

## Medical Position Paper

# Probiotic Bacteria in Dietetic Products for Infants: A Commentary by the ESPGHAN Committee on Nutrition

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## INTRODUCTION

There is considerable interest in including probiotics in dietetic products for children, and such products are marketed in many countries. This commentary by the ESPGHAN Committee on Nutrition reviews available information on the effects of adding probiotic bacteria to infant formulas, follow-on formulas, and special medical foods. It also discusses the safety of these products and the appropriate conditions for their use. The Committee reviewed expert consensus documents on probiotics in foods and dietetic products for infants. The Committee also systematically reviewed all randomized clinical trials on dietetic products containing probiotics which involved infants. Because probiotics are available in many forms, such as capsules and powders, the Committee reviewed controlled clinical trials that examined the effects of different probiotic preparations for infants. The conclusions of this commentary may require revision in the future as new information becomes available.

## GUT MICROFLORA

Most studies report that the stool flora of breast-fed infants differs from that of formula-fed infants (1). Breast-fed infant stools contain predominantly *Bifidobacterium* and *Lactobacillus*, which may account for as much as 90% of the total flora (2). In contrast, the flora

of formula-fed infants is more diverse, containing *Bacteroides*, *Bifidobacterium*, *Staphylococcus*, *Escherichia coli*, and *Clostridia* (2–4). The species of *Bifidobacterium* in the stools of breast- and formula-fed infants differ (5). A variety of factors has been proposed as causes for the different fecal flora of breast- and formula-fed infants, including the lower content and different composition of proteins in human milk, its lower phosphorus content, the large variety of oligosaccharides in human milk, and numerous humoral and cellular mediators of immunologic function in breast milk (6).

The gut flora appear to modulate health and well-being of the host (7,8). The lower incidence of gastrointestinal and other infections in breast-fed infants (9–11) may in part be related to their gut flora. *Bifidobacterium* and *Lactobacillus* inhibit the growth of pathogenic microorganisms through the production of lactic, acetic, and other organic acids, with a consequent decrease of intraluminal pH, whereas formula feeding favors propionate and butyrate production and a near neutral fecal pH. Moreover, *Bifidobacterium* and *Lactobacillus* compete with potentially pathogenic bacteria for nutrients and epithelial adhesion sites. The gut flora also promote the recovery of energy and nutrients through fermentation of nondigestible carbohydrate, nitrogen salvage, and beneficial effects on mucosal growth and water and nutrient absorption (12). Evidence is accumulating that gut flora also modulate mucosal physiology, barrier function, and systemic immunologic and inflammatory responses (13). The growing interest in the role of the bacterial gut flora on health has stimulated different strategies to modify the human intestinal flora, including the provision of bacteria considered probiotics and nondigestible carbohydrates considered prebiotics.

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## DEFINITIONS

The term *probiotic* was introduced in 1965 by Stillwell and Lilly (14). A widely accepted definition of probiotics is “live microbial food ingredients that are beneficial to health” (15). However, the scientific basis of this definition has recently been questioned because animal studies suggest that some probiotic effects can be achieved by nonviable bacteria and even by bacterial DNA (16–18). Therefore, probiotics have more recently been defined as “microbial cell preparations or components of microbial cells with a beneficial effect on the health and well being of the host” (19).

*Prebiotics* are “non-digestible food components that benefit the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thereby improve host health” (15). *Synbiotics* are “mixtures of probiotics and prebiotics that benefit the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract” (15).

