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Clinical Practice Guideline

Clinical Efficacy of Probiotics: Review of the Evidence With Focus on Children

ABSTRACT
Probiotics are marketed in several countries and widely used by pediatric health care providers. Although probiotics can be helpful for specific disorders, they have been broadly prescribed for disorders without clear evidence to support their use. Furthermore, in certain specific conditions, probiotics cause clinical deterioration. This report is a review and evaluation of the evidence or lack thereof to support a beneficial effect of probiotic agents in a variety of pediatric conditions and to review the safety and potential adverse events that may be encountered when using probiotics. It is also important to emphasize that probiotics are highly heterogeneous with differences in composition, biological activity, and dose among the different probiotic preparations. ***JPGN 43:550–557, 2006.***
Key Words: Probiotics—Children—Pediatric—Probiotic safety.

INTRODUCTION

The origin of probiotics, fermented foods and cultured milk predates recorded history. However, it was not until 1908 that Metchnikoff (1) made observations that human health and longevity are associated with the ingestion of lactic acid–producing bacteria. His observation stemmed from the fact that Bulgarian peasants who lived longer consumed large quantities of sour milk containing what is now known as *Lactobacillus bulgaricus*. The concept of probiotics evolved based on such observations. "Probiotics" mean "for life" and are defined as live microorganisms, which when consumed in adequate amounts, confer a health effect on the host. In vitro studies suggest that probiotics potentially act favorably in the host through several different mechanisms. They have an antimicrobial effect through modifying the microflora, secreting antibacterial substances, competing with pathogens to prevent their adhesion to the intestinal epithelium, competing for nutrients necessary for pathogen survival, producing an antitoxin effect and reversing some of the consequences of infection on the intestinal epithelium, such as secretory changes and neutrophil migration (2,3). Probiotics are also capable of modulating the immune system (4), regulating the allergic immune cell response of the body (5) and reducing cell proliferation in cancer (6). The effects of these agents may go beyond the gastrointestinal tract to distant areas, such as the urogenital and respiratory mucosa, and it may not be necessary to administer the intact probiotic organism to achieve benefits. At the basic research level, products of probiotics such as secreted proteins and DNA can block inflammation and stop the death of epithelial cells (7,8). For example, DNA from some probiotic preparations can suppress experimental colitis in several animal models (9). The bacteria can also be genetically modified for use as carriers for antigen delivery into diseased sites in the intestine (10).

A variety of probiotic agents have been studied as single agents or as combination therapies. Examples of such strains include lactobacilli, bifidobacteria, saccharomyces, *Escherichia coli* and streptococci. Considerable differences exist in the bioavailability, biological activities, doses and composition among probiotic preparations. Moreover, most studies have not been reproduced or confirmed. Further studies are necessary to increase understanding of how probiotic agents produce effects on the host as various strains of probiotic bacteria may work by distinct mechanisms. It is important to recognize that in vitro effects of a probiotic may display opposite behavior in vivo (11). Therefore, although probiotics are promising agents to unravel the mystery of gut microbial interactions, our understanding of their use for children in the appropriate clinical circumstances is just beginning. Considerably more supporting evidence beyond what is currently provided in the literature is required as numerous fundamental questions remain unanswered.

The purpose of this clinical report is to review the evidence regarding the use of probiotics in a variety of gastrointestinal and nonintestinal conditions, as well as to review reported adverse events. PubMed and MEDLINE searches were performed for all human trial studies related to probiotic therapy. Case reports and

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studies only published in the abstract form were excluded. The quality of the evidence was rated according to the following categories (12):

I. Evidence obtained from at least one properly designed randomized controlled study.
II-1. Evidence obtained from well-designed cohort or case-controlled trials without randomization.
II-2. Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3. Evidence obtained from multiple time series with or without the intervention.
III. Evidence obtained from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

This review provides clinicians caring for children a tool to guide their decisions regarding the use of these agents. For a full review on the use of probiotics in dietetic products for infants, the reader is referred to an excellent recent commentary published by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition (13).

