

Probiotics in the Prevention and Treatment of Gastrointestinal Infections

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Although the use of probiotics has gained popularity in recent years, the concept dates back almost a century. Metchnikoff [1] described the potential health benefits of lactic acid bacteria in 1908 and advocated their use to promote health and prolong life. Reports later surfaced in the veterinary literature, with the use of microorganisms as supplements in animal feed. Over the past few decades there has been increasing interest in the use of probiotics in humans. In 2001, an expert panel defined these substances as “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host” [2].

This concept is particularly appealing in the setting of gastrointestinal (GI) infections, when the balance of endogenous microflora may become disrupted. Probiotics have been given in an attempt to maintain or restore the normal microflora, and thus, to promote colonization resistance and prevent the overgrowth of pathogenic microorganisms. Proposed mechanisms by which this might occur include competition for nutrients, stimulation of immunity, inhibition of mucosal adherence, and production of antimicrobial substances [3]. Studies in the pediatric population evaluated the use of probiotics in acute diarrhea and several other disease states. Recently, some evidence has supported a role for probiotics in adult GI infections, including *Helicobacter pylori*, traveler’s diarrhea, antibiotic-associated diarrhea, recurrent *Clostridium difficile*-associated disease, and pancreatitis.

HELICOBACTER PYLORI

Infection with *H pylori* is associated with several GI conditions, including chronic gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma. Because of concern for increasing

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antibiotic resistance, alternate options for eradication of this organism have been explored, including the use of probiotics.

Perhaps the best studied are *Lactobacillus* species, which can tolerate a low pH, and thus, may reside transiently in the stomach. Several in vitro and animal studies showed inhibition of *H pylori* by these organisms, with proposed mechanisms of action including lactic acid production [4], induction of cell autolysis [5], antibiotic production [6], and decreased binding to gastric mucosa [7,8]. Several human studies also suggested a suppressive effect. Michetti and colleagues [9] enrolled 20 volunteers who were infected with *H pylori* into a study that compared *L johnsonii* La1 plus omeprazole or *L johnsonii* La1 with placebo; they found a marked decrease in urea breath test values in both groups. Values remained low 6 weeks after treatment, although biopsies showed persistent infection. Other groups have found similar results with this strain in asymptomatic adults [10] and children [11], which suggested a decrease in bacterial load with probiotic therapy. When given in combination with clarithromycin, La1 decreased *H pylori* density in the gastric antrum and corpus when compared with placebo, although it did not improve the eradication rate [12]. In a separate study, *L johnsonii* LC1 led to slight improvement in the severity and activity of antral gastritis, as well as an increase in mucus thickness [13].

Several additional species also seem to decrease the bacterial load of *H pylori*. Linsalata and colleagues [14] compared therapy with *L brevis* (CD2) with placebo in *H pylori*-positive patients who had dyspepsia. They found a decrease in urea breath test values, as well as a significant decrease in gastric ornithine decarboxylase activity and polyamine biosynthesis. Another group gave yogurt containing *L acidophilus* La5 or *Bifidobacterium lactis* Bb12 to 59 adult volunteers who were infected with *H pylori*; they found a decrease in urease activity, compared with placebo, after 6 weeks of therapy [15]. Cats and colleagues [16] found that administration of *L casei* strain Shirota led to a trend toward decreased urease activity that was not statistically significant. Sakamoto and colleagues [17] found improvement in urea breath test results after treatment with *L gasseri* OLL2716 (LG21). This study also showed improvement in serum pepsinogen assays, which suggested a reduction of gastric mucosal inflammation. A study of *L gasseri* OLL2716 in children, however, did not demonstrate a benefit [18].