## EXPERT COMMITTEE REPORTS ON THE USE OF PROBIOTICS IN HUMANS

The joint FAO/WHO *Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria* concluded that probiotic strains belong primarily to two genera, *Lactobacillus* and *Bifidobacterium*, which must survive the passage through the digestive tract and proliferate in the large bowel. *Enterococcus* strains should not be used as probiotic microorganisms (20). It was recommended that strains be named according to the International Code of Nomenclature, be deposited in an internationally recognized culture collection, and that strain identification be performed by phenotypic tests followed by genetic identification with methods such as DNA/DNA hybridization and 16sRNA sequencing (21). Stock cultures should be maintained under appropriate conditions and be checked periodically for strain identity and probiotic properties. Because no *in vitro* tests predict the probiotic activity of a strain, activity should be determined in clinical trials following accepted standards of scientific quality. Beneficial effects must be related to dosage regimens and duration of use in each product or strain. Safety considerations should include transmission of antibiotic or drug resistance inherent in some probiotic microorganisms. The Expert Consultation further recommended that dried milk powders containing live lactic acid bacteria should preserve adequate numbers of viable probiotic bacteria with stable probiotic properties throughout shelf-life, and that labeling should include the microbial species or strain and the proportion of viable organisms. Claims for health benefits should be substantiated with scientific evidence. Subsequently published *Guidelines for the Evaluation of*

*Probiotics* (22) further emphasize the need to fully evaluate the safety of probiotics, in particular the risk of infection in subjects with compromised immunity and subjects at risk for endocarditis.

The French Agency for Food Safety (AFFSA) reviewed the safety of probiotics in infants, excluding genetically modified and nonviable microorganisms from its definition of probiotics (23). The report distinguished two distinct periods of modification of intestinal colonization: the first week of life, when breast-fed infants develop a flora dominated by bifidobacteria and formula-fed infants develop a more complex flora, and the period when complementary feeding is started. The report concluded that the possible health consequences of the enzymatic activities of the more diversified flora of formula-fed infants compared with that of breast-fed infants are not known. For infants without lactose intolerance, the lactose-fermenting capacity of probiotic bacteria confers no appreciable benefit. No conclusion was made as to whether reduced bacterial translocation, seen in animals supplemented with certain probiotic strains, occurred in infants. The Agency recommended for safety reasons that probiotics should not be given to immunocompromised or premature infants. In addition to requirements on strain identity, viability, strain stability, and number of probiotic bacteria in a food at the end of its shelf life, the Agency recommended that instructions for preparation, storage, and heating of the formula be specific to guarantee the survival of the desired number of microorganisms until the time of feeding. The Agency further recommended that nutritional, physiological, and therapeutic effects be documented in appropriate clinical studies.

The Scientific Committee on Food of the European Commission also commented on the use of probiotic bacteria in food products for infants (24). It recommended that infant formulas with probiotic microorganisms should be marketed only if their benefit and safety have been evaluated according to the principles outlined by the same Committee. The Committee did not object to the addition of probiotic bacteria to follow-on formulas. However, the Committee stated that only bacterial strains with identity and genetic stability demonstrated by cultural and molecular methods should be used. The identity of the probiotic strain should be described by molecular methods in a dossier and be available to the food control authorities. The content of viable bacteria should be adequate throughout shelf-life to achieve  $10^6$  to  $10^8$  colony-forming units (CFU) per gram of formula prepared as ready for consumption.

## SYSTEMATIC REVIEW OF CLINICAL TRIALS ON DIETETIC PRODUCTS WITH PROBIOTICS IN INFANTS

Three databases (MEDLINE, EMBASE, and Cochrane Controlled Trials Register) were searched up to

July 2003. We reviewed randomized and quasirandomized (i.e., allocating participants according to date of birth, the number of hospital records, etc.) controlled trials (RCT) of infant or follow-up formulas, or special medical foods, supplemented with bacteria generally considered probiotics. All references to review articles in the identified trials were reviewed. A separate search was made using the names of authors considered experts in this field. No limit was imposed as to the language of publication. Letters to the editor, abstracts, and proceedings from scientific meetings were excluded. Only clinically important outcomes (end points) were considered. Surrogate outcome measures (laboratory parameters) were excluded. After the exclusion criteria were applied, the search strategies yielded six articles on the clinical effects of feeding dietetic products supplemented with probiotics, including four on infant or follow-on formulas (25–28) and two on special medical foods (29,30) (Table 1). When scoring trial quality using Jadad's criteria (31), only one study was of good methodological quality (25).

