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Guidance for the Clinician in Rendering Pediatric Care

Clinical Report—Probiotics and Prebiotics in Pediatrics

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KEY WORDS
probiotics, prebiotics, pediatrics, supplements, nutrition

ABBREVIATIONS
LGG—*Lactobacillus rhamnosus* GG
FOS—fructo-oligosaccharide
IBD—inflammatory bowel disease
RCT—randomized controlled trial
CI—confidence interval
RR—relative risk
OR—odds ratio
NEC—necrotizing enterocolitis
CUC—chronic ulcerative colitis
IBS—irritable bowel syndrome
GOS—galacto-oligosaccharide
FDA—Food and Drug Administration

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

www.pediatrics.org/cgi/doi/10.1542/peds.2010-2548

doi:10.1542/peds.2010-2548

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

abstract

FREE

This clinical report reviews the currently known health benefits of probiotic and prebiotic products, including those added to commercially available infant formula and other food products for use in children. Probiotics are supplements or foods that contain viable microorganisms that cause alterations of the microflora of the host. Use of probiotics has been shown to be modestly effective in randomized clinical trials (RCTs) in (1) treating acute viral gastroenteritis in healthy children; and (2) preventing antibiotic-associated diarrhea in healthy children. There is some evidence that probiotics prevent necrotizing enterocolitis in very low birth weight infants (birth weight between 1000 and 1500 g), but more studies are needed. The results of RCTs in which probiotics were used to treat childhood *Helicobacter pylori* gastritis, irritable bowel syndrome, chronic ulcerative colitis, and infantile colic, as well as in preventing childhood atopy, although encouraging, are preliminary and require further confirmation. Probiotics have not been proven to be beneficial in treating or preventing human cancers or in treating children with Crohn disease. There are also safety concerns with the use of probiotics in infants and children who are immunocompromised, chronically debilitated, or seriously ill with indwelling medical devices.

Prebiotics are supplements or foods that contain a nondigestible food ingredient that selectively stimulates the favorable growth and/or activity of indigenous probiotic bacteria. Human milk contains substantial quantities of prebiotics. There is a paucity of RCTs examining prebiotics in children, although there may be some long-term benefit of prebiotics for the prevention of atopic eczema and common infections in healthy infants. Confirmatory well-designed clinical research studies are necessary. *Pediatrics* 2010;126:1217–1231

INTRODUCTION

Microbes are ubiquitous and are important factors in the overall health of humans as well as the Earth. Efforts to optimize the intestinal microbial milieu have increased the interest in adding probiotics and prebiotics to nutritional products. As with antibiotics, the use and efficacy of probiotics and prebiotics should be supported by evidenced-based medicine. The purpose of this clinical report is to review the medical uses of probiotics and prebiotics and to summarize what is currently known about their health benefits as dietary supplements added to food products marketed to children, including infant formula. The guidance in this report will help pediatric health care providers to make appropriate decisions regard-

ing the usefulness and benefit of probiotics and prebiotics for their patients.

DEFINITIONS

Probiotic: An oral supplement or a food product that contains a sufficient number of viable microorganisms to alter the microflora of the host and has the potential for beneficial health effects.[1–3]

Prebiotic: A nondigestible food ingredient that benefits the host by selectively stimulating the favorable growth and/or activity of 1 or more indigenous probiotic bacteria.[1–4]

Synbiotic: A product that contains both probiotics and prebiotics. Evidence for synergy of a specific prebiotic for a probiotic in the product is not essential. Synbiotics may be separate supplements or may exist in functional foods as food additives.[1–3]

Postbiotic: A metabolic byproduct generated by a probiotic microorganism that influences the host's biological functions.[5,6]

Functional food: Any modified food or food ingredient that provides a health benefit beyond that ascribed to any specific nutrient/nutrients it contains. It must remain a food, and it must demonstrate its effect in amounts normally expected to be consumed in the diet. Benefits may include functions relevant to improving health and well-being and/or reduction of risk of disease. Any food that contains probiotics or prebiotics is a functional food. An example of a functional food is live-culture yogurt that contains probiotic bacteria, prebiotics, and other dietary nutrients. Human milk may also be considered a functional food; it contains substantial amounts of oligosaccharides (prebiotics) and may contain some naturally occurring probiotic bacteria (10^3 of bifidobacteria per mL of expressed human milk, as reported in 1 study).[7]

WHAT ARE PROBIOTICS?

Probiotic microorganisms are typically members of the genera *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*.[1–3,8–14] These bacteria are fermentive, obligatory, or facultative anaerobic organisms, which are typically nonmotile and of varying shapes. They typically produce lactic acid. Their inherent biological features enable them to predominate and prevail over potential pathogenic microorganisms in the human digestive tract. It is currently hypothesized that these microbes generate small molecular metabolic byproducts that exert beneficial regulatory influence on host biological functions, including short-chain fatty acids such as butyrate. These metabolic byproducts are sometimes referred to as "postbiotics" and may function biologically as immune modulators.[5,6,15] The most studied probiotic bacteria to date include *Lactobacillus rhamnosus* GG (LGG), *Bifidobacterium lactis*, and *Streptococcus thermophilus*. These probiotic bacteria are biologically different from the Gram-negative, motile, non–lactic-acid–producing bacteria such as *Klebsiella*, *Pseudomonas*, *Serratia*, and *Proteus* species, which also may be prominent flora in the human digestive system. These potentially harmful bacteria may translocate across the intestinal epithelium and could result in disease in humans.[16,17] Some yeasts and yeast byproducts have also been studied and have been frequently used as probiotic agents, such as the yeast *Saccharomyces boulardii*. Probiotic bacteria can be delivered and ingested separately as medicinals or supplements. They can also be mixed with, added to, or naturally exist in functional foods.

WHAT ARE PREBIOTICS?

Prebiotics are usually in the form of oligosaccharides, which may occur naturally but can also be added as dietary supplements to foods, beverages, and infant formula.[4] Although indigestible by humans, their presence in the digestive system selectively enhances proliferation of certain probiotic bacteria in the colon, especially *Bifidobacteria* species. Prebiotic oligosaccharides often contain fructose chains with a terminal glucose and typically consist of 10 or fewer sugar molecules. Examples of prebiotic oligosaccharides include fructo-oligosaccharides (FOSs), inulin, galacto-oligosaccharides (GOSs), and soybean oligosaccharides. Inulin is a composite oligosaccharide that contains several FOS molecules. The complex polysaccharides that constitute dietary fiber can also be considered to be prebiotic agents.

Although dietary nucleotides do not fit the exact definition of a prebiotic, they are prebiotic-like agents and have immunomodulating and direct intestinal biological properties.[18] Some infant formulas contain a limited amount of added free nucleotides (7–20 mg/dL).[18] Human milk, on the other hand, contains a substantial but variable amount of oligosaccharides (14 g/L) as well as free nucleotides (up to 20% of nonprotein nitrogen).[19] Some infant-formula manufacturers now add prebiotic oligosaccharides to their products.

Beverages and nutritional supplements marketed for older infants, children, and adults contain oligosaccharides and nucleotide additives in varying amounts.

INTESTINAL BACTERIAL COLONIZATION AND DEVELOPMENT OF THE INTESTINAL MUCOSAL DEFENSE SYSTEM

Similar to the fetus, an infant at the time of birth has a sterile gastrointestinal tract, but bacterial colonization occurs rapidly.[20–22] The newborn in-

fant's gestational age, mode of delivery, and diet seem to have significant effects on this process. Neonates who are born by Caesarian delivery, born preterm, and/or exposed to perinatal or postnatal antibiotics have a delay in intestinal commensal probiotic bacterial colonization. When delivered vaginally, breastfed infants and formula-fed infants have a similar pattern of bacterial colonization at 48 hours of age. However, by 7 days of age, approximately two-thirds of formula-fed infants have a predominance of *Bacteroides fragilis*, compared with only 22% of breastfed infants.[20]

Toward the end of the first month of life in developing countries, breastfed infants are found to have *Bifidobacteria*-predominant colonization, whereas formula-fed infants have equal colonization with *Bacteroides* and *Bifidobacteria* species. In resource-rich countries, however, differences are less pronounced between breastfed and formula-fed infants.[15]

The composition of intestinal microflora does not change significantly after infancy. Therefore, the composition of fecal flora in older children and adults is less variable and not as dependent on diet. In fact, beyond infancy, bacterial concentrations in the colon are typically 10^{12} colony-forming units per mL of intestinal contents (10-fold the total number of human cells in the human body), and anaerobic bacteria far outnumber aerobic coliforms.[23] Typically, 500 different bacterial species contribute to an adult's colonic microflora, but 99% of the microflora are accounted for by 30 to 40 species.[23] The descriptive terms of "microbiota" and "microbiome" are newer terms that are replacing such terms as "microflora" in an attempt by researchers in the field to better define one's microbial environment.[24] "Microbiota" refers to a population of microscopic organisms that inhabit a bodily organ or portion of a person's body, and human "microbiome" refers to the unique entire population of microorganisms and their complete genetic elements that inhabit one's body.