Other studies have shown a favorable role for probiotics in improving the eradication rate of *H pylori*. Canducci and colleagues [19] enrolled 120 *H pylori*-positive individuals into a study of standard therapy with rabeprazole, clarithromycin, and amoxicillin combined with *L acidophilus* or placebo. They found a significant improvement in eradication with *L acidophilus* (88% versus 72%). Another group found similar results using yogurt that contained *Lactobacillus* and *Bifidobacterium* plus traditional triple therapy, with eradication rates of 91% (compared with 78% with triple therapy alone) in the intention-to-treat analysis [20]; however, the per-protocol eradication rates were similar in both groups. In children, the addition of *L casei* DN-114 001 to standard treatment with omeprazole, amoxicillin, and clarithromycin led to improvement in

H pylori eradication (84.6% versus 57.5% without probiotics) [21]. *L casei* was studied as a second-line therapy in patients who were resistant to an initial course of treatment for *H pylori*; it led to slight improvement in eradication over that seen with a 10-day course of quadruple therapy alone [22]. Wenda-koon and colleagues [23] studied yogurt that contained several *Lactobacillus* species, but they did not find an effect on *H pylori* eradication. Urea breath test values were not reported in this study; therefore, it is unclear whether the bacterial load may have been decreased.

Several studies suggested a reduction in side effects related to traditional eradication therapy with probiotic supplementation. *Lactobacillus* GG led to improvement in several symptoms, including nausea, bloating, taste disturbance, and diarrhea [24,25]. Another group found a lower frequency of diarrhea and taste disturbance with the use of *Lactobacillus* GG, *Saccharomyces boulardii*, or a combination of *Lactobacillus* species when compared with placebo, with no significant difference between groups [26]. Improved tolerability also was found with *Bacillus clausii* [27]. In a separate study that used a combination of several probiotics, however, there was no significant difference in the frequency of new or aggravated symptoms in the treatment group compared with placebo [28].

In summary, several lactobacillus species have shown efficacy at decreasing the bacterial load of *H pylori* in controlled trials, although their effect on eradication remains unclear. Probiotics may have an adjunctive role in reducing the side effects that are associated with traditional eradication therapy.

TRAVELER'S DIARRHEA

Acute diarrhea develops in approximately 20% to 60% of travelers to developing countries, and is the most common illness that is experienced by these individuals. Although many organisms can be responsible, enterotoxigenic *Escherichia coli* seem to be the most common. Although most cases are self-limited, symptoms can result in substantial morbidity and disruption of travel plans. Because travelers may find it difficult to avoid exposure to causative organisms, prophylaxis is a desirable alternative. Several investigators have evaluated the use of probiotics in this setting.

One study of Austrian travelers showed a modest, dose-dependent reduction in the incidence of diarrhea with prophylactic ingestion of the yeast *S boulardii*. In this study, 28.7% of individuals who received high-dose therapy had diarrhea compared with 39.1% who received placebo. The protective effect varied geographically, with the highest benefit occurring in travelers to North Africa and Turkey [29]. In travelers to Egypt, a mixture of *L acidophilus*, *Bifidobacterium bifidum*, *L bulgaricus*, and *S thermophilus* also reduced the frequency of diarrhea (43% versus 71%) [30]. Oksanen and colleagues [31] compared *Lactobacillus* GG with placebo in travelers to Turkey, and found a reduction in diarrhea (23.9% versus 39.5% in the placebo group). Another placebo-controlled trial of *Lactobacillus* GG in United States travelers also showed a modest effect, with diarrhea developing in 3.9% per day at risk compared with 7.4% in the placebo group [32].

Other studies have failed to show a beneficial effect. In 50 United States travelers to Mexico, prophylactic ingestion of a mixture of *L. acidophilus* and *L. bulgaricus* was not effective in reducing the frequency or duration of new-onset diarrhea [33]. In a study of British soldiers who were deployed to Belize, there was no significant difference in the prevalence of diarrhea between groups that received *L. fermentum* strain KLD, *L. acidophilus*, or placebo (25.0%, 29.7%, and 27.7%, respectively.) Studies have shown conflicting results, and it is premature to recommend the routine use of probiotics for prevention of traveler's diarrhea.

ANTIBIOTIC-ASSOCIATED DIARRHEA

Diarrhea is a common complication of antimicrobial therapy and occurs in 5% to 39% of patients [34]. The result is longer hospital stays, an increased incidence of other nosocomial infections, and a higher cost of care. Although the underlying pathogenesis is not understood completely, it is postulated that disruption of the normal fecal flora leads to overgrowth of opportunistic pathogens, alteration in the metabolic function of the flora, and diarrhea. *C. difficile* is responsible for approximately 26% to 50% of cases [34]. Several probiotics have been studied in the prevention of antibiotic-associated diarrhea (AAD), with the strongest evidence supporting a role for *Lactobacillus* GG and *S. boulardii* [35,36].