REVIEW OF EVIDENCE

Digestive Disorders

Inflammatory Bowel Disease

Pouchitis

Pouchitis is defined as acute or chronic inflammation of the ileal reservoir created after colectomy and ileal pouch–anal anastomosis. Small controlled studies suggest that a probiotic preparation (VSL no. 3) combining 8 different probiotic bacteria can be effective in preventing pouchitis in adult patients (Table 1). However, the supporting data for children are lacking. A randomized placebo-controlled study included 40 adult patients with history of chronic relapsing pouchitis who achieved clinical and endoscopic remissions with antibiotics. Patients were randomly assigned to probiotic or placebo. After 9 months, 15% of patients receiving VSL no. 3 experienced a relapse, whereas 100% of patients receiving placebo relapsed. Within 3 months of discontinuing the probiotic, all patients in the probiotic group relapsed (14). Another study using the same probiotic preparation showed significantly more patients who received probiotics remaining in remission (85% vs 6%). Subjects in this study were adult patients who required antibiotics at least twice in the previous year for treating refractory pouchitis (15). A third study using the same probiotic showed significantly fewer episodes of pouchitis (10% vs 40%) when adult patients who underwent ileal pouch–anal anastomosis for ulcerative colitis were given VSL no. 3 immediately after ileostomy closure (16). It is worthy to note that development of pouchitis in the untreated group was fairly high. Patients who developed pouchitis had a low bacterial and a high fungal diversity. Bacterial diversity was increased, and fungal diversity was reduced when patients were maintained in remission with VSL no. 3 (17).

In contrast, the use of *Lactobacillus rhamnosus* GG was not beneficial in a small controlled study of adult patients with pouchitis (18). In evaluating these studies, one has to consider the heterogeneity of the study population being tested.

Ulcerative Colitis

Several probiotic compounds have shown promise in the therapy of ulcerative colitis. However, a strong sustained benefit remains to be seen. One large randomized study of 116 patients with ulcerative colitis demonstrated that nonpathogenic *E. coli* (Nissle 1917) was equally effective as mesalamine in preventing relapse (19). In this study, remission was induced with corticosteroids, and patients were randomized to receive either probiotic or mesalamine. The median time to relapse was 206 days in the mesalamine group and 221 days in the *E. coli* group. However, the maintenance dose of mesalamine used in this trial was low (1500 mg daily). Thus, it is unclear from this particular study whether probiotics would be more effective than low-dose mesalamine as a maintenance agent. Two other studies support a similar benefit of this *E. coli* strain when compared with low-dose 5-aminosalicylic acid (5-ASA) (20,21). Uncontrolled pilot studies suggest that VSL no. 3 maintains remission in mild to moderate ulcerative colitis in 75% of patients and reduces active inflammation in 87% (22,23). A recent open-label study suggests a 53% remission rate in ambulatory adult patients with active disease who received VSL no. 3 (23). Bifidobacteria-fermented milk has been found to decrease the rate of relapse in a small study (24). In mild to moderate ulcerative colitis, *Saccharomyces boulardii* given for 4 weeks induced remission in 17 of 24 patients (25).

Crohn Disease

Clinical trials with probiotics have shown inconsistent results in treating adult Crohn disease (26,27). A small pediatric nonrandomized pilot study suggested that Lactobacillus GG may improve gut barrier function and clinical status in children with mildly to moderately active, stable Crohn disease (28). However, in a larger controlled double-blind pediatric study, Lactobacillus GG did not prolong time to relapse in children with Crohn disease (28,29).