The intestinal mucosal defense system is an integral part of a sophisticated immunoregulatory network that includes the intestinal microflora.[21,25–30] Recognition of self- and non–self-antigens begins early in life, perhaps even in utero, and is significantly influenced by events that occur within the digestive system soon after birth. The immunoresponsiveness of the digestive system is significantly affected by the young infant's diet, state of bacterial colonization, and early exposure to potential infectious pathogens and antibiotics as well as the infant's genotype. It is thought that the occurrence of many diseases, both intestinal and nonintestinal, can be related to dysregulation or interference with the early development of the intestinal mucosal defense system.[28,29] Examples of these diseases include those thought to be atopic (asthma, eczema, and allergic rhinitis) or autoimmune (multiple sclerosis, type 1 diabetes mellitus, and chronic inflammatory bowel disease [IBD]).[28] Certainly, the overriding determining factor in development of the immune system is one's genetic predisposition.[25]

The molecular basis for innate and acquired immunity is thought to reside in the recognition and response of mature T lymphocytes to trigger molecules, such as those derived from dietary and bacterial-breakdown products within the intestinal tract.[29] Trigger molecules also include dietary nucleotides and oligosaccharides. Toll-like receptors located in the surface membrane of T lymphocytes facilitate recognition of these trigger molecules, which eventually leads to specialized T-lymphocyte recognition and response to subsequent exposure to the same or very similar molecules. Thus, T-lymphocyte recognition of specific oligosaccharides bound to intestinal pathogens plays an important role in preventing gastrointestinal illness.

Given these important influences on intestinal microflora colonization and immune function, the infant's early diet and intestinal microbial environment are thought to serve as pivotal factors in overall health. Probiotic bacteria, postbiotic bacterial byproducts, and dietary prebiotics are believed to exert positive effects on the development of the mucosal immune system. It is also believed that exposure to "nonbeneficial" microorganisms and antimicrobial agents in the newborn period may result in immune dysregulation in susceptible individuals and may lead to some chronic disease states. There is evidence that human milk contains mononuclear cells that traffic intestinally derived bacterial components from the mother to her infant. The ingested human milk containing the bacterial components derived from the mother are thought to influence her young infant's developing immune system. This process is termed "bacterial imprinting," and its overall biological effect requires further study.[31]

USE OF PROBIOTICS IN PREVENTION AND TREATMENT OF CLINICAL DISEASES

Reviews on the clinical applications of probiotics and prebiotics can be found in the references.[4,8–14] Results of evidence-based analyses of the clinical effectiveness of probiotics and prebiotics are discussed below. It must be stressed that the current lack of evidence of efficacy does not mean that future clinical research will not establish significant health benefits for probiotics and prebiotics.

Acute Infectious Diarrhea

Prevention of Acute Infectious Diarrhea

Results of published randomized controlled trials (RCTs) have indicated that there is modest benefit of giving probiotics in preventing acute gastrointestinal tract infections in healthy infants and children.[32–35] Most of the studies were conducted in child care centers. The strains of probiotics used included LGG, *S thermophilus*, *Lactobacillus casei*, *B lactis*, or *Lactobacillus reuteri* mixed with milk or infant formula or given as an oral supplement. Rotavirus was the most common cause of acute diarrhea in the RCTs.

In a double-blind, placebo-controlled trial by Weizman et al,[36] 201 infants (4–10 months of age) received either a probiotic-supplemented formula containing either *B lactis* or *L reuteri* or a control formula without an added probiotic over a 12-week study period. The study was conducted at 14 different child care centers over a 2-year period. Infants fed a probiotic-supplemented formula had fewer and shorter episodes of diarrhea than did infants in the control group. Infants in the control group had a mean of 0.59 days of diarrhea (95% confidence interval [CI]: 0.34–0.84 days) per infant compared with 0.37 days (95% CI: 0.08–0.66 days) in the *B lactis* and 0.15 days (95% CI: 0.12–0.18 days) in the *L reuteri* probiotic-supplemented study groups ($P < .001$). During the 12-week study period, the infants in the control group were found to have a mean of 0.31 episodes of diarrhea (95% CI: 0.22–0.44 episodes) compared with 0.12 episodes (95% CI: 0.05–0.21 episodes) and 0.02 episodes (95% CI: 0.01–0.05 episodes) in the *B lactis*– and *L reuteri*–supplemented study groups, respectively ($P < .001$). There was no significant effect found on the incidence of acute respiratory illnesses. In another study conducted in child care centers in France,[37] 928 healthy children were randomly assigned to be fed either standard yogurt or yogurt supplemented with *L casei* for 4 months. The children who were fed the probiotic-supplemented yogurt had fewer episodes of diarrhea during the study period than did those who were fed standard yogurt (15.9% vs 22%; $P = .03$).

The results of a meta-analysis of probiotic prevention of acute rotavirus gastroenteritis in child care centers indicated that approximately 7 children would need to have been given LGG to prevent 1 child from developing nosocomial rotavirus gastroenteritis in a child care center setting.[38] To date, the available data do not support routine use of probiotics to prevent nosocomial rotavirus diarrhea in child care centers. However, there may be special circumstances in which probiotic use in children in long-term health care facilities or in child care centers is beneficial. The use of the newly available pentavalent rotavirus vaccine in the United States[39] will likely be a more formidable preventative agent than the use of probiotics in reducing the incidence of the most common form of acute infantile infectious diarrhea.

Treatment of Acute Infectious Diarrhea

Well-conducted RCTs in healthy children in developed countries have provided good data on the therapeutic benefit of probiotics in children with acute infectious diarrhea. In a randomized, double-blind, placebo-controlled trial by Szymanski et al,[40] administration of LGG significantly shortened the duration of acute rotavirus diarrhea by a mean of 40 hours, but duration of diarrhea of any other etiology was not affected. Probiotic administration also shortened the time necessary for intravenous rehydration by a mean of 18 hours. Results of several other meta-analyses[41–43] and a Cochrane review[44] have been published on the benefit of probiotics for treatment of acute infectious diarrhea in children. These reports indicate that probiotics reduce the number of diarrheal stools and the duration of the diarrhea by approximately 1 day. The benefit is strain-dependent. LGG is the most effective probiotic reported to date and is dose-dependent for doses greater than 10^{10} colony-forming units. Probiotics also seem to be more effective when given early in the course of diarrhea and are most helpful for otherwise healthy infants and young children with watery diarrhea secondary to viral gastroenteritis but not invasive bacterial infections. Thus, there is evidence to support the use of probiotics, specifically LGG, early in the course of acute infectious diarrhea to reduce the duration by 1 day.

Antibiotic-Associated Diarrhea

Prevention of Antibiotic-Associated Diarrhea

Meta-analysis of published results of RCTs of probiotic use in the prevention of antibiotic-associated diarrhea in children indicates a beneficial effect.[45–48] Treatment with a probiotic was started when antibiotic therapy was initiated for treatment of an acute respiratory infection (otitis media) in most of these studies. Treatment with probiotics compared with placebo reduced the risk of developing antibiotic-associated diarrhea from 28.5% to 11.9% (relative risk [RR]: 0.44 [95% CI: 0.25–77]; $P = .006$).[45] LGG, *B lactis*, *S thermophilus*, and *S boulardii* have been the most common agents used in RCTs. Approximately 1 in 7 cases of antibiotic-associated diarrhea was prevented by the use of a probiotic.[45] Children in these studies received either a probiotic-supplemented formula or a separate

probiotic as preventive treatment. According to 1 reported meta-analysis, probiotic treatment significantly reduced odds of antibiotic-associated diarrhea as compared with placebo (odds ratio [OR]: 0.39 [95% CI: 0.25–0.62]; $P < .001$) for both the yeast byproduct *S boulardii* and LGG. There was no significant difference between the 2 treatments; the overall combined OR was 0.37 (95% CI: 0.26–0.53; $P < .001$) in favor of active probiotic treatment over placebo.[48] Thus, probiotics can be used to reduce the incidence of antibiotic-associated diarrhea.

Treatment of Antibiotic-Associated Diarrhea

There have been no published RCTs of children that have investigated the effect of probiotics for treatment of antibiotic-associated diarrhea. Thus, their use cannot be recommended. The clinician who is caring for a child with antibiotic-induced diarrhea must weigh the benefits of considering therapy with a probiotic or discontinuing or modifying the antibiotic treatment when possible. No RCTs have been published concerning treatment with probiotics of children with *Clostridium difficile* antibiotic-associated diarrhea.