The use of *Lactobacillus* GG has been evaluated in adults and children. In adults who were treated with erythromycin, fewer cases of diarrhea occurred in those who took yogurt that contained *Lactobacillus* GG than in controls [37]. This organism also led to a decreased incidence of AAD in children who received antibiotics for respiratory infections (5% compared with 16% in the placebo group) [38]. Another study in the pediatric population found similar results [39]; however, a 14-day course of *Lactobacillus* GG did not reduce the rate of AAD in a study of 267 hospitalized adults who were receiving antibiotics [40].

Other lactobacilli preparations, including a combination of *L. acidophilus* and *L. bulgaricus* (Lactinex), have failed to show convincing results. When coadministered to 98 patients who were receiving ampicillin this preparation failed to demonstrate significant improvement [41]. Likewise in a small study of pediatric patients who were receiving amoxicillin, Lactinex did not prevent diarrhea consistently [42]. Another study found variable results in patients who had neomycin-associated diarrhea, with lot-to-lot variations in lactobacillus preparations [43].

S. boulardii demonstrated efficacy in the prevention of AAD in several controlled trials. In a French study, AAD occurred in 4% of outpatients who were receiving *S. boulardii* compared with 17% who were receiving placebo [44]. A United States study of 180 hospitalized patients showed AAD rates of 9% with *S. boulardii* compared with 22% with placebo [45]. In hospitalized patients who were receiving β -lactam antibiotics, AAD rates of 7% were reported with prophylactic *S. boulardii* (versus 15% with placebo) [46]. Diarrhea also was reduced with this organism in a study of critically ill tube-fed patients [47], as well as in patients who were receiving antibiotics for eradication of *H. pylori* [48]; however, a British study of 69 hospitalized patients failed to demonstrate

efficacy [49]. Recently, a randomized controlled trial showed a decreased risk for AAD with *S. boulardii* in the pediatric population [50].

Other organisms have shown modest efficacy in small trials. In one study, the use of *Enterococcus faecium* SF68 led to AAD in 9% of patients (compared with 27% with placebo) [51]. Another group found similar results with this strain, with AAD rates of 3% compared with 18% in the placebo group [52]. Bifidobacteria also demonstrated some benefit, with reduction in gastrointestinal discomfort in patients who were receiving clindamycin [53] and lower stool weight and frequency in those who were receiving erythromycin [54]. Larger studies of these organisms are necessary before adopting their use.

In conclusion, controlled trials support the use of probiotics for the prevention of antibiotic-associated diarrhea, with the strongest evidence in favor of *Lactobacillus* GG and *S. boulardii*. Their role in the treatment of this condition remains to be determined.

RECURRENT CLOSTRIDIUM DIFFICILE-ASSOCIATED DIARRHEA

C. difficile is a gram-positive bacteria that produces two toxins (A and B) that lead to diarrhea and colitis. Although an initial episode usually responds to antibiotic therapy, recurrent disease can develop in up to one third of patients. In this setting, multiple recurrences are common and can be difficult to treat. Although several probiotics have been studied in the treatment of recurrent *C. difficile*-associated disease (RCDAD), only *S. boulardii* demonstrated efficacy in randomized controlled trials.

Initial work in an animal model of RCDAD found *S. boulardii* to be effective [55]. This led to an open trial in humans, in which 11 of 13 patients who received *S. boulardii* plus vancomycin had no further recurrences [56]. In another uncontrolled trial, 5 of 7 patients who had renal failure and RCDAD showed improvement following treatment with this organism [57]. In an initial randomized trial, recurrences occurred in 9 of 26 (34%) patients who had RCDAD following therapy with *S. boulardii*, compared with 22 of 34 (65%) who received placebo [58]. A subsequent trial showed similar efficacy in patients who were treated with *S. boulardii* plus high-dose vancomycin (2 g/d). Three of 18 patients (17%) had a recurrence, compared with 7 of 14 patients (50%) in the placebo group; however, no significant difference was found in subgroups of patients who took lower doses of vancomycin or metronidazole [59].

