Clinical Indications for Use of Probiotics in the Pediatric Population

An increasing interest in health benefits achieved from the ingestion of live microorganisms has led to a dramatic expansion in the use of probiotics to treat or prevent human diseases. Clinical studies have reported beneficial effects of probiotics, primarily lactic acid producing bacteria, for infectious diarrhea, allergic diseases, irritable bowel syndrome, inflammatory bowel disease and necrotizing enterocolitis. This review will summarize recent clinical evidence on the use of probiotics in children with a focus on randomized controlled trials when available.

INTRODUCTION

Although the use of live bacteria to promote health evolved from the work of Metchnikoff in 1908 it has only been recently that probiotics, defined as “live microorganisms which when supplemented in adequate amounts confers a health benefit on the host” have achieved widespread use (1,2). The most typical probiotic bacteria include those that are lactic acid producing such as Lactobacilli and Bifidobacter (Table 1). Currently, probiotics are being administered for health maintenance, immune enhancement and the prevention and treatment of a variety of medical conditions. The introduction of probiotics into food products has also helped spur a dramatic interest in this field by the lay population. However, the advertised health benefits of these products need to be viewed at this point with skepticism since probiotic dosages provided may be inadequate for therapeutic benefit and food processing may result in variable numbers of viable organisms compared to the commercially prepared probiotic formulations.
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PROBIOTICS: THE HOPE, THE HYPE, AND THE REALITY, SERIES #4

Table 1
Microorganisms used as probiotics in clinical studies

Lactobacillus Species
- L. acidophilus
- L. casei (rhamnosus)
- L. reuteri
- L. bulgaricus
- L. johnsonni
- L. lactis

Bifidobacterium Species
- B. bifidum
- B. longum
- B. breve
- B. lactis
- B. infantis
- B. adolescentis

Other Species
- Bacillus cereus
- Escherichia coli
- Saccharomyces cerevisiae
- Saccharomyces boulardii
- Enterococcus fecalis
- Streptococcus thermophillus
- Propionibacterium freudenreichii ssp. shermanii JS

While the spectrum of indications for probiotics expands, their therapeutic use in children has also gained popularity. In this review we summarize the current indications for probiotic use as medical therapy in pediatric clinical practice. It is important to keep in mind that efficacy with one particular strain of probiotic does not imply that other strains will be equally efficacious, thus attention needs to be given to the organisms and preparations used in particular studies.

INFECTIONOUS DIARRHEA

The most well documented probiotic studies involve the treatment and prevention of infectious diarrhea, particularly acute rotavirus diarrhea (3). Lactobacillus rhamnosus GG (LGG) and Lactobacillus reuteri have been shown to significantly reduce the severity and duration of acute viral enteritis in two trials enrolling well-nourished infants and children who presented with at least two days of diarrhea (4, 5). In one of these trials, a multi-center European study, a decrease was observed in the duration of rotavirus diarrhea from 76.6 hours to 56.2 hours when patients were offered oral rehydrating solution plus LGG after initial rehydration (6). Other studies have shown a reduction in rotavirus shedding as well as an increased antibody response to rotavirus infection and rotavirus vaccine in children given LGG (7–9). The doses of probiotics used in these studies ranged from 1 to 10 billion colony forming units per gram (CFU/g).

Three meta-analyses (Table 2) of existing clinical trials focusing on diarrhea in pediatric patients concluded that probiotic therapy shortens the duration of acute diarrhea in children by approximately 1 day (0.7–1.6 days) and decreases the number of stools with a beneficial effect starting at 3 days (7,8,10). Doses of 10 billion CFU/g appeared to be most efficacious suggesting that a certain threshold dose may be needed to achieve a therapeutic benefit. One meta-analysis demonstrated a significant linear association between the log of Lactobacillus dose and reduction in diarrhea duration in 8 of the studies reviewed (10). However, the authors of all three meta-analyses cautioned that no clear conclusion could be drawn regarding precise dose, duration of therapy and type of probiotic as different studies used different strains.

While most controlled trials have focused on treatment of infectious diarrhea, a few have addressed diarrhea prevention (Table 3). These trials used B. lactis, S. thermophilus and LGG and demonstrated a decreased incidence and shorter duration of diarrheal illness concomitant with a decreased rate of viral shedding (12–14). The studies were done in high risk populations of children where the burden of infectious diarr-

(continued on page 55)
rhea was considered to be significant such as infants in a chronic medical care hospital and undernourished children in an underdeveloped country (12,14).

**ANTIBIOTIC-ASSOCIATED DIARRHEA**

Diarrhea occurs in approximately 20% of patients who receive antibiotics (15). Two randomized controlled trials have demonstrated that LGG reduces the risk of antibiotic-associated diarrhea in children (16,17). In the larger of the two trials, 188 children (ages 6 months–10 years) receiving a 10 day course of antibiotics were given 10–20 billion CFU/g of LGG per day (17). The group receiving LGG had an 18% decrease in the incidence of diarrhea and a decrease in duration of diarrhea by 1.17 days compared to the placebo group. Randomized, placebo-controlled trials in adults using *Saccharomyces boulardii* and LGG have shown similar reductions in the incidence of antibiotic-associated diarrhea (18,19). Probiotics have also been used to prevent antibiotic associated diarrhea with antibacterial therapy for *H. pylori* infection (20).