Atopic Diseases

Prevention of Atopic Disease

As previously mentioned, the sequence of bacterial intestinal colonization of neonates and young infants is probably important in the development of the immune response.[21] Recognition by the immune system of self and nonself, as well as the type of inflammatory responses generated later in life, are likely affected by the infant's diet and acquisition of the commensal intestinal bacterial population superimposed on genetic predisposition. During pregnancy, the cytokine inflammatory-response profile of the fetus is diverted away from cell-mediated immunity (T-helper 1 [Th1] type) toward humoral immunity (Th2 type). Hence, the Th2 type typically is the general immune response in early infancy. The risk of allergic disease could well be the result of a lack or delay in the eventual shift of the predominant Th2 type of response to more of a balance between Th1- and Th2-type responses.[49] Administration of probiotic bacteria during a time period in which a natural population of lactic-acid–producing indigenous intestinal bacteria is developing could theoretically influence immune development toward more balance of Th1 and Th2 inflammatory responses.[50] The intestinal bacterial flora of atopic children has been demonstrated to differ from that of nonatopic children. Specifically, atopic children have more *Clostridium* organisms and fewer *Bifidobacterium* organisms than do nonatopic study subjects,[15,51] which has served as the rationale for the administration of probiotics to infants at risk of atopic diseases, particularly for those who are formula fed.

In a double-blinded RCT, LGG or a placebo was given initially to 159 women during the final 4 weeks of pregnancy. If the infant was at high risk of atopic disease (atopic eczema, allergic rhinitis, or asthma), the treatment was continued for 6 months after birth in both the lactating woman and her infant.[52] A total of 132 mother-infant pairs were randomly assigned to receive either placebo or LGG and treated for 6 months while breastfeeding. The primary study end point was chronic recurrent atopic eczema in the infant. Atopic eczema was diagnosed in 46 of 132 (35%) of these study children by 2 years of age. The frequency of atopic eczema in the LGG-treated group was 15 of 64 (23%) versus 31 of 68 (46%) in the placebo group (RR: 0.51 [95% CI: 0.32–0.84]; $P < .01$). The number of mother-infant pairs required to be treated with LGG to prevent 1 case of chronic recurrent atopic eczema was 4.5. By 4 years of age, eczema occurred in 26% of the infants in the group treated with LGG, compared with 46% in the placebo group (RR: 0.57 [95% CI: 0.33–0.97]; $P < .01$). However, only 67% of the original study group was analyzed at the 4-year follow-up. These results support a preventive effect for giving a probiotic to mothers late in pregnancy and to both mothers and infants during the first 6 months of lactation for the prevention of atopic eczema in infants who are at risk of atopic disease. However, these results have not been confirmed in subsequent clinical trials, as summarized in a recent review by Kopp and Salfeld.[53] Conversely, Taylor et al[54] found that probiotic supplementation did not reduce the risk of atopic dermatitis in children at high risk with the report of some increased risk of subsequent allergen sensitization. As concluded in a review by Prescott and Björkstén[55] and in a 2007 Cochrane review,[56] despite the encouraging results of some studies, there is insufficient evidence to warrant the routine supplementation of probiotics to either pregnant women or infants to prevent allergic diseases in childhood. Explanations for varied study results include host factors such as genetic susceptibility, environmental factors such as geographic region and diet, and study variables including probiotic strains and doses used.[55,57]

Treatment of Atopic Disease

In an RCT, 53 Australian infants with moderate-to-severe atopic dermatitis were given either *Lactobacillus fermentum* or placebo for 8 weeks. At final assessment at 16 weeks, significantly more children who received the probiotic had improved extent and severity of atopic dermatitis as measured by the Severity of Scoring of

Atopic Dermatitis (SCORAD) index over time compared with those who received placebo ($P = .01$).[58,59] These results are encouraging, but as summarized in a 2008 Cochrane review,[60] probiotics have not yet been proven to be effective in the treatment of eczema.

Prevention of Necrotizing Enterocolitis in Low Birth Weight Neonates

A newborn's gut is sterile at birth, with bacterial colonization beginning shortly after birth.[20–22] Preterm infants frequently have delayed and aberrant acquisition of the "normal" digestive microflora, possibly because of restricted enteral feedings and frequent use of antibiotic therapy.[61,62] Delayed enteral feeding, frequent use of antibiotic therapy, and altered acquisition of normal digestive microflora are believed to be primary contributing factors for the increased risk of necrotizing enterocolitis (NEC) in preterm infants[63,64] and is the rationale for probiotic supplements.

In a 2008 Cochrane review[65] based on 9 RCTs,[66–74] enteral probiotic supplementation significantly reduced both the incidence of NEC (stage II or more) (RR: 0.32 [95% CI: 0.17–0.60]) and mortality (RR: 0.43 [95% CI: 0.25–0.75]).[65] Nosocomial sepsis was not reduced significantly (RR: 0.93 [95% CI: 0.73–1.19]). A total of 1425 infants who were born at less than 37 weeks' gestational age and/or less than 2500 g birth weight were included in this meta-analysis. No systemic infections or serious adverse events that were directly attributed to the administered probiotic organism were reported for these RCTs. The authors concluded that the results of their analysis supported a change in clinical practice to supplement preterm infants who weighed more than 1000 g at birth with a probiotic. Data regarding the outcome of preterm extremely low birth weight infants who weighed less than 1000 g at birth could not be used by the authors to reliably estimate the efficacy and safety of probiotic supplementation to this high-risk group. A large RCT was recommended to investigate the potential benefit and safety of probiotic supplementation to extremely low birth weight infants.

However, because the of large heterogeneity of the studies included in the Cochrane review,[65] caution is urged in interpreting the results, which are somewhat problematic. The studies all used different probiotics, including LGG, *Bifidobacterium breve*, *Saccharomyces* species, and mixtures of *Bacteroides bifidus*, *S thermophilus*, *Lactobacillus acidophilus*, and *Bifidobacterium infantis*. Doses of individual probiotics varied and were administered with human milk feedings, formula feedings, or both human milk and formula feedings in some studies. Not all of the studies had the same end points, including the primary outcome of NEC. A second and larger study by Lin et al,[75] the results of which were published after the Cochrane review, repeated the 2005 study[71] by using a different mixture of probiotics: *L acidophilus* and *B bifidus*. The overall incidence of NEC and death was less in the second study[75] compared with that in the first[71] in the controls, and the second study revealed that probiotics did not reduce the incidence of sepsis compared with that in the first, and the intervention group actually had a higher incidence of sepsis. The number needed to treat to prevent 1 case of NEC was 27 in the first study by Lin et al[71] and 21 in the second study.[75] Another point that makes the data problematic is that the combinations of probiotics used in the Lin et al studies, which are the most convincing for NEC prevention, are not available in the United States. Not all probiotics have been studied; therefore, all probiotics cannot be generally recommended.

Treatment of Helicobacter pylori *Infection*

There is a modest and encouraging benefit in published RCT results for probiotics used as adjunctive therapy for *H pylori* gastritis in adults.[76] One RCT in children has been published,[77] and the results demonstrated that the probiotics-supplemented treatment group had better *H pylori* eradication than did the placebo group (84.6% vs 57.5%; RR: 1.47 [95% CI: 1.1–2.0]). The adverse effects of diarrhea, nausea, and vomiting in both the placebo and probiotic treatment group did not differ significantly. Thus, probiotics may be of some benefit in the eradication of *H pylori* in children, but more studies are required.

Chronic IBD

The term IBD is inclusive of patients with either chronic ulcerative colitis (CUC) or Crohn disease. It is estimated that approximately 40% to 70% of children and adult patients suffering with IBD routinely use alternative medicines, including probiotics, as adjunctive or replacement therapy for prescribed medications.[78–80] In theory, probiotics may be beneficial in the treatment of IBD.[21] It has been proposed that in individuals with genetic susceptibility to IBD, chronic inflammation occurs in response to commensal digestive microflora because of various inherited defects of innate inflammatory-response pathways. One such identified inherited defect found in patients with Crohn disease is a mutation of the *CARD15* gene on chromosome 16, which results in abnormal chronic inflammation in response to bacteria such as *Escherichia coli* in the digestive tract.[21] Hence, modulating the commensal intestinal bacterial environment with probiotic supplements

may reduce the inflammatory response in patients with IBD.[80]

Treatment of Chronic Ulcerative Colitis

Data from RCTs of probiotics for the treatment of adults with CUC are encouraging.[81–84] The administration of probiotics to adults with mild-to-moderate CUC disease activity has comparable efficacy when compared with treatment with anti-inflammatory drugs used to treat CUC, such as mesalamine, as reported in a recently published Cochrane review.[85] The same is true in adult patients with ileoanal pouchitis after colectomy surgery for CUC. Most of these studies use the probiotic mixture VSL#3 (Sigma-Tau Pharmaceuticals, Gaithersburg, MD), which is a combination of *S thermophilus*, *Bifidobacterium* species, and *Lactobacillus* species. The probiotic *E coli* Nissle 1917 (Ardeypharm GmbH, Herdacke, Germany) has also been used successfully to treat mild-to-moderate pouchitis or CUC in adults.[86] One RCT in which 29 children with newly diagnosed CUC were randomly assigned to receive either VSL#3 or a placebo for 1 year had promising results.[87] All study patients were also given standard corticosteroid induction therapy combined with mesalamine maintenance therapy. Remission occurred in 13 patients (92.8%) in the VSL#3 group and 4 patients (36.4%) in the placebo group ($P < .001$). Relapse occurred in 3 of 13 (23%) patients in the VSL#3 group versus 11 of 15 (73.3%) in the placebo group within the 1-year study period (RR: 0.32 [95% CI: 0.25–0.773]; $P = .014$). Although these results are promising, more studies are needed in larger numbers of children to substantiate the benefit of probiotics in managing children with mild-to-moderate CUC. Thus, probiotics for CUC cannot be generally recommended at this time without further confirmatory research.