Summary of Inflammatory Bowel Disease Studies

In general, probiotic studies in Crohn disease and ulcerative colitis have small sample sizes, lack of controls and inconsistent results. The use of probiotics for the prevention of pouchitis is supported by multiple randomized placebo-controlled trials in adult patients

showing efficacy with high doses of VSL no. 3 (Table 1). Probiotics have no proven role in inducing or maintaining remission in Crohn disease. With regards to ulcerative colitis, *E. coli* Nissle 1917 has been found to be equivalent to mesalamine in some studies and may be a viable alternative to mesalamine.

Irritable Bowel Syndrome

A number of studies have evaluated the response of irritable bowel syndrome to probiotic preparations. Although results between studies are difficult to compare because of differences in study design, probiotic dose, strain and duration of therapy, some studies suggest symptom improvement. There are 9 randomized and 2 open studies in adults, whereas there is only 1 randomized pediatric study. Ten of the 12 studies report amelioration of symptoms such as bloating, abdominal pain or colonic transit. Many of the studies were fairly short and do not reflect improvement in the quality of life. Table 2 summarizes the results of those studies.

Antibiotic-associated Diarrhea and Clostridium difficile *Infection*

Antibiotic-associated Diarrhea

Many of the studies evaluating the efficacy of probiotics in antibiotic-associated diarrhea (AAD) are small and have significant methodological flaws. However, 2 meta-analyses suggest a reduction in AAD by approximately 60%. The probiotic agents showing efficacy in this condition were *S. boulardii* in adult patients and Lactobacillus GG in children (47,48). A recent meta-analysis of data from 5 randomized controlled trials showed *S. boulardii* to be moderately effective in preventing AAD in children and adults treated with antibiotics. For every 10 patients treated, 1 will not develop AAD (49). Not all probiotics are equally effective in this condition as a combination of *Lactobacillus acidophilus* and *L. bulgaricus* was ineffective in preventing diarrhea in children receiving amoxicillin therapy during a double-blind placebo-controlled trial (50). Furthermore, a study from the Mayo Clinic failed to show superiority of Lactobacillus GG over placebo in preventing diarrhea in 302 hospitalized adult patients receiving antibiotics (51).

Clostridium difficile *Prevention and Treatment*

A randomized placebo-controlled trial of *S. boulardii* plus standard antimicrobial therapy in adult patients with recurrent *Clostridium difficile* infection showed a risk reduction of recurrence down to 34.6% as compared with 64.7% in the placebo group (52). Surawicz et al. (53) demonstrated benefit from using *S. boulardii* when combined with high doses of oral vancomycin to prevent recurrent *C. difficile* disease. In general, the benefit of probiotic therapy in *C. difficile* diarrhea was mostly seen in a subgroup of patients characterized by

TABLE 1. *Summary of clinical trials for the use of probiotics in inflammatory bowel disease*

Disease	Author	Year published	Type of probiotic	Type of trial	Outcome	Type of evidence
Pouchitis	Mimura et al. (15)	2004	VSL no. 3	Adult, R, PC	Effective prevention	I
	Gionchetti et al. (16)	2003	VSL no. 3	Adult, R, PC	Effective prevention	I
	Gionchetti et al. (14)	2000	VSL no. 3	Adult, R, PC	Effective prevention	I
	Kuisma et al. (18)	2003	Lactobacillus GG	Adult, R, PC	Ineffective treatment	I
	Laake et al. (30)	2003	*L. acidophilus* and *Bifidobacterium lactis*	Adult, open trial	Ineffective prevention	II-1
	Gosselink et al. (31)	2004	Lactobacillus GG	Adult, retrospective observation	Effective prevention	II-1
Crohn disease	Bousvaros (29)	2005	Lactobacillus GG	Pediatric, R, PC	Ineffective maintenance	I
	Malchow (26)	1997	*E. coli*	Adult, R, PC	Ineffective maintenance	I
	Prantera et al. (32)	2002	Lactobacillus GG	Adult, R, PC	Ineffective maintenance	I
Ulcerative colitis	Rembacken et al. (19)	1999	*E. coli*	Adult, R	Equivalent to 5-ASA	I
	Kruis et al. (21)	1997	*E. coli*	Adult, R	Equivalent to 5-ASA	I
	Kruis et al. (20)	2001	*E. coli*	Adult, R	Equivalent to 5 ASA	I
	Venturi et al. (22)	1999	VSL no. 3	Adult, open trial	Maintain remission	II-1
	Fedorak et al. (33)	2003	VSL no. 3	Adult, open trial	Maintain remission	II-1
	Bibiloni et al. (23)	2005	VSL no. 3	Adult, open trial	Induce remission	II-1
	Guslandi et al. (25)	2003	*S. boulardii*	Adult, uncontrolled pilot	Induce remission	II-1
	Ishikawa et al. (24)	2003	Bifidobacteria	Adult, R, PC	Maintain remission	I
	Furrie et al. (34)	2005	*Bifidobacterium longum*	Adult, R, PC, pilot	Initiate remission	I