Lactobacillus GG also showed efficacy in RCDAD, although only in uncontrolled trials. In one report of five patients who were treated with this organism, four had an immediate response and no further relapses, and the fifth responded to two courses of therapy [60]. Additional trials reported efficacy in two of four children [61] and five of nine adults [62]. Although a preliminary report of a controlled trial suggested efficacy, no final report has been published [63]. A small randomized, controlled trial evaluated *L. plantarum* 299v therapy in RCDAD, but it was not powered adequately to show a significant benefit [64].

Several alternate approaches to the treatment of RCDAD have been attempted. Several reports described benefit with stool donation, which can be

administered by rectal infusion [65], fecal enema [66], colonoscopy [67], or nasogastric tube [68]. One group studied the rectal instillation of a mixture of aerobic and anaerobic bacteria, and found loss of *C difficile* and its toxin from the stool of six patients who had RCDAD [69]. This treatment led to bowel colonization by *Bacteroides* species. Oral administration of nontoxicogenic strains of *C difficile* also was effective in a report of two patients [70]. Because these therapies only have been evaluated in small numbers of patients and in uncontrolled studies, their use should be considered investigational at this time.

In summary, although several probiotics have been evaluated in the management of RCDAD, the strongest evidence supports the use of *S boulardii*. Additional controlled trials are indicated.

PANCREATITIS

In patients who have severe acute pancreatitis, necrosis and infection contribute to poor outcomes and increased mortality. Probiotics have been used in this setting in the hopes of reducing bacterial translocation, and thus, preventing secondary pancreatic infections. Animal models of acute pancreatitis showed a reduction in bacterial translocation with the use of *L plantarum* 299v [71] and *S boulardii* [72]. In a human study, the use of live *L plantarum* 299v resulted in reduced rates of pancreatic infection, with abscess formation occurring in 1 of 22 patients compared with 7 of 23 patients who received an inactivated preparation [73]. More recently, these investigators evaluated a preparation of four different lactobacilli species, and found a trend toward lower incidence of multi-organ failure, septic complications, and mortality that was not statistically significant [74]. Although initial trials seem to be promising, controlled trials are not available. A larger multicenter trial is investigating the infectious complications of acute pancreatitis using a multispecies probiotic preparation [75].

ACUTE DIARRHEA IN INFANTS AND CHILDREN

The use of probiotics for the prevention and treatment of acute diarrhea in the pediatric population was reviewed recently by Vanderhoof and Young [76]. Several placebo-controlled studies showed efficacy for *Lactobacillus* GG in reducing the severity and duration of acute diarrhea. A meta-analysis of 18 studies concluded that probiotic therapy shortens the duration of acute diarrheal illness in children by approximately 1 day [77]. Placebo-controlled studies also suggest a benefit for *Lactobacillus* GG in the prevention of community-acquired acute diarrhea, and for combination probiotic therapy in the prevention of nosocomial diarrhea [76].

SUMMARY

Probiotics have been studied in a variety of GI infections, and are an appealing concept given their favorable safety profiles. Several placebo-controlled trials indicated that lactobacilli have a suppressive effect on *H pylori* infection. Although some studies reported improvement in *H pylori* eradication, others failed to confirm this. Controlled trials support the use of *Lactobacillus* GG and *S boulardii*

for the prevention of AAD, and have demonstrated the effectiveness of *S boulardii* as adjunctive therapy for RCDAD. Several placebo-controlled trials showed a reduction in the severity and duration of acute diarrhea in children with use of *Lactobacillus GG*. Studies of probiotics for the prevention of traveler's diarrhea yielded conflicting results, and their routine use cannot be recommended in this setting. Preliminary evidence suggests a potential role for reducing secondary pancreatic infections, although conclusive evidence is not available at this time. Additional clinical trials are indicated to define the role of probiotics further before widespread use can be recommended.

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