Treatment of Crohn Disease

One RCT in which LGG was used in pediatric patients with Crohn disease resulted in no significant benefit.[88] Treating adults with Crohn disease with the probiotics *S boulardii,* LGG, and *E coli* Nissle 1917 has not yielded promising results thus far.[89–92] A recent Cochrane review indicated that there is, as yet, no proven benefit for maintaining remission by administering probiotics to adults with Crohn disease.[93] Because of the lack of efficacy, treatment of Crohn disease with probiotics cannot be recommended for children.

Irritable Bowel Syndrome and Constipation: Treatment

There has been a single published RCT of the treatment of irritable bowel syndrome (IBS) in children.[94] LGG reduced abdominal distension and discomfort in a group of 50 pediatric patients over a 6-week study period. Response to therapy was recorded and collected on a weekly basis by using the Digestive Symptom Rating Scale. Various probiotics were shown to be helpful in several other RCTs of treatment of IBS in adults.[95–97] One published RCT addressed the use of probiotics (LGG) or a placebo as adjunct therapy to a stool softener (lactulose) to treat functional constipation in 84 children.[98] LGG was not an effective adjunct to lactulose in treating constipation in children. Thus, probiotics may be of benefit in children with IBS on the basis of a single RCT, but a recommendation for them use cannot be made without further confirmatory studies. Probiotics cannot be recommended at this time for treatment of constipation.

Infantile Colic

Prevention of Colic

To date, no RCTs have been conducted with colic as a primary end point.

Treatment of Colic

Colic is a common condition that typically affects infants in the first 4 months of life. The primary mechanism remains unknown. Available evidence suggests that colic potentially has a number of independent causes, including dietary protein hypersensitivity.[99,100] A recent unblinded RCT examined the effect of the administration of *L reuteri* versus simethicone in the treatment of colic in 90 exclusively breastfed infants in Italy.[100] The administration of *L reuteri* improved the symptoms of colic (minutes of crying per day) within 1 week of treatment, compared with simethicone therapy. The breastfeeding mothers were instructed to eliminate dairy products from their diets during the study period to minimize potentially confounding adverse effects of dietary protein hypersensitivity. The authors of the study proposed several theories for a positive therapeutic benefit, including probiotic modulation of proinflammatory responses. Further confirmatory RCTs are required to recommend routine use of probiotics in the treatment of infantile colic in both breastfed and formula-fed infants. On the basis of limited information, probiotics may be of benefit in treatment of colic in exclusively breastfed infants, but more studies are needed before they can be recommended.

Extraintestinal Infections

Prevention of Extraintestinal Infections

In a 2001 RCT in 17 Finnish child care centers, 571 healthy children 1 to 6 years of age were studied for 7 months in winter.[33] Children were randomly assigned to receive milk 3 times per day with or without LGG. When the data were adjusted for age, children who were fed milk with LGG, compared with controls, did not have significantly fewer days with respiratory symptoms

or fewer days of child care absences because of illness. There were also no significant differences in the numbers of children with a doctor's diagnosis of infection or number of prescriptions for antibiotics when adjusted for age, although the trends favored the children who were fed milk with LGG. Thus, probiotics for the prevention of extraintestinal infections in children cannot be recommended at this time.

Treatment of Extraintestinal Infections

No RCTs in children have demonstrated definite beneficial effects of administering probiotics to treat extraintestinal infections. The beneficial effects that have been reported in uncontrolled trials in adults with 1 or more types of extraintestinal infection have typically used LGG as a supplement or probiotics added to dairy products.[101–103] Thus, probiotics are not recommended for children for treatment of extraintestinal infections.

Cancer: Prevention and Treatment

Results of published studies have demonstrated the positive benefits of functional foods, such as yogurt, and the administration of probiotics to prevent carcinogenic processes in animal models.[104] As yet, no published RCTs warrant recommendation of routine administration of probiotics to either treat or prevent cancer in adults or children.

USE OF PREBIOTICS IN PREVENTION AND TREATMENT OF CLINICAL DISEASES

Few RCTs have been conducted to evaluate the use of prebiotics in preventing or treating specific childhood diseases.[8]

Prevention and Treatment of Allergy

A 2007 Cochrane review[105] concluded that there was inconclusive evidence for giving prebiotics to prevent allergic disorders in infants. However, in 2008, Arslanoglu et al[106] reported on a 2-year follow-up of an RCT in 132 infants at risk of atopy because of parental atopy. Infants were fed a partially hydrolyzed formula with either an added mixture of FOS and GOS or maltodextrin placebo in the first 6 months of life. Those given the prebiotic mixture of FOS and GOS had a reduced incidence of atopic disease. Cumulative incidences of atopic eczema, recurrent wheezing, and allergic urticaria were higher in the maltodextrin placebo group (27.9%, 20.6%, and 10.3%, respectively) than in the intervention group (13.6%, 7.6%, and 1.5%) ($P = .05$). In a 2009 review, van der Aa et al[107] analyzed relevant publications to date and concluded that there is presently not enough evidence to support the use of probiotics, prebiotics, or synbiotics for the prevention or treatment of allergic dermatitis in children. Confirmatory studies of the benefits of prebiotics, especially for children fed formula that is not partially hydrolyzed or infants fed partially hydrolyzed formula, which are already being promoted to reduce the incidence of atopic disease, are needed before any recommendations can be made for the use of prebiotics in infants and toddlers to prevent infection or atopic disease.

Other Disorders

It has been shown that the addition of dietary fiber has ameliorated diarrheal stools when added to infant formula.[108] Prebiotics, such as oligosaccharides, inulin, and dietary fiber supplements that are contained in bran, psyllium, and barley fiber, are beneficial in maintaining clinical remission in adult patients with CUC,[109] but no RCT results support their use. There have been controlled animal research studies that have shown that prebiotics may prevent or lessen carcinogenic processes,[104] but there have been no RCTs in humans.

COMBINED PREBIOTICS AND PROBIOTICS TO PREVENT ALLERGY

Clinical benefit in preventing allergic diseases by co-therapy with probiotics and prebiotics in pregnant women and their infants was demonstrated in an RCT in Finland.[110] A total of 1223 pregnant women who had been identified to deliver infants who would be at high risk of atopic disease because of parental atopic disease history were randomly assigned to be given a mixture of 4 probiotic strains plus GOS or placebo daily for 2 to 4 weeks before delivery. After delivery, their infants then either received the same probiotic mixture plus GOS or the same placebo as the mother. Probiotic/prebiotic treatment showed no effect on the cumulative occurrence of allergic diseases but tended to reduce immunoglobulin E–associated (atopic) diseases (OR: 0.71 [95% CI: 0.50–1.00]; $P = .052$). Probiotic and prebiotic treatment reduced the occurrence of eczema (OR: 0.74 [95% CI: 0.55–0.98]; $P = .035$) and atopic eczema (OR: 0.66 [95% CI: 0.46–0.95]; $P = .025$). Confirmatory studies are necessary.

PREBIOTICS AND PROBIOTICS IN INFANT FORMULA

Prebiotics

As mentioned earlier in this review, human milk contains a number of substances that are prebiotic, the most plentiful of which are oligosaccharides.[19,30] Oligosaccharide prebiotics are also added to many commercially available dietary food supplements. Regarding their addition to infant formula, the European Commission's Scientific Committee on Food concluded in 2003[111] that they had no major concerns regarding the addition of oligosaccharides to infant formulas, including follow-up infant formulas (formulas modified especially for 6- to 12-month-old infants), up to a total

concentration of 0.8 g/dL in ready-to-feed formula products.

Few RCTs have examined the effects of adding prebiotic oligosaccharides to infant formula.[106,112,113] Boehm et al[113] studied the effect of the addition of oligosaccharides at a concentration of 1 g/dL to preterm infant formula for 1 month (90% GOSs and 10% FOSs). Stool bifidobacteria counts in the oligosaccharide-supplemented group increased significantly compared with the nonsupplemented group, and the bifidobacteria counts reached the range of a breastfed reference group. In a separate study, Moro et al[114] fed term infants the same oligosaccharide-supplemented formula. These infants had higher counts of bifidobacteria as well as lactobacilli in their stools. Schmelzle et al[115] conducted a multicenter trial that also examined the efficacy of the addition of prebiotics to infant formula. They reported good overall tolerance and no adverse effects during the 12-week study period. A large multicenter trial to evaluate the safety of FOS-supplemented infant formula was conducted in the United States in 2004.[116] The study demonstrated that infant growth was maintained during the 12-week study period for the FOS-supplemented infant-formula group without any adverse effects. After weaning infants from formula, the addition of prebiotics to solid food seems to have a bifidogenic effect, as shown by the results of a recently published RCT by Scholtens et al.[117] Infant formulas that contain either GOS or FOS are now marketed in the United States. However, more information, including data from RCTs, is needed before the efficacy of adding prebiotics to infant formulas can be determined.