One meta-analysis of nine studies, which included the two pediatric trials mentioned above, has been published on probiotic use in antibiotic-associated diarrhea (21). The odds ratio in favor of active treatment over placebo in preventing diarrhea associated (continued on page 59)
with antibiotics was 0.39 (p < 0.001) for *S. boulardii* and 0.34 (p < 0.01) for *Lactobacilli* giving a combined odds ratio of 0.37 (p < 0.001) in favor of active treatment over placebo (22).

**CLOSTRIDIUM DIFFICILE COLITIS**

There are no published clinical trials for probiotic use in children at risk for developing recurrent *C. difficile* colitis. Two randomized controlled trials done in adults using *LGG* and *Bifidobacter* have shown a decrease in the rate of *C. difficile* toxin excretion in stools. (23, 24) In one of these trials, in patients with diarrhea the incidence of stool samples positive for *C. difficile*-associated toxins was 2.9% in the probiotic group compared with 7.2% in the placebo-control group (24).

**TRAVELER’S DIARRHEA**

*S. boulardii* and *LGG* have been used in adult placebo-controlled trials for the prevention of traveler’s diarrhea (25,26). In 245 American travelers who received *LGG* for 1–3 weeks, the incidence of diarrhea in the treated group was 3.9% as compared to 7.5% in the placebo group (25). *S. boulardii* similarly showed a diminished incidence of diarrhea (28.7% versus 39.1% for placebo) in Austrian travelers but these results varied depending on the region of travel (26). No studies have been performed for this indication in children.

**ALLERGIC DISEASES**

In two landmark studies, Kalliomaki, et al demonstrated a decreased incidence of atopic eczema at 24 and 48 months in children who had been given *LGG* for six months after birth and whose mothers had received *LGG* during the last trimester of pregnancy (27, 28). In these studies, doses of probiotics exceeded one billion CFU/g. Another blinded, placebo-controlled trial randomized 230 infants to receive either *LGG* (ATCC 53103) or a mixture of 4 probiotics (*LGG*, *L. rhamnosus LC705* (LC705), *B. breve* Bbi99 and *Propionibacterium freudenreichii ssp. shermanii JS*) or placebo. Only the *LGG* group was noted to significantly improve clinical symptoms in infants with
IgE-associated atopic/eczema dermatitis syndrome, which highlights the importance of strain specific benefits (29). Other randomized controlled trials in pediatric patients have shown a benefit of LGG and B. lactis in the treatment and prevention of atopic eczema and dermatitis (Table 4).

Clinical trials have also shown significant improvement in the course of atopic eczema in infants given probiotic-supplemented elimination diets. Isolauri, et al showed an improvement in the extent and severity of eczema in cow’s milk sensitive infants with atopic dermatitis who were given LGG (ATCC 53103), or B. lactis Bb12 in a hydrolyzed whey formula. A validated atopic dermatitis index score (SCORAD—SCORE of Atopic Dermatitis) with a range of 0 (absence of signs and symptoms) to > 40 (severe symptoms) was used to measure outcome. With a mean starting score of 16 the SCORAD decreased in the B. lactis group to 0 (0–3.8), and in the LGG group to 1 (0.1–8.7) compared to 13.4 (4.5–18.2) in the unsupplemented group (30).

The importance of probiotic viability was brought to light in a randomized, control trial which evaluated viable LGG or heat-inactivated LGG versus placebo in infants with atopic eczema and cow’s milk allergy. Heat-inactivated LGG was associated with adverse gastrointestinal symptoms leading to premature termination of study. However, the group of children receiving the viable-LGG demonstrated the greatest mean decrease in SCORAD score (19 to 5) compared with placebo (13 to 8) (31).

INFLAMMATORY BOWEL DISEASE (IBD)

In the only randomized, placebo-controlled trial using a probiotic in pediatric patients with Crohn’s disease, the effects on maintenance of clinical remission of LGG or placebo added to standard medical therapy was evaluated in a group of 75 children (32). In those receiving the probiotic, the median time to relapse of clinical symptoms was 9.8 months compared to 11.0 months in the placebo group (P = 0.24). Twelve of 30 (31%) children receiving LGG developed a relapse compared with 6/36 (17%) receiving placebo (P = 0.18). This study suggests that LGG does not prolong time to relapse in children with CD when given as an adjunct to standard therapy. A beneficial effect in reducing intestinal permeability and improving disease activity scores was demonstrated in an open labeled study in which 4 children with Crohn’s disease were given $10^{10}$ CFU of LGG twice daily for 6 months (33).