### A. Clinical Effects

*Infant and follow-on formulas.* One high-quality double-blind RCT of 55 infants and young children aged 5 to 24 months in a chronic medical care hospital in a developed country found that administration of standard infant formula supplemented with *Bifidobacterium lactis* (formerly called *Bifidobacterium bifidum*) ( $1.9 \times 10^8$  CFU/g powdered formula) and *Streptococcus thermophilus* ( $0.14 \times 10^8$  CFU/g) reduced the prevalence of nosocomial diarrhea compared with placebo (7% versus 31%; relative risk [RR]: 0.2; 95% confidence interval [CI]: 0.06–0.8). The risk of rotavirus gastroenteritis was significantly lower in those receiving probiotics supplemented formula (RR: 0.3; 95% CI: 0.09–0.8). Feeding *B. bifidum* and *S. thermophilus* led to a significantly lower rate of rotavirus shedding (25).

One low quality RCT (no blinding, allocation concealment unclear, dropout and withdrawal rate not documented) involving 175 children living in an orphanage in a developing country reported no protective effect of infant formula supplemented with *Bifidobacterium Bb12* ( $10^8$  CFU/g) alone on episodes of diarrhea (40/62; 65%) or in combination with *S. thermophilus* (dose not given) (29/56; 52%) compared with placebo (14/57; 25%). Rotavirus accounted for only 3 of 81 (3.7%) episodes of diarrhea, and bacterial pathogens accounted for 45 of 81 (56%) episodes of diarrhea (26).

*Foods for special medical purposes.* Two small RCTs of infants with atopic dermatitis and cow's milk allergy during formula feeding or breastfeeding were found (29,30). Neither study provided details of randomization and blinding. Allocation concealment was unclear. In the first study (29), infants ( $n = 27$ ) with atopic eczema and

cow's milk allergy were randomly assigned to receive extensively hydrolyzed whey formula supplemented with *Lactobacillus GG* ( $5 \times 10^8$  CFU/g formula) or placebo for 1 month. There was a statistically significant reduction in the clinical score of atopic dermatitis (SCORAD) during the 1-month study. However, by 2 months the SCORAD was similar in both groups. In the second study (30), infants ( $n = 27$ ) with atopic eczema during exclusive breastfeeding were randomly assigned to receive extensively hydrolyzed whey formula supplemented with *Lactobacillus GG* ( $3 \times 10^8$  CFU/g), or *Bifidobacterium lactis Bb-12* ( $1 \times 10^9$  CFU/g), or the same formula without probiotics. No details on the duration of intervention were given. After 2 months, a statistically significant reduction in SCORAD score was observed in the groups consuming probiotics compared to placebo. A significant change in the SCORAD scores at the 2-month evaluation was seen in 9 of 9 patients receiving *B. lactis Bb-12*, and in 9 of 9 patients in the *Lactobacillus GG* group, as compared with 4 of 9 patients not receiving probiotics.

In conclusion, there are very limited published data on the clinical effects of probiotic supplementation of infant formulas, follow-up formulas, and special medical foods. Although some short-term benefits are scientifically demonstrable, until more studies are available it is not possible to conclude that the clinical effects of probiotic supplementation are preventive or therapeutic for any childhood disease.

### B. Growth Parameters

It is recommended that the safety of breast milk substitutes be evaluated carefully before they are introduced to the market (32,33). An important part of this evaluation is assessing the impact on growth. Below we have summarized growth data from studies evaluating the effect of infant formulas and foods for special medical purposes.

*Infant and follow-on formulas.* Three RCTs evaluating growth of children fed formulas supplemented with probiotic bacteria were found (Table 1) (25,27,28). The first RCT (27) evaluated newborn infants randomized to formula with or without *Streptococcus thermophilus* and *Lactobacillus helveticus* for the first 2 months of life. There were 20 infants in each group, and the two groups were compared with a group of 14 fully breast-fed infants. Weight, length, and head circumference were recorded at birth, 1 month, and 2 months. No data on growth were given. It was stated that that the three kinds of feeding assured normal growth during the first 2 months of life without any significant difference, but there was no information on how this conclusion was tested.