Probiotics

Two infant formulas currently contain a probiotic. One contains *B lactis*, and the other contains LGG. These probiotics are only added to powdered formulas at present. The rationale for adding probiotic organisms to infant formula was discussed in the introduction of this clinical report. The overall health-benefit efficacy of adding probiotics to infant formula remains to be demonstrated in large RCTs.

SAFETY OF PROBIOTICS AND PREBIOTICS IN INFANTS AND CHILDREN

Concerns exist about the overall safety of administering probiotic products to high-risk patient groups, including adults, children, and term and preterm infants. Cases of serious infection have occurred and been reported in the literature.[10,118–125] Patients at risk would be those who are immunocompromised, including ill preterm neonates, and/or children who have intravenous catheters or other indwelling medical devices. In most cases, the offending organism that caused the sepsis seems to have stemmed from bacteria from the individual's own endogenous flora. Sepsis has also been reported in adults, children, and infants who received probiotic supplements.[118,124–126] Land et al[126] recently reported LGG probiotic sepsis occurring in immunocompromised infants and children. A medically fragile infant 6 weeks of age became septic with a strain of LGG that was being provided as a supplement. Molecular DNA-fingerprinting confirmed that the LGG probiotic supplement was the bacterial isolate from the infant. Neonatal sepsis and meningitis that were apparently associated with the administration of a probiotic supplement were also reported.[118,120]

A recent report focused on probiotic tolerance and safety in healthy term infants who were randomly assigned to be given a high-dose probiotic formula, a low-dose probiotic formula, or control formula for 18 months.[35] There were no apparent reported adverse events. All infants demonstrated normal growth. Reports of colic were significantly fewer in the 2 probiotic-formula–fed groups, and the frequency of health care visits and antibiotic use was less ($P < .001$) compared with those in the control formula group. In a separate study, Petschow et al[127] reported that healthy term infants given varying amounts of LGG in infant formula for 2 weeks resulted in good overall feeding tolerance with successful intestinal tract colonization, without adverse events.

The apparent safety to date of adding prebiotics to infant formula has been evaluated in the previously discussed RCTs reported by Boehm et al,[113] Moro et al,[114] Schmelzle et al,[115] and Bettler and Euler.[116]

SUMMARY ON SAFETY

The Committee on Nutrition of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition previously concluded that more studies are required to establish the safety and efficacy of probiotic and prebiotic products in children.[12] To date, these products seem to be safe for healthy infants and children. The committee also stated that it would be optimal to have a centralized mechanism of oversight to ensure probiotic microorganism safety, identity, and genetic stability.[12] Centralized oversight and probiotic product monitoring was also recommended in a report from the Food and Agriculture Organization of the United Nations World Health Organization.[1,2,128] This organization supports the addition of prebiotic products to infant formulas designed as follow-up formulas meant for infants aged 5 months and older. It was reasoned that these infants are more likely to have a more mature immune response and established intestinal

colonization. In terms of oversight and product safety in the United States, products marketed as dietary supplements, such as probiotics, do not require premarket review and approval by the US Food and Drug Administration (FDA). However, probiotics or prebiotics that are marketed specifically for the treatment or prevention of a disease are classified as biological products and do require FDA review and approval. Infant formulas must be made with compliance with what are considered good manufacturing practices under the Infant Formula Act of 1980 and are under the regulatory auspices of the FDA[129] because these products are often used as the sole source of nutrition by infants during a critical period of growth and development. Additional statutory and regulatory requirements address appropriate infant formula manufacture, composition, and nutrient content. All ingredients used in infant formula must be safe and lawful—that is, food ingredients that are, to date, generally regarded as safe (GRAS) for use in infant formula and those that are used in accordance with the food-additive regulations of the FDA. Prebiotics and probiotics now being added to commercial infant formulas are classified as GRAS. Information on FDA regulations for infant formula and food ingredients and packaging may be found at www.fda.gov/Food/FoodSafety/ProductSpecificInformation/InfantFormula/default.htm and www.fda.gov/Food/FoodIngredientsPackaging/default.htm.

DEVELOPMENT OF THIS REPORT

The AAP Committee on Nutrition and Section on Gastroenterology, Hepatology, and Nutrition used review of the literature, including Cochrane reviews, and reports from other groups.[12,111,128] Comments also were solicited from committees, sections, and councils of the AAP; 9 entities responded. Additional comments were sought from the Centers for Disease Control and Prevention, the National Institutes of Health, the US Department of Agriculture, and the FDA because these governmental agencies have official liaisons to the Committee on Nutrition and were present during the development of the statement. For recommendations for which high levels of evidence are absent, the expert opinions and suggestions of the members of the Committee on Nutrition and other groups and authorities consulted were taken into consideration in developing this clinical report.

SUMMARY

1. Human milk, a natural prebiotic, is preferred for infants through 6 months of age.[130] The oligosaccharide content of human milk is substantial and is part of the prebiotic components of the human milk. Breastfed infants typically have a preponderance of naturally occurring probiotic bacteria in their digestive systems. There may be some naturally occurring probiotic bacteria contained in human milk.
2. There is some evidence in otherwise healthy infants and young children to support the use of probiotics early in the course of diarrhea from acute viral gastroenteritis and that use of probiotics reduces its duration by 1 day. However, the available evidence does not support the routine use of probiotics to prevent infectious diarrhea unless there are special circumstances. There is some evidence to support the use of probiotics to prevent antibiotic-associated diarrhea but no evidence that it is beneficial for treatment.
3. Although the results of some studies support the prophylactic use of probiotics during pregnancy and lactation and during the first 6 months of life in infants who are at risk of atopic disorders, further confirmatory evidence is necessary before a recommendation for routine use can be made.
4. There is some evidence to support the use of probiotics to prevent NEC in preterm infants with a birth weight of 1000 g or higher. However, the amount and specificity of which probiotic or mixture of probiotics to use is problematic, given the many unanswered questions from a review of the available literature. Furthermore, many of the probiotics used and cited in the literature for treatment in preterm infants are not readily available.
5. At the present time, the sustained or long-term benefit of using probiotics for treating disorders such as Crohn disease, IBS, constipation, and extraintestinal infections requires further RCTs and cannot be recommended in children. There may benefit for treating *H pylori* infections, CUC, and infantile colic with probiotics in childhood, but further studies are necessary.
6. Long-term health benefits of probiotics in the prevention of cancer, allergy, or other diseases or providing sustained beneficial results on the developing immune system beyond early infancy remain to be proven.
7. Addition of probiotics to powdered infant formulas has not been demonstrated to be harmful to healthy term infants. On the other hand, evidence of clinical efficacy for their addition is insufficient to recommend the routine use of these formulas. No RCTs have directly compared the health benefits of feeding human milk versus infant formula supplemented with probiotics.

8. Probiotics should not be given to children who are seriously or chronically ill until the safety of administration has been established.
9. Prebiotics may prove to be beneficial in reducing common infections and atopy in otherwise healthy children. However, confirmatory studies, especially in children fed formula that is not partially hydrolyzed, are needed before any recommendations can be made.
10. Addition of oligosaccharides as prebiotics to infant formula is not unreasonable but lacks evidence demonstrating clinical efficacy at this time. Cost/benefit studies are also necessary to support their addition to infant formulas.
11. Important questions remain in establishing the clinical applications for probiotics, including the optimal duration of probiotic administration as well as preferred microbial dose and species. The long-term impact on the gut microflora in children is unknown. It also remains to be established whether there is significant biological benefit in the administration of probiotics during pregnancy and lactation, with direct comparison to potential biological benefit derived from probiotic-containing infant formulas. Similar questions exist for the use of prebiotics.

Appendix 1 contains examples of currently available probiotic products and the probiotic content of various functional foods in the United States. This list demonstrates the wide variation in probiotic content in these products. Information about other probiotics can also be found on a Web site maintained by industry (www.usprobiotics.org).