R, randomized; PC, placebo controlled.

TABLE 2. *Summary of published reports of probiotic role in irritable bowel syndrome*

Author	Year	Type of probiotic	Duration of use (weeks)	Population studied	Type of trial	Outcome of study	Level of evidence
Busserman and Michail (35)	2005	Lactobacillus GG	6	Pediatric patients (n = 50)	R, DB, PC	Reduced abdominal distension otherwise negative	I
Kim (36)	2005	VSL no. 3	4 and 8	Adult patients (n = 48)	R, DB, PC	Reduced flatulence and slowed colonic transit	I
O'Mahoney et al. (37)	2005	*Lactobacillus salivarius* and B infantis	8	Adult patients (n = 77)	R, DB, PC	Reduced pain, bloating and bowel movement difficulty	I
Kim et al. (38)	2003	VSL no. 3	8	Adult patients, (n = 25 diarrhea-predominant)	R, DB, PC	Reduced bloating otherwise negative	I
Niedzielin et al. (39)	2001	LP299v	4	Adult patients (n = 40)	Open trial	Effective	II-1
O'Sullivan et al. (40)	2000	L GG	4	Adult patients (n = 19)*	DB, PC crossover	No effect	I
Sen et al. (41)	2002	LP299v	4	Adult patients (n = 12)*	DB, PC, crossover	No effect	I
Brigidi et al. (42)	2001	VSL no. 3	3	Adult patients (n = 10)*	Open, no placebo	Effective	II-1
Saggioro (43)	2004	LP0 1 and bifidocterium Breve	4	Adult patients (n = 70)	R, PC	Effective	I
Nobaek et al. (44)	2000	LP299v	4	Adult patients (n = 60)	R, PC	Effective	I
Tsuchiya et al. (45)	2004	Synbiotic (SCM-III)	12	Adult patients (n = 68)	Single-blinded	Effective	II-1
Halpern et al. (46)	1996	Lacteol Fort, antidiarrheal drug containing heat-killed *L. acidophilus*	6	Adult patients (n = 14)*	DB, PC, crossover	Effective	II-1

*Very small number of subjects studied. R, randomized; PC, placebo controlled; DB, double-blinded.

severe disease (54). A small open-label trial of Lactobacillus GG in children also suggests this agent may be of benefit in prevention of relapsing *C. difficile* (55). However, larger controlled studies have not been performed in children.

Infectious Diarrhea

Perhaps the most studied potentially beneficial effect of probiotics is mild to moderate infectious diarrhea. Results have been summarized in several meta-analyses, all of which found an overall reduction in the duration of diarrhea by about 1 day (56–59). The probiotic agent showing consistent benefit was Lactobacillus GG (58). However, in children with more severe diarrhea, there was no demonstrable benefit (60,61). This phenomenon is further supported in a recent study from Bangladesh showing lack of efficacy of *Lactobacillus paracasei* strain ST11 in severe diarrhea while being effective in ameliorating less severe, nonrotavirus diarrhea (62).