In the second RCT (25), infants aged 5 to 24 months with chronic illnesses and in a chronic medical care hos-

**TABLE 1.** *Trials with dietetic products for infants and young children supplemented with probiotics*

Author	Study	Allocation concealment	Age (mo)	Patients/ Setting	Intervention	Main results	Jadad score
Infant and follow-on formulas							
Saavedra et al. <sup>25</sup>	RCT	Adequate	5–24	Chronic medical care hospital (USA)	FOF with <i>Bifidobacterium bifidum</i> ( $1.9 \times 10^9$ CFU/g) and <i>Streptococcus thermophilus</i> ( $0.14 \times 10^7$ CFU/g of powder) (n = 29) or control formula (n = 26), mean duration 81 days	Reduced number of patients with diarrhea (RR 0.2 [0.06–0.8]; NNT 5 (3–20))	5
Phuapradit et al. <sup>26</sup>	RCT*	Unclear	6–36	Orphanage (Thailand)	FOF with <i>Bifidobacterium lactis</i> Bb12 ( $10^8$ /g of powder, n = 62) or with Bb12 + <i>Streptococcus thermophilus</i> (ST) (dose not reported, n = 56) or cow's milk formula (n = 57) for 8 mo	Episodes of observed diarrhea; control 25%, Bb 65%, Bb + ST 52% (significance not reported)	1
Langhendries et al. <sup>27</sup>	RCT*	Unclear	0–2	Home (Belgium)	IF + <i>Streptococcus thermophilus</i> and <i>Lactobacillus helveticus</i> ( <i>Bifidobacterium bifidum</i> ) $10^6$ /g of powder, (n = 20) or control (n = 20) or breast-fed infants (n = 14; not randomized)	Colonization with bifidobacteria at 1 month, similar in Bb formula (12/20) v breast-fed (8/14), but significantly higher ( $P < 0.05$ ) than in the group fed standard infant formula (4/20) Mean bacterial count of bifidobacteria similar in all colonized infants. Fecal pH significantly lower in the breast-fed infants than in the nonacidified bottle-fed infants.	3
Nopchinda et al. <sup>28</sup>	RCT*	Unclear	6–36	Orphanage (Thailand)	FOF (?) with <i>Bifidobacterium bifidum</i> Bb12 ( $3 \times 10^7$ CFU/g of powder, n = 51) or with Bb12 + <i>Streptococcus thermophilus</i> (ST) ( $3 \times 10^7$ CFU/g of powder n = 54) or cow's milk formula (FOF) (no details given) (n = 43) for 6 mo	Nutritional status (mean Z score of: weight; change of weight; height; height change; weight/height during 6 mo of intervention) Significant differences between groups at entry; no data on the amount of formula consumed and on the duration of intervention in each group. At 6 mo, data of 84/184 (57%) subjects enrolled (Bb12 71%; Bb12 + ST 43%, FOF 58%)	2