REFERENCES

1. Food and Agriculture Organization of the United Nations; World Health Organization. Guidelines for the evaluation of probiotics in food: joint FAO/WHO Working Group report on drafting guidelines for the evaluation of probiotics in food. Available at: ftp://ftp.fao.org/es/esn/food/wgreport2.pdf. Accessed October 1, 2010
2. Food and Agriculture Organization of the United Nations; World Health Organization. Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria: report of a joint FAO/WHO expert consultation on evaluation of health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. Available at: www.who.int/foodsafety/publications/fs_management/en/probiotics.pdf. Accessed October 1, 2010
3. Council for Agricultural Science and Technology. *Probiotics: Their Potential to Impact Human Health*. Ames, IA: Council for Agricultural Science and Technology; 2007. Available at: www.cast-science.org/websiteUploads/publicationPDFs/CAST%20Probiotics%20Issue%20Paper%20FINAL144.pdf. Accessed October 1, 2010
4. Roberfroid M. Prebiotics: the concept revisited. *J Nutr*. 2007;137(3 suppl 2):830S–837S
5. Commane DM, Shortt CT, Silvi S, Cresci A, Hughes RM, Rowland IR. Effects of fermentation products of pro- and prebiotics on trans-epithelial electrical resistance in an in vitro model of the colon. *Nutr Cancer*. 2005;51(1):102–109
6. Falony G, Vlachou A, Verbrugghe K, De Vuyst L. Cross-feeding between *Bifidobacterium longum* BB536 and acetate-converting, butyrate-producing colon bacteria during growth on oligofructose. *Appl Environ Microbiol*. 2006;72(12):7835–7841
7. Grönlund MM, Gueimonde M, Laitinen K, et al. Maternal breast-milk and intestinal bifidobacteria guide the compositional development of the *Bifidobacterium* microbiota in infants at risk of allergic disease. *Clin Exp Allergy*. 2007;37(12):1764–1772
8. Kullen MJ, Bettler J. The delivery of probiotics and prebiotics to infants. *Curr Pharm Des*. 2005;11(1):55–74
9. Michail S, Sylvester F, Fuchs G, Issenman R. Clinical efficacy of probiotics: review of the evidence with focus on children. *J Pediatr Gastroenterol Nutr*. 2006;43(4):550–557
10. Boyle RJ, Robins-Browne RM, Tang ML. Probiotic use in clinical practice: what are the risks? *Am J Clin Nutr*. 2006;83(6):1256–1264; quiz 1446–1257
11. Szajewska H, Setty M, Mrukowicz J, Guandalini S. Probiotics in gastrointestinal diseases in children: hard and not-so-hard evidence of efficacy. *J Pediatr Gastroenterol Nutr*. 2006;42(5):454–475
12. Agostoni C, Axelsson I, Braegger C, et al. Probiotic bacteria in dietetic products for infants: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. 2004;38(4):365–374
13. Saavedra JM. Clinical applications of probiotic agents. *Am J Clin Nutr*. 2001;73(6):1147S–1151S

14. Matarese LE, Seidner DL, Steiger E. The role of probiotics in gastrointestinal disease. *Nutr Clin Pract*. 2003;18(6):507–516
15. Björkstén B, Naaber P, Sepp E, Mikelsaar M. The intestinal microflora in allergic Estonian and Swedish 2-year-old children. *Clin Exp Allergy*. 1999;29(3):342–346
16. Heller F, Duchmann R. Intestinal flora and mucosal immune responses. *Int J Med Microbiol*. 2003;293(1):77–86
17. Berg RD. Bacterial translocation from the gastrointestinal tract. *Adv Exp Med Biol*. 1999;473:11–30
18. Quan R, Barness LA. Do infants need nucleotide supplemented formula for optimal nutrition? *J Pediatr Gastroenterol Nutr*. 1990;11(4):429–434
19. Boehm G, Stahl B. Oligosaccharides from milk. *J Nutr*. 2007;137(3 suppl 2):847S–849S
20. Yoshioka H, Iseki K, Fujita K. Development and differences of intestinal flora in the neonatal period in breast-fed and bottle-fed infants. *Pediatrics*. 1983;72(3):317–321
21. Weng M, Walker W. Bacterial colonization, probiotics, and clinical disease. *J Pediatr*. 2006;149(5):S107–S114
22. Pietzak M. Bacterial colonization of the neonatal gut. *J Pediatr Gastroenterol Nutr*. 2004;38(4):389–391
23. Tannock G. The intestinal microflora. In: Fuller R, Perdigón G, eds. *Gut Flora, Nutrition, Immunity and Health*. Oxford, England: Blackwell Press; 2003:1–23
24. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. *Nature*. 2007;449(7164):804–810
25. Winkler P, Ghadimi D, Schrezenmeir J, Kraehenbuhl JP. Molecular and cellular basis of microflora-host interactions. *J Nutr*. 2007;137(3 suppl 2):756S–772S
26. Calder PC. Immunological parameters: what do they mean? *J Nutr*. 2007;137(3 suppl 2):773S–780S
27. Corthésy B, Gaskins HR, Mercenier A. Cross-talk between probiotic bacteria and the host immune system. *J Nutr*. 2007;137(3 suppl 2):781S–790S
28. Matsuzaki T, Takagi A, Ikemura H, Matsuguchi T, Yokokura T. Intestinal microflora: probiotics and autoimmunity. *J Nutr*. 2007;137(3 suppl 2):798S–802S
29. Yuan Q, Walker WA. Innate immunity of the gut: mucosal defense in health and disease. *J Pediatr Gastroenterol Nutr*. 2004;38(5):463–473
30. Donovan S. Role of human milk components in gastrointestinal development: current knowledge and future needs. *J Pediatr*. 2006;149(5):S49–S61
31. Perez PF, Doré J, Leclerc M, et al. Bacterial imprinting of the neonatal immune system: lessons from maternal cells? *Pediatrics*. 2007;119(3). Available at: www.pediatrics.org/cgi/content/full/119/3/e724
32. Oberhelman RA, Gilman RH, Sheen P, et al. A placebo-controlled trial of *Lactobacillus* GG to prevent diarrhea in undernourished Peruvian children. *J Pediatr*. 1999;134(1):15–20
33. Hatakka K, Savilahti E, Ponka A, et al. Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. *BMJ*. 2001;322(7298):1327
34. Thibault H, Aubert-Jacquin C, Goulet O. Effects of long-term consumption of a fermented infant formula (with *Bifidobacterium breve* c50 and *Streptococcus thermophilus* 065) on acute diarrhea in healthy infants. *J Pediatr Gastroenterol Nutr*. 2004;39(2):147–152
35. Saavedra JM, Abi-Hanna A, Moore N, Yolken RH. Long-term consumption of infant formulas containing live probiotic bacteria: tolerance and safety. *Am J Clin Nutr*. 2004;79(2):261–267
36. Weizman Z, Asli G, Alsheikh A. Effect of a probiotic infant formula on infections in child care centers: comparison of two probiotic agents. *Pediatrics*. 2005;115(1):5–9
37. Pedone CA, Arnaud CC, Postaire ER, Bouley CF, Reinert P. Multicentric study of the effect of milk fermented by *Lactobacillus casei* on the incidence of diarrhoea. *Int J Clin Pract*. 2000;54(9):568–571
38. Szajewska H, Kotowska M, Mrukowicz JZ, Armanska M, Mikolajczyk W. Efficacy of *Lactobacillus* GG in prevention of nosocomial diarrhea in infants. *J Pediatr*. 2001;138(3):361–365
39. Cortese MM, Parashar UD. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP) [published correction appears in *MMWR Recomm Rep*. 2010;59(33):1074]. *MMWR Recomm Rep*. 2009;58(RR-2):1–25
40. Szymański H, Pejcz J, Jawień M, Chmielarczyk A, Strus M, Heczko PB. Treatment of acute infectious diarrhoea in infants and children with a mixture of three *Lactobacillus rhamnosus* strains: a randomized, double-blind, placebo-controlled trial. *Aliment Pharmacol Ther*. 2006;23(2):247–253
41. Szajewska H, Mrukowicz JZ. Probiotics in the treatment and prevention of acute infectious diarrhea in infants and children: a systematic review of published randomized, double-blind, placebo-controlled trials. *J Pediatr Gastroenterol Nutr*. 2001;33(suppl 2):S17–S25
42. Van Niel CW, Feudtner C, Garrison MM, Christakis DA. *Lactobacillus* therapy for acute infectious diarrhea in children: a meta-analysis. *Pediatrics*. 2002;109(4):678–684
43. Huang JS, Bousvaros A, Lee JW, Diaz A, Davidson EJ. Efficacy of probiotic use in acute diarrhea in children: a meta-analysis. *Dig Dis Sci*. 2002;47(11):2625–2634
44. Allen SJ, Okoko B, Martinez E, Gregorio G, Dans LF. Probiotics for treating infectious diarrhoea. *Cochrane Database Syst Rev*. 2004;(2):CD003048
45. Szajewska H, Ruszczynski M, Radzikowski A. Probiotics in the prevention of antibiotic-associated diarrhea in children: a meta-analysis of randomized controlled trials. *J Pediatr*. 2006;149(3):367–372
46. Corrêa NB, Péret Filho LA, Penna FJ, Lima FM, Nicoli JR. A randomized formula controlled trial of *Bifidobacterium lactis* and *Streptococcus thermophilus* for prevention of antibiotic-associated diarrhea in infants. *J Clin Gastroenterol*. 2005;39(5):385–389
47. Hawrelak JA, Whitten DL, Myers SP. Is *Lactobacillus rhamnosus* GG effective in preventing the onset of antibiotic-associated diarrhoea: a systematic review. *Digestion*. 2005;72(1):51–56
48. D'Souza AL, Rajkumar C, Cooke J, Bulpitt CJ. Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. *BMJ*. 2002;324(7350):1361
49. Neaville WA, Tisler C, Bhattacharya A, et al. Developmental cytokine response profiles and the clinical and immunologic expression of atopy during the first year of life. *J Allergy Clin Immunol*. 2003;112(4):740–746
50. Majamaa H, Isolauri E. Probiotics: a novel approach in the management of food allergy. *J Allergy Clin Immunol*. 1997;99(2):179–185
51. Kalliomäki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. *J Allergy Clin Immunol*. 2001;107(1):129–134
52. Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up