The role of probiotics in preventing nosocomial infectious diarrhea has shown contradicting evidence. A double-blinded randomized control trial using Lactobacillus GG in 81 children ages 1 to 36 months showed a significant reduction in the risk of rotavirus gastroenteritis (2.2% vs 6.7%) (63). Seven children would need to be treated with the probiotic to prevent 1 patient from developing nosocomial rotaviral gastroenteritis (63). However, a larger double-blinded randomized study in 220 children did not show a statistically significant protective effect of the same probiotic for nosocomial rotaviral infection (64). Another randomized trial studying 55 infants admitted to a chronic care pediatric hospital showed a lower risk of developing nosocomial diarrhea when infants were fed probiotic-containing formula (7% vs 31%) (65). This protective effect becomes far less significant if the incidence of diarrhea (episodes per patient-month) rather than the percentage of patients with diarrhea is taken into account (66).

With regards to the prevention of community-acquired diarrhea, randomized controlled studies suggest a modest protective effect. A Peruvian study of 204 malnourished children showed a reduction of the number of episodes of diarrhea per child per year from 6.02 to 5.21 favoring Lactobacillus GG. A second study from Finland involving 571 children attending daycare centers did not show a significant difference in the number of days with diarrhea when Lactobacillus GG was used. However, there was a 16% reduction in the number of days of absence due to gastrointestinal and respiratory illnesses (67). Another study involving 210 healthy children in child health care centers showed a

lower frequency and shorter duration of diarrhea when *Lactobacillus reuteri* or *B. lactis* were given to the children (68).

Miscellaneous Digestive Disorders

Necrotizing enterocolitis is a condition seen mostly in premature infants and can result in small bowel resection in severe cases. Review of the literature shows an inconsistent effect of probiotics in this condition. In 3 studies, the use of a combination probiotic therapy administered to premature infants reduced the incidence of necrotizing enterocolitis (69–71). Other investigators, however, were unable to demonstrate any benefit of Lactobacillus GG in necrotizing enterocolitis prevention (72).

The role of probiotics in the treatment of hepatic encephalopathy was examined in a few pilot studies. Therapy with probiotics or prebiotics resulted in improvement of hepatic encephalopathy and lower blood ammonia levels (73–75). This effect may be related to colonization of the intestine with acid-resistant, nonurease-producing bacteria (76).

Probiotics are generally not effective in eradicating *Helicobacter pylori* infection, but they can reduce side effects of recommended antimicrobial therapy (77).

Nondigestive Disorders

Allergic Disorders

Probiotics have been shown to reduce inflammatory cytokines and intestinal permeability in vitro. Such an effect would be beneficial in allergic disorders. Therefore, several studies have looked at the efficacy of probiotics in allergic conditions, such as eczema, allergic rhinitis and food allergies. The results of these studies are promising, but a definitive role is yet to be confirmed. When Lactobacillus GG or placebo was given to pregnant mothers with a strong family history of eczema, allergic rhinitis or asthma and to their infants for the first 6 months after delivery, the frequency of developing atopic dermatitis in the offspring was significantly reduced at 2 (78) and 4 years (79). Another placebo-controlled study showed significant improvement in children with atopic dermatitis after a 6-week administration of *L. rhamnosus* 19070-2 and *L. reuteri* DSM 122460. Children with high immunoglobulin E levels and 1 or more positive skin tests were more responsive to probiotic therapy (80). Infants with atopic eczema and cow's milk allergy responded more effectively to hydrolyzed whey formula when Lactobacillus GG was added in a large controlled study (81). When *L. paracasei* 33 was given for 30 days to 80 children with perennial rhinoconjunctivitis, the quality of life questionnaire scores significantly improved relative to placebo (82). However, *L. rhamnosus* supplementation failed to show any benefit in birch-pollen allergic children in a placebo-controlled trial (83).

Cancer Prevention

Clinical evidence is insufficient to support the use of probiotics in cancer prevention.