TABLE 1. Continued

Author	Study	Allocation concealment	Age (mo)	Patients/Setting	Intervention	Main results	Jadad score
Foods for special medical purposes							
Isolauri et al. <sup>30</sup>	RCT*	Unclear	Mean age 4.6 (age range not given)	Infants with atopic eczema during breast feeding (Finland)	Extensively hydrolyzed whey formula (H) (n = 9) Extensively hydrolyzed whey formula + <i>Bifidobacterium lactis</i> Bb-12 (HBb12) (1 × 10 <sup>9</sup> CFU/g) (n = 9); Extensively hydrolyzed whey formula + <i>Lactobacillus</i> GG (HLLG) (3 × 10 <sup>8</sup> CFU/g) (n = 9) Duration of intervention not reported (2 mo?)	After 2 mo: SCORAD significantly decreased in both groups treated with probiotic supplemented hydrolysates (HBb12 before treatment: 12 (5.5–18); after treatment: 0 (0–3.8); HLLG before treatment: 14.5 (6–25.3); after treatment: 1 (0.1–8.7); no significant difference in HS group; before treatment: 10 (6.5–26.5); after treatment: 13.4 (4.5–18.2). SCORAD significantly improved in 9/9 in HS-Bb-12 group after 2 mo v 9/9 in HS/LGG group v 4/9 in HS group; RR: 2.2 (95% CI: 1.5–5). After 6 mo: no difference in SCORAD.	2
Majamaa and Isolauri <sup>29</sup>	RCT*	Unclear	2.5–15.7	Infants with atopic eczema and cow's milk allergy (Finland)	Extensively hydrolyzed whey formula (n = 14) or extensively hydrolyzed whey formula + <i>Lactobacillus</i> GG (5 × 10 <sup>8</sup> CFU/g) (n = 13) for 1 mo; follow-up for 2 mo	SCORAD after 1 mo significantly [from 26 (17–38) to 15 (7–28)], but no change in controls (from 21 (14–31) to 19 (13–31)]. After 2 mo: no significant difference between the study groups.	2

\*No details on randomization given.

RCT = randomized controlled trial; IF = infant formula; FOF = follow-on formula; CFU = colony forming units; RR = relative risk; NNT = number needed to treat; SCORAD = score of atopic dermatitis.

pital were randomized to receive standard infant formula (n = 26) or the same formula supplemented with *Bifidobacterium bifidum* and *Streptococcus thermophilus* (n = 29). The average duration of treatment was 81 days. There was no difference in the mean weight and height of the groups at enrollment. Weight was measured weekly, but no data were presented on growth during the treatment, and the groups were not compared. It was stated only that all infants maintained or improved their nutritional status during the study.

The third RCT (28) of 148 malnourished children aged 6–36 months was conducted in a nursing home in Thailand. The children were randomized to three formulas, which they received for 6 months: one group received infant formula with *Bifidobacterium lactis* Bb-12 and

*Streptococcus thermophilus* (n = 54), one group received the same formula with only Bb-12 (n = 51), and one group received formula without probiotics (n = 43). Weight and length were measured monthly, and the change in standard deviation score was used to evaluate growth. There were no significant differences in rate of weight gain among the groups. The two groups with probiotics had a significantly better length growth velocity toward the end of the intervention than did the control group. The difference was equal to about 0.5 SD. Unfortunately, the evidence is of poor quality because no details of randomization were given, allocation concealment was unclear, there were significant differences between the study groups in baseline characteristics (because of inadequate randomization?), no data were given

on amounts of formula consumed, and the follow-up at 6 months was incomplete (Table 1).

*Foods for special medical purposes.* Only one study has measured growth in 27 infants randomly assigned into three groups: extensively hydrolyzed whey formula with either *Bifidobacterium lactis* Bb-12, *Lactobacillus* GG, or no probiotics added (30). Weight and length were measured at start and after 2 and 6 months of intervention. It was stated that the growth of all children was normal, but the groups were not compared.

In conclusion, only one study has provided growth data adequate to assess the effects of infant formula with added probiotics. This study was performed in malnourished infants living in a residential facility in Thailand. One limitation of that study was its large age range, from 6 to 36 months, because growth velocity and regulation of growth are different in young infants and toddlers. This study found a positive effect of probiotics on linear growth, but because the evidence is of poor quality, the conclusion is of limited value. The other studies were too small with insufficient power to identify relevant effects on growth. Furthermore, most of the studies did not present the growth data. With a lack of robust evidence, no conclusions can be made regarding the impact of probiotic bacteria in dietetic products on infant growth. However, there are no indications from the available data that probiotics have any adverse effects on growth.