of a randomised placebo-controlled trial. *Lancet*. 2003;361(9372):1869–1871

53. Kopp MV, Salfeld P. Probiotics and prevention of allergic disease. *Curr Opin Clin Nutr Metab Care*. 2009;12(3):298–303
54. Taylor AL, Dunstan JA, Prescott SL. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial. *J Allergy Clin Immunol*. 2007;119(1):184–191
55. Prescott SL, Björkstén B. Probiotics for the prevention or treatment of allergic diseases. *J Allergy Clin Immunol*. 2007;120(2):255–262
56. Osborn DA, Sinn JK. Probiotics in infants for prevention of allergic disease and food hypersensitivity. *Cochrane Database Syst Rev*. 2007;(4):CD006475
57. Penders J, Stobberingh EE, van den Brandt PA, Thijs C. The role of the intestinal microbiota in the development of atopic disorders. *Allergy*. 2007;62(11):1223–1236
58. Weston S, Halbert A, Richmond P, Prescott SL. Effects of probiotics on atopic dermatitis: a randomised controlled trial. *Arch Dis Child*. 2005;90(9):892–897
59. Viljanen M, Savilahti E, Haahtela T, et al. Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial. *Allergy*. 2005;60(4):494–500
60. Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, Murrell DF, Tang ML. Probiotics for treating eczema. *Cochrane Database Syst Rev*. 2008;(4):CD006135
61. Gewolb IH, Schwalbe RS, Taciak VL, Harrison TS, Panigrahi P. Stool microflora in extremely low birthweight infants. *Arch Dis Child Fetal Neonatal Ed*. 1999;80(3):F167–173
62. Penders J, Thijs C, Vink C, et al. Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics*. 2006;118(2):511–521
63. Kliegman RM. The relationship of neonatal feeding practices and the pathogenesis and prevention of necrotizing enterocolitis. *Pediatrics*. 2003;111(3):671–672
64. Cotten CM, Taylor S, Stoll B, et al; NICHD Neonatal Research Network. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. *Pediatrics*. 2009;123(1):58–66
65. Alfaleh K, Bassler D. Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane Database Syst Rev*. 2008;(1):CD005496
66. Bin-Nun A, Bromiker R, Wilschanski M, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. *J Pediatr*. 2005;147(2):192–196
67. Costalos C, Skouteri V, Gounaris A, et al. Enteral feeding of premature infants with *Saccharomyces boulardii*. *Early Hum Dev*. 2003;74(2):89–96
68. Dani C, Biadaioli R, Bertini G, Martelli E, Rubaltelli FF. Probiotics feeding in prevention of urinary tract infection, bacterial sepsis and necrotizing enterocolitis in preterm infants: a prospective double-blind study. *Biol Neonate*. 2002;82(2):103–108
69. Kitajima H, Sumida Y, Tanaka R, Yuki N, Takayama H, Fujimura M. Early administration of *Bifidobacterium breve* to preterm infants: randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed*. 1997;76(2):F101–F107
70. Li Y, Shimizu T, Hosaka A, Kaneko N, Ohtsuka Y, Yamashiro Y. Effects of *Bifidobacterium breve* supplementation on intestinal flora of low birth weight infants. *Pediatr Int*. 2004;46(5):509–515
71. Lin HC, Su BH, Chen AC, et al. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. *Pediatrics*. 2005;115(1):1–4
72. Manzoni P, Mostert M, Leonessa ML, et al. Oral supplementation with *Lactobacillus casei* subspecies rhamnosus prevents enteric colonization by *Candida* species in preterm neonates: a randomized study. *Clin Infect Dis*. 2006;42(12):1735–1742
73. Millar MR, Bacon C, Smith SL, Walker V, Hall MA. Enteral feeding of premature infants with *Lactobacillus* GG. *Arch Dis Child*. 1993;69(5 spec No.):483–487
74. Reuman PD, Duckworth DH, Smith KL, Kagan R, Bucciarelli RL, Ayoub EM. Lack of effect of *Lactobacillus* on gastrointestinal bacterial colonization in premature infants. *Pediatr Infect Dis*. 1986;5(6):663–668
75. Lin HC, Hsu CH, Chen HL, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter, randomized, controlled trial. *Pediatrics*. 2008;122(4):693–700
76. Lesbros-Pantoflickova D, Corthesy-Theulaz I, Blum AL. *Helicobacter pylori* and probiotics. *J Nutr*. 2007;137(3 suppl 2):812S–818S
77. Sýkora J, Valeckova K, Amlerova J, et al. Effects of a specially designed fermented milk product containing probiotic *Lactobacillus casei* DN-114 001 and the eradication of *H. pylori* in children: a prospective randomized double-blind study. *J Clin Gastroenterol*. 2005;39(8):692–698
78. Day AS, Whitten KE, Bohane TD. Use of complementary and alternative medicines by children and adolescents with inflammatory bowel disease. *J Paediatr Child Health*. 2004;40(12):681–684
79. Heuschkel R, Afzal N, Wuerth A, et al. Complementary medicine use in children and young adults with inflammatory bowel disease. *Am J Gastroenterol*. 2002;97(2):382–388
80. Sartor RB. Therapeutic manipulation of the enteric microflora in inflammatory bowel diseases: antibiotics, probiotics, and prebiotics. *Gastroenterology*. 2004;126(6):1620–1633
81. Kruis W, Schutz E, Fric P, Fixa B, Judmaier G, Stolte M. Double-blind comparison of an oral *Escherichia coli* preparation and mesalazine in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther*. 1997;11(5):853–858
82. Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon AT. Non-pathogenic *Escherichia coli* versus mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet*. 1999;354(9179):635–639
83. Kruis W, Fric P, Pokrotnieks J, et al. Maintaining remission of ulcerative colitis with the probiotic *Escherichia coli* Nissle 1917 is as effective as with standard mesalazine. *Gut*. 2004;53(11):1617–1623
84. Ishikawa H, Akedo I, Umesaki Y, Tanaka R, Imaoka A, Otani T. Randomized controlled trial of the effect of bifidobacteria-fermented milk on ulcerative colitis. *J Am Coll Nutr*. 2003;22(1):56–63
85. Mallon P, McKay D, Kirk S, Gardiner K. Probiotics for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2007;(4):CD005573
86. Mimura T, Rizzello F, Helwig U, et al. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut*. 2004;53(1):108–114
87. Miele E, Pascarella F, Giannetti E, Quaglietta L, Baldassano RN, Staiano A. Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with ulcerative colitis. *Am J Gastroenterol*. 2009;104(2):437–443
88. Bousvaros A, Guandalini S, Baldassano RN, et al. A randomized, double-blind trial of *Lactobacillus* GG versus placebo in addition to standard maintenance therapy for