Treatment of pouchitis has been the one area in IBD where the literature has provided the most convincing evidence for the use of probiotics (34,35). In a randomized controlled trial of adults with pouchitis in remission, 40 patients were randomized to receive 9 months of placebo or 600 billion viable lyophilized bacteria daily of the probiotic preparation VSL#3 (VSL Pharmaceuticals, Inc., Ft. Lauderdale, FL) which contained 4 strains of Lactobacillus (L. casei, L. plantarum, L. acidophilus, and L. delbrueckii subsp. bulgaricus), 3 strains of Bifidobacterium (B. longum, L. breve, and B. infantis), and 1 strain of Streptococcus (salivarius subsp. thermophilus). Eighty-five percent of those receiving VSL#3 were able to maintain remission compared to 0% of those receiving placebo during the study period. A subsequent study aimed at comparing VSL#3 to placebo in preventing onset of acute pouchitis during the first year after ileal pouch-anal anastomosis showed that only 10% of patients treated with VSL#3 had an episode of acute pouchitis compared with 40% treated with placebo (P < 0.05) (35). VSL#3 has also been used to induce remission in adults with active ulcerative colitis (36).

IRRITABLE BOWEL SYNDROME (IBS)

In a short 4 week trial of adults randomized to receive preparations containing L. plantarum LP01 and B. breve BR03 or L. plantarum LP01 and L. acidophilus LA 02 in doses greater than 5 billion CFU/g per day there was a significant decrease in clinical pain and IBS symptom indices after 14 and 28 days with both probiotic preparations compared to placebo (37). Another double-blind, placebo-controlled trial, randomized adults to receive either Lactobacillus spp or Bifidobacterium spp for 8 weeks (38). Incorporating all symptoms, the researchers noted significant improvement in response to Bifidobacterium during all weeks of the study. Symptom and quality of life improvement was also greater with Bifidobacterium (continued on page 63)
than with placebo or *Lactobacillus*. Similar to what has been noted in other trials, after the patients discontinued treatment, both symptoms and quality of life returned to baseline which highlights the necessity for continued ingestion of the probiotic to maintain a benefit (38). No studies have been performed in children with irritable bowel syndrome.

**NECROTIZING ENTEROCOLITIS (NEC)**

A multicenter Italian trial administering 6 billion CFU/g *LGG* daily to preterm infants for 47.3 ± 26.0 days showed a trend towards the prevention of NEC as compared to a placebo treated group (39). Two subsequent randomized controlled trials have also shown a protective effect of probiotics in NEC (40, 41). In one, a Chinese study enrolling 367 very low birth weight infants, subjects were randomized to be fed breast milk with placebo or Infloran (Swiss Serum and Vaccine Institute, Berne, Switzerland) containing *L. acidophilus* and *B. infantis* at a dose of 125 mg/kg twice daily until hospital discharge (40,41). A significantly lower incidence of NEC was observed in the probiotic supplemented group (2 of 180) compared to the control group (10 of 187). No episodes of bacteremia or sepsis from the probiotic were noted in the treatment group. While the evidence in NEC prevention is promising, more standardized longitudinal studies are needed to establish therapeutic guidelines.

**OTHER INDICATIONS**

The number of clinical conditions being treated with probiotics is on the rise. Some have yielded encouraging results, but overall, the data on all of these remains limited. One randomized, controlled trial has evaluated probiotic use in prevention of *Helicobacter pylori* infection (42). Three hundred twenty-six asymptomatic Chilean children from a low socioeconomic area diagnosed with *H. pylori* infection by a (13) C-urea breath test were randomized to receive placebo or either viable or heat-killed *Lactobacillus johnsonii* La1 or *L. paracasei* ST11 for 4 weeks. A moderate but significant difference in *H. pylori* colonization was detected in children receiving live *L. johnsonii* La1 and no differences were observed in the other groups.

One clinical trial has used a probiotic as an adjunct to lactulose for the treatment of constipation in children. Eighty-four school children with constipation were randomized to receive 2 billion CFU/g *LGG* daily or placebo for 12 weeks. The primary treatment outcome measure, defined as passage of 3 or more spontaneous bowel movements per week, failed to show any difference between the treatment and placebo groups (43).

Few studies have evaluated efficacy of probiotic supplementation (*L. reuteri, B. lacis, S. thermophilus and LGG*) to reduce the rate of infections in day care centers. These only reaffirmed the role of probiotics in reducing the incidence of diarrhea but failed to show a decrease in respiratory infections, urinary tract infections and otitis media (12,39,44).

Even beyond exploiting the natural capability of probiotics for therapeutic intervention, experimentation with probiotics genetically manipulated to deliver regulatory cytokines, replacement enzymes and pharmacologic agents has already begun and has the potential to revolutionize the use of probiotics (45).

**CONCLUSION**

In spite of the many questions that remain, and the larger clinical trials that need to be executed, the interest in therapeutic uses for probiotics in the pediatric population continues to increase. Of all the probiotic strains used, *LGG* has been the most frequently studied, however, the variability in doses, dosing frequency and strains used have made it difficult to develop general therapeutic guidelines. Nonetheless, given the ease of tolerance, excellent safety profile, and observed positive impact, probiotics appear to be reasonable therapeutic interventions in children for acute infectious diarrhea, antibiotic-associated diarrhea and atopic eczema/dermatitis syndrome.

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**References**

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