#### OTHER RANDOMIZED CONTROLLED CLINICAL TRIALS ON THE USE OF PROBIOTICS IN CHILDREN

There is extensive literature on the effects of probiotics supplied in other forms (e.g., pills, powdered supplements, fermented dairy foods) but relatively few RCTs. Best documented are the therapeutic effects of certain probiotic strains in acute infectious gastroenteritis, as recently summarized in two systematic reviews (34,35). A moderate beneficial effect was found in the treatment of watery diarrhea caused by rotavirus, which was strain and dose dependent. Some benefit also appears to be achieved in diarrhea caused by other viruses, but no efficacy was found in invasive bacterial diarrhea. Beneficial effects were more pronounced when treatment with probiotics was initiated early in the course of disease (36,37).

Two recent systematic reviews show that probiotics given in combination with antibiotics reduce the risk of antibiotic-associated diarrhea (38,39). In particular, the yeast *Saccharomyces boulardii* and several strains of lactobacilli have been used in this situation. However, with few exceptions, the trials were performed in adults, and thus the authors' conclusion may not be applicable to children. Thus, the Committee looked specifically at the studies in children. Four trials were identified. One small RCT (38 children treated with *L. acidophilus* and *L. bul-*

*garicus*) found no significant prevention of antibiotic-associated diarrhea (odds ratio [OR]: 0.88; 95% CI: 0.22–3.52) (40). A further double-blind RCT looked at *L. acidophilus* and *Bifidobacterium infantis*, but methodological limitations (i.e., small sample size, lack of definition of diarrhea as an end point) preclude drawing reliable conclusions (41). Two RCTs showed a moderate preventive effect of *L. rhamnosus* GG for mild antibiotic-associated diarrhea in children (42,43), but results in adults are conflicting (44). Lower dosage of *Lactobacillus* GG used in adults, differences in administered antibiotics, and age-related differences in the pathologic mechanism of antibiotic-associated diarrhea may be responsible for conflicting results. There are no randomized studies in children on the incidence of antibiotic-associated diarrhea caused by *Clostridium difficile*.

Three studies of the efficacy of probiotics for preventing nosocomial diarrhea were identified. One small trial (discussed earlier) suggested beneficial effects of *Bifidobacterium bifidum* and *Streptococcus thermophilus* (25). Evidence for the effectiveness of *Lactobacillus* GG is conflicting, with one RCT claiming substantial benefit (45) and another (using different dosing) showing none (46).

A modest protection against community-acquired diarrhea was shown in a trial of *Lactobacillus rhamnosus* GG used in a developing country in a community with a high burden of diarrheal disease. This benefit was particularly evident in children 18 to 29 months of age who were not breast fed (4.7 v 5.9 episodes/child/year;  $P = 0.005$ ) (47). However, no preventive effect was found in a similar trial in Finland (48). In a double-blind, randomized, long-term study of 571 healthy children 1 to 6 years of age from 18 day care centers, milk containing *Lactobacillus* GG conferred no significant protection against diarrhea, as measured by the number of days with diarrheal symptoms or the proportion of children without diarrhea during the 7-month study period. However, the group treated with *Lactobacillus* GG seemed to have less severe disease, with a 16% (95% CI, 2–27) reduction in the number of days absence caused by gastrointestinal and respiratory illness during the study (4.9 v 5.8 days;  $P = 0.03$ ). The same study demonstrated a slight reduction of respiratory infections (RR: 0.8; 95% CI: 0.7–0.99; number needed to treat [NNT] 12; 95% CI: 6–1,685), and antibiotic courses (RR: 0.8; 95% CI: 0.7–0.98; NNT: 11; 95% CI: 6–108) in children fed milk with added *Lactobacillus rhamnosus* GG. After adjustment for age, however, none of these differences was statistically significant.

In the same study, significant reduction in the risk of dental caries was seen (OR 0.56;  $P = 0.01$ ; controlled for age and gender, OR 0.51;  $P = 0.004$ ) (49). Whether the use of *Lactobacillus* GG is more cost-effective than fluoride has not been established.