children with Crohn's disease. *Inflamm Bowel Dis*. 2005;11(9):833–839

89. Schultz M, Timmer A, Herfarth HH, Sartor RB, Vanderhoof JA, Rath HC. *Lactobacillus* GG in inducing and maintaining remission of Crohn's disease. *BMC Gastroenterol*. 2004;4:5
90. Plein K, Hotz J. Therapeutic effects of *Saccharomyces boulardii* on mild residual symptoms in a stable phase of Crohn's disease with special respect to chronic diarrhea: a pilot study. *Z Gastroenterol*. 1993;31(2):129–134
91. Malchow HA. Crohn's disease and *Escherichia coli*: a new approach in therapy to maintain remission of colonic Crohn's disease? *J Clin Gastroenterol*. 1997;25(4):653–658
92. Prantera C, Scribano ML, Falasco G, Andreoli A, Luzi C. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with *Lactobacillus* GG. *Gut*. 2002;51(3):405–409
93. Rolfe VE, Fortun PJ, Hawkey CJ, Bath-Hextall F. Probiotics for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2006;(4):CD004826
94. Bausserman M, Michail S. The use of *Lactobacillus* GG in irritable bowel syndrome in children: a double-blind randomized control trial. *J Pediatr*. 2005;147(2):197–201
95. Kim HJ, Vazquez Roque MI, Camilleri M, et al. A randomized controlled trial of a probiotic combination VSL# 3 and placebo in irritable bowel syndrome with bloating. *Neurogastroenterol Motil*. 2005;17(5):687–696
96. O'Mahony L, McCarthy J, Kelly P, et al. *Lactobacillus* and *Bifidobacterium* in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology*. 2005;128(3):541–551
97. Kim HJ, Camilleri M, McKinzie S, et al. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther*. 2003;17(7):895–904
98. Banaszkiewicz A, Szajewska H. Ineffectiveness of *Lactobacillus* GG as an adjunct to lactulose for the treatment of constipation in children: a double-blind, placebo-controlled randomized trial. *J Pediatr*. 2005;146(3):364–369
99. Hill DJ, Roy N, Heine RG, et al. Effect of a low-allergen maternal diet on colic among breastfed infants: a randomized, controlled trial. *Pediatrics*. 2005;116(5). Available at: www.pediatrics.org/cgi/content/full/116/5/e709
100. Savino F, Pelle E, Palumeri E, Oggero R, Miniero R. *Lactobacillus reuteri* (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: a prospective randomized study. *Pediatrics*. 2007;119(1). Available at: www.pediatrics.org/cgi/content/full/119/1/e124
101. Reid G. Probiotic therapy and functional foods for prevention of urinary tract infections: state of the art and science. *Curr Infect Dis Rep*. 2000;2(6):518–522
102. Tagg JR, Dierksen KP. Bacterial replacement therapy: adapting "germ warfare" to infection prevention. *Trends Biotechnol*. 2003;21(5):217–223
103. Golledge CL, Riley TV. "Natural" therapy for infectious diseases. *Med J Aust*. 1996;164(2):94–95
104. Burns AJ, Rowland IR. Anti-carcinogenicity of probiotics and prebiotics. *Curr Issues Intest Microbiol*. 2000;1(1):13–24
105. Osborn DA, Sinn JK. Prebiotics in infants for prevention of allergic disease and food hypersensitivity. *Cochrane Database Syst Rev*. 2007;(4):CD006474
106. Arslanoglu S, Moro GE, Schmitt J, Tandoi L, Rizzardi S, Boehm G. Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. *J Nutr*. 2008;138(6):1091–1095
107. van der Aa LB, Heymans HS, van Aalderen WM, Sprikkelman AB. Probiotics and prebiotics in atopic dermatitis: review of the theoretical background and clinical evidence. *Pediatr Allergy Immunol*. 2010;21(2 pt 2):e355–e367
108. Brown KH, Perez F, Peerson JM, et al. Effect of dietary fiber (soy polysaccharide) on the severity, duration, and nutritional outcome of acute, watery diarrhea in children. *Pediatrics*. 1993;92(2):241–247
109. Hanai H, Kanauchi O, Mitsuyama K, et al. Germinated barley foodstuff prolongs remission in patients with ulcerative colitis. *Int J Mol Med*. 2004;13(5):643–647
110. Kukkonen K, Savilahti E, Haahtela T, et al. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol*. 2007;119(1):192–198
111. European Commission, Scientific Committee on Food. *Report of the Scientific Committee on Food on the Revision of Essential Requirements of Infant Formulae and on Formulae*. Brussels, Belgium: European Commission; 2003. Available at: http://ec.europa.eu/food/fs/sc/scf/out199_en.pdf. Accessed October 12, 2010
112. Arslanoglu S, Moro GE, Boehm G. Early supplementation of prebiotic oligosaccharides protects formula-fed infants against infections during the first 6 months of life. *J Nutr*. 2007;137(11):2420–2424
113. Boehm G, Lidestri M, Casetta P, et al. Supplementation of a bovine milk formula with an oligosaccharide mixture increases counts of faecal bifidobacteria in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2002;86(3):F178–F181
114. Moro G, Minoli I, Mosca M, et al. Dosage-related bifidogenic effects of galacto- and fructooligosaccharides in formula-fed term infants. *J Pediatr Gastroenterol Nutr*. 2002;34(3):291–295
115. Schmelzle H, Wirth S, Skopnik H, et al. Randomized double-blind study of the nutritional efficacy and bifidogenicity of a new infant formula containing partially hydrolyzed protein, a high beta-palmitic acid level, and nondigestible oligosaccharides. *J Pediatr Gastroenterol Nutr*. 2003;36(3):343–351
116. Bettler J, Euler R. An evaluation of the growth of term infants fed formula supplemented with fructo-oligosaccharides. *Int J Probiotics*. 2006;1:19–26
117. Scholtens PA, Alles MS, Bindels JG, van der Linde EG, Tolboom JJ, Knol J. Bifidogenic effects of solid weaning foods with added prebiotic oligosaccharides: a randomised controlled clinical trial. *J Pediatr Gastroenterol Nutr*. 2006;42(5):553–559
118. Kunz AN, Noel JM, Fairchok MP. Two cases of *Lactobacillus bacteremia* during probiotic treatment of short gut syndrome. *J Pediatr Gastroenterol Nutr*. 2004;38(4):457–458
119. Thompson C, McCarter YS, Krause PJ, Herson VC. *Lactobacillus acidophilus* sepsis in a neonate. *J Perinatol*. 2001;21(4):258–260
120. Broughton RA, Gruber WC, Haffar AA, Baker CJ. Neonatal meningitis due to *Lactobacillus*. *Pediatr Infect Dis*. 1983;2(5):382–384
121. Perapoch J, Planes AM, Querol A, et al. Fungemia with *Saccharomyces cerevisiae* in two newborns, only one of whom had been treated with ultra-levura. *Eur J Clin Microbiol Infect Dis*. 2000;19(6):468–470
122. Salminen MK, Rautelin H, Tynkkynen S, et al. *Lactobacillus bacteremia*, clinical significance, and patient outcome, with special focus on probiotic *L. rhamnosus* GG. Clin Infect Dis. 2004;38(1):62–69
123. Kalima P, Masterton RG, Roddie PH,

Thomas AE. *Lactobacillus rhamnosus* infection in a child following bone marrow transplant. *J Infect*. 1996;32(2):165–167

124. Soleman N, Laferl H, Kneifel W, et al. How safe is safe? A case of *Lactobacillus paracasei* ssp. paracasei endocarditis and discussion of the safety of lactic acid bacteria. *Scand J Infect Dis*. 2003;35(10):759–762
125. Salminen MK, Tynkkynen S, Rautelin H, et al. *Lactobacillus bacteremia* during a rapid increase in probiotic use of *Lactobacillus rhamnosus* GG in Finland. *Clin Infect Dis*. 2002;35(10):1155–1160
126. Land MH, Rouster-Stevens K, Woods CR, Cannon ML, Cnota J, Shetty AK. *Lactobacillus* sepsis associated with probiotic therapy. *Pediatrics*. 2005;115(1):178–181
127. Petschow BW, Figueroa R, Harris CL, Beck LB, Ziegler E, Goldin B. Effects of feeding an infant formula containing *Lactobacillus* GG on the colonization of the intestine: a dose-response study in healthy infants. *J Clin Gastroenterol*. 2005;39(9):786–790
128. European Food Safety Authority. Microorganisms in food and feed: qualified presumption of safety-QPS. Available at: www.efsa.europa.eu/en/events/event/colloque041213.htm. Accessed October 12, 2010
129. Infant Formula Act of 1980. Available at: http://thomas.loc.gov/cgi-bin/bdquery/z?d096:HR06940:@@@L&summ2=m&. Accessed October 12, 2010
130. American Academy of Pediatrics, Work Group on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics*. 1997; 100(6):1035–1039

APPENDIX 1 Selected Dietary Supplements

Product	Active Ingredient	CFU Count per Dose
VSL#3	*S thermophilus, Bifidobacterium* species, *Lactobacillus* species	450 billion, combined
Culturelle	LGG	10 billion
Florastor	*S boulardii*	5 billion
GNC	*L acidophilus*	1.6 billion
	B bifidum	1.6 billion
CVS brand	*L acidophilus, Bifidobacterium longum*	1 billion
Nature Made	*L acidophilus*	500 million
Selected functional foods		
Dannon Activia yogurt	*Bifidus regularis*	100 000–1 million/g
Stonyfield Farm yogurt, refrigerated (not frozen)	*Lactobacillus bulgaricus, S thermophilus, L acidophilus, Lactobacillus casei, L reuteri, Bifidus* species	10 million/g, combined (throughout shelf-life)
Sweet acidophilus milk (Purity Dairy), refrigerated	*L acidophilus*	4 million/mL
Kefir, refrigerated (Lifeway Foods)	*B lactis, Lactobacillus casei, L acidophilus, Lactobacillus rhamnosus, Streptococcus diacetylactis, L plantarum, Saccharomyces florentinus, Leuconostoc cremoris, B longum, B breve*	20–40 million/mL
Nestle Good Start natural cultures	*B lactis*	10^7/100 kcal
Mead Johnson Nutramigen with Enflora LGG	LGG	10^7/100 kcal

CFU indicates colony-forming unit.