Extraintestinal Mucosal Effects

Probiotics, such as Lactobacillus GG, colonizing the gastrointestinal tract have been shown to influence distant mucosal sites such as respiratory and urogenital tracts. They have been shown to be of benefit in urinary tract infections (84), vulvo-vaginal candidiasis, otitis media (85) and bacterial vaginosis (86). Lactobacillus GG, in the form of a milk preparation, was recently reported as having some modest but consistent benefits in terms of preventing and reducing the severity of

TABLE 3. *Summary of the quality of evidence for the use of probiotics in different diseases*

Type of disease	Comments	Quality of evidence
Pouchitis	Efficacy clearly shown in adult studies with VSL no. 3	I
Pediatric Crohn disease	No clear efficacy (mostly Lactobacillus GG data)	I
Ulcerative colitis	Efficacy suggested (equivalent to ASA preparations)	I
Irritable bowel syndrome	Efficacy possible	I
AAD	Efficacy clearly shown but not all probiotics are effective (mainly *S. boulardii* and Lactobacillus GG)	I
C. difficile diarrhea	Efficacy clearly shown but mainly in severe recurrent disease using *S. boulardii* and Lactobacillus GG	I
Mild to moderate acute diarrhea	Efficacy clearly shown; treatment shortens duration of illness by 1 day (mostly lactobacilli, 10 billion per dose or more)	
	Prevention, modest effect with some conflicting reports	I
Necrotizing enterocolitis	Efficacy possible	I
Hepatic encephalopathy	Efficacy possible; small studies favoring efficacy in adults; large studies as well as pediatric studies are necessary	I
H. pylori eradication	No efficacy supported	I
Allergy	Efficacy clearly shown in preventing atopic dermatitis	I
Cancer therapy and prevention	Efficacy possible; inconsistent clinical data	II
Urogenital disorders		
Respiratory tract infections		

respiratory tract infections at daycare centers (67). More pediatric data are necessary before recommending their use in children with extraintestinal disorders.

SAFETY

In general, probiotics are considered safe in children. Some studies on immune-compromised patients with HIV (87) and transplant (88) population have been reassuring. However, there are multiple reports of bacteremia and fungemia (89–104) with lactobacilli and saccharomyces organisms, especially in patients that are immunocompromised or have indwelling central venous catheters. Interestingly, some of these patients did not directly receive probiotics but were in the same hospital unit with patients who had the probiotics. Contamination of the air, environmental surfaces and hands is suggested in these cases (97). Caution should be used especially when considering probiotics in patient populations with indwelling venous catheters. In addition, another potential concern is the fact that D-lactate can be produced by some lactic acid bacterial strains, which may result in neurological changes (105).

It is also worthy to note that the effect of probiotics on the developing immune system in neonates, especially preterm infants, is not known and long-term studies are vital in addressing this concern.

CONCLUSIONS

Probiotics hold promise for a variety of digestive and nondigestive disorders. In specific clinical circumstances, there is clear evidence of benefit such as acute viral gastrointestinal tract infections and AAD. The beneficial effect of the probiotic can be modest, and the anticipated advantage must be viewed along with associated cost and available alternatives. The evidence or lack thereof to support the use of probiotics in a variety of disorders is summarized in Table 3. When prescribing probiotics, one must consider the probiotic formulation, including live, dead, compounded preparations or their products, the effective dose to use and the type of disease targeted. Inasmuch as "not all probiotics are created equal," one cannot extrapolate specific actions or doses of a given probiotic and generalize these properties to other doses or strains of probiotic bacteria. It is also important for the prescribing clinician to realize that the US Food and Drug Administration does not currently regulate probiotic products. Thus, there is no governing agency overlooking quality control, and the actual number of viable organisms in commercial products may be quite different from what is being advertised (106). In summary, future large-scale clinical trials controlling dosing, viability and other critical variables will be crucial to provide the necessary scientific evidence required to determine efficacy of the ever-increasing use of probiotics.

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