Another recent randomized, placebo-controlled study from Finland found that *Lactobacillus* GG ( $1 \times 10^{10}$  CFU) given to the mother for 2 to 4 weeks before delivery and then postnatally to the child for 6 months substantially reduced the incidence of atopic eczema in children at 2 (RR: 0.51; range, 0.32–0.84; NNT: 5; range, 3–17) (50) and 4 years of age (RR: 0.57; range, 0.33–0.97; NNT: 6; range, 3–64) (51). One double-blind, placebo-controlled, crossover study suggested that a combination of *L. rhamnosus* 19070–2 and *L. reuteri* DSM 122460 given for 6 weeks to children 1 to 13 years of age might be beneficial in the treatment of atopic dermatitis (52). Characterization of possible underlying mechanisms and confirmation of the clinical effects by further investigations in other populations is necessary.

Data from animal models and patients with inflammatory bowel disease have highlighted the importance of the enteric microflora in the pathogenesis of the disease, yet in clinical trials, probiotics have had only limited efficacy against active disease. In children with Crohn disease, a preliminary open-labeled trial of *Lactobacillus* GG suggested that *Lactobacillus* GG reduced intestinal permeability and disease activity (53). However, a recent placebo-controlled randomized study (65 children with small and large bowel Crohn disease in remission) showed that *Lactobacillus* GG in a dose of  $10^9$  CFU twice daily was not helpful in maintaining remission when added to standard maintenance therapy for Crohn disease (54).

In children, we conclude that the best proven health effect of probiotics is the reduction of the duration of acute infectious gastroenteritis. The true benefit of probiotics in other conditions is yet to be defined. However, there is a body of promising evidence to suggest that they may be effective in the prevention of nosocomial and antibiotic-associated diarrhea, respiratory diseases, and allergic diseases. Effects appear to be strain specific and cannot be extrapolated from strain to strain.

#### REPORTS ON THE USE OF PROBIOTICS IN PRETERM INFANTS

Prematurity and low birth weight are risk factors for morbidity and mortality from sepsis and neonatal necrotizing enterocolitis (NEC) (55). It has been suggested that enteral administration of probiotics to premature newborns with patterns of intestinal colonization different from those of healthy, full-term newborns could prevent infection and NEC and thus the use of antibiotics (56).

Several studies have examined the ability of probiotics to colonize the gut of preterm and low-birth-weight infants. Reports on the colonizing capability of *Lactobacillus* GG have varied (57–59). An 86% colonization rate was reported in a randomized controlled trial of *L. acidophilus* (60). One RCT in 91 very low-birth-weight in-

fants found that infants whose feedings were supplemented with *Bifidobacterium breve* ( $10^9$  CFU/day) had higher rates of fecal bifidobacterial colonization at 2 weeks of age (73% v 12%), decreased gastric aspirates, improved weight gain, and improved feeding tolerance. Clinical outcomes were not reported (61). In Columbia, the prophylactic administration of *L. acidophilus* and *Bifidobacterium infantis* to all neonates in an intensive care nursery with a high incidence of NEC reduced the incidence of disease compared with historical controls (62). The study is limited by not being appropriately controlled. A recent multicenter randomized controlled trial in 585 preterm infants found that *Lactobacillus* GG supplementation ( $6 \times 10^9$  CFU once daily) starting with the first feeding did not reduce urinary tract infections, NEC, or sepsis (63).

In summary, only a limited number of controlled trials have studied health outcomes following enteral administration of probiotic organisms in preterm infants. Additional studies are needed.

#### SAFETY ASPECTS

The safety of probiotics has been extensively reviewed recently (64,65). Although the probiotics so far used in clinical trials generally have been described as safe and well tolerated, there have been some concerns that this conclusion requires additional evaluation. In recent years several microorganisms in probiotics have been isolated from patients with endocarditis, bacteremia or local infections (66–70), and infections with *Lactobacillus* species in infants and children have been reported (71–76).

