC with probiotics. The first study compared the incidence of NEC and the mortality of very-low-birth-weight (VLBW) infants fed breast milk with or without added probiotics. Infants (n=187) were randomized to receive breast milk or breast milk with L. acidophilus and B. infantis. In the intervention group the incidence of NEC was significantly decreased compared with the incidence in infants given breast milk alone [93]. The second study compared neonates receiving B infantis, S thermophilus, and B bifidus with neonates receiving no probiotic supplement. The incidence of NEC was 4% in 72 supplemented infants versus 16, 4% in 73 controls. The severity of NEC was less severe in the probiotic group. Three of 15 infants with NEC died, all in the control group [94].

A meta-analysis of RCTs evaluated if probiotic supplementation in preterm (<34 weeks gestation) VLBW(< 1500 gr) neonates could prevent NEC. The risk for NEC and death was significantly lower in the intervention group, while the risk for sepsis was not significantly different between the intervention group and the placebo. No significant adverse effects were reported [95].

In conclusion, specific clinical benefits are increasingly demonstrated for specific bacteria, which determine their probiotic capability. The protective and immune modulatory mechanisms that explain these effects are increasingly being documented.

5. Safety concerns of probiotics use

Newborn infants can develop infection from many species of resident microflora. The mechanisms for these infections and route of contamination are unclear. Many strains of Lactobacilli and Bifidobacteria are generally recognized as safe for use in the food supply. Documented correlations between systemic infections and probiotic consumption are few, and they have all occurred in patients with underlying medical conditions. Sporadic lactobacillemia from environmental, dietary, or fecal lactobacilli has been very rarely reported. Case reports of L rhamnosus (GG) infections possibly associated with probiotic consumption, in immunocompromised patients have been even less common [96, 97].

As opposed to the rarely reported episodes of lactobacillemia (some associated to ingested Lactobacilli), bifidobacteremia has not been sporadically reported, whether associated with consumption of commercial products containing Bifidobacteria or not. Bifidobacteria have also been consumed in infant formulas for more than 15 years worldwide and have not been

associated with any pathologic or adverse event. Studies so far have documented safety and adequate growth with B. lactis in infants from birth [39] and in vulnerable populations, including preterm infants, [33, 19] malnourished infants, [98] and infants born to mothers with HIV disease [99]

From the safety point of view, according to current available information, Bifidobacteria, particularly B lactis, has a uniquely strong safety profile, making it a good probiotic candidate for newborns and young infants. Lactobacilli, particularly L rhamnosus (GG), also seems generally safe and be appropriate for older infants and children. Until adequate data are available for each specific probiotic bacterium, use of probiotics in general cannot be recommended in immunocompromised populations. However, as safety is better documented for specific bacteria, we may be able to use them in certain populations that may benefit the most from probiotic use.

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