Almost all patients with infections in these studies have had underlying conditions predisposing them to infection, e.g. structural heart defects in the case of endocarditis, or indwelling catheters in the case of sepsis. In most cases of infection, the organism appears to have come from the patient's own microflora. Only a limited number of cases have been reported in which the organism was thought (although not necessarily proven) to be related to the use or consumption of a commercial probiotic product (*L. rhamnosus* (69,77), *Saccharomyces* (78), *Bacillus* (79–81)). In these patients too, serious underlying conditions were common. Cases of infection with *Bifidobacterium* during supplementation with this organism have not been reported. A recent report from Finland indicated that the increased use of *Lactobacillus* GG in food has not resulted in an increased incidence of *Lactobacillus* bacteremia or in the proportion of *Lactobacillus* bacteremia among all cases of bacteremia (82). Bacteremia associated with enterally administered probiotics has not been reported in infants or children but is a theoretical risk.

Several evaluations of the published literature have concluded that the risk of infection with probiotic lactobacilli or bifidobacteria is similar to that of infection with

commensal strains, and that consumption of such products is a negligible risk to consumers, including immunocompromised hosts (65). Other side effects in which probiotics could theoretically play a role include deleterious metabolic activities, excessive immune stimulation, and gene transfer (83). However, the available data from preclinical and clinical evaluations do not provide any indication that such adverse effects would occur with the probiotic strains currently in use.

In summary, probiotics so far used in clinical trials can be generally considered as safe. However, surveillance for possible side effects, such as infection in high-risk groups, is lacking and is needed.

### CONCLUSIONS

Our review of available clinical trials found only limited data on the safety and clinical effects probiotic preparations added to infant formulas, follow-up formulas, and special medical foods. There is no published evidence for any long-term clinical benefit of infant formulas supplemented with probiotic bacteria. No data are available on possible long-term effects on intestinal colonization and its effects on long-term gastrointestinal and immune functions. Acquisition of such data would be highly desirable given the suggestion that bacteria ingested during early infancy are more likely to permanently colonize the intestine than those ingested during later life (84). There are some data supporting a short-term benefit of some probiotic strains in infants and young children with infectious diarrhea.

The Committee recommends that when adding probiotics to dietetic products for infants, only bacterial strains for which identity and genetic stability have been demonstrated by cultural and molecular methods and strains considered as generally safe when added to the food in question should be used. The content of viable bacteria in dietetic products must provide a dose shown to be safe and effective with regard to defined outcomes in clinical trials throughout the shelf-life of the product.

The Committee concludes that further evaluation of the safety and efficacy of supplemental probiotic bacteria in dietetic products for infants is necessary. Each strain to be used must be evaluated at the range of doses intended for use, and minimal and optimal effective doses must be defined. Specific safety questions that should be addressed are the effects on nutrient use, the possible transfer of antibiotic resistance, the short- and long-term effects on the immune response, and the risk of infection.

The Committee is concerned that the available data are not sufficient to support the safety of probiotics in healthy newborn and very young infants with immature defense systems, infants with immunocompromised systems, premature infants, and infants with congenital heart disease.

The Committee recommends that infant formulas with added bacteria regarded as probiotics should be marketed

only if a full evaluation of benefits and safety following the general principles of current standards (32,33) has been performed. Although the available data on the use of supplemented follow-on formulas is limited, the Committee has fewer concerns about potential adverse effects of these products because they are designed for use in infants older than 5 months, when there is a more mature immune response, an established intestinal colonization, and a history of exposure to a variety of organisms from the environment. The addition of probiotic bacterial strains to infant foods prescribed for special medical purposes and used under strict medical supervision may be justified if a clinical benefit has been established in adequate clinical trials, even if a full evaluation of all safety aspects has not been performed, for example because of the limited number of patients to be treated with a the specific dietetic product.

The Committee recognizes that there is evidence that some probiotic preparations have benefits on health and well-being. Reported benefits include a reduced severity of diarrhea, potential preventive effects on diarrhea, promising results of in vitro and animal studies on digestive and immune functions, and indications from human studies on possible short-term preventative and therapeutic effects on atopic eczema. In view of the potential for benefits on child health that might be achieved by the use of some probiotic bacteria, major efforts on their thorough evaluation are justified.

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