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Probiotics

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Abstract and Introduction

Abstract

Purpose. The pharmacology, uses, dosages, safety, drug interactions, and contraindications of probiotics are reviewed.
Summary. Probiotics are live nonpathogenic microorganisms administered to improve microbial balance, particularly in the gastrointestinal tract. They consist of *Saccharomyces boulardii* yeast or lactic acid bacteria, such as *Lactobacillus* and *Bifidobacterium* species, and are regulated as dietary supplements and foods. Probiotics exert their beneficial effects through various mechanisms, including lowering intestinal pH, decreasing colonization and invasion by pathogenic organisms, and modifying the host immune response. Probiotic benefits associated with one species or strain do not necessarily hold true for others. The strongest evidence for the clinical effectiveness of probiotics has been in the treatment of acute diarrhea, most commonly due to rotavirus, and pouchitis. More research is needed to clarify the role of probiotics for preventing antibiotic-associated diarrhea, *Clostridium difficile* infection, travelers' diarrhea, irritable bowel syndrome, ulcerative colitis, Crohn's disease, and vulvovaginal candidiasis. There is no consensus about the minimum number of microorganisms that must be ingested to obtain a beneficial effect; however, a probiotic should typically contain several billion microorganisms to increase the chance that adequate gut colonization will occur. Probiotics are generally considered safe and well tolerated, with bloating and flatulence occurring most frequently. They should be used cautiously in patients who are critically ill or severely immunocompromised or those with central venous catheters since systemic infections may rarely occur. Bacteria-derived probiotics should be separated from antibiotics by at least two hours.
Conclusion. Probiotics have demonstrated efficacy in preventing and treating various medical conditions, particularly those involving the gastrointestinal tract. Data supporting their role in other conditions are often conflicting.

Introduction

In recent years, both research and consumer interest in probiotics have grown. Increasing clinical evidence supports some of the proposed health benefits related to the use of probiotics, particularly in managing certain diarrheal diseases. Probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[1] The term *probiotic* was initially used in the 1960s and comes from a Greek word meaning "for life." Although a relatively new word, the beneficial effects of certain foods containing live bacteria have been recognized for centuries. However, it was not until the early 20th century that investigators suggested gut flora could be altered with beneficial bacteria replacing harmful microbes, leading to the concept of probiotics.[2–4]

Probiotics, which are regulated as dietary supplements and foods, consist of yeast or bacteria. They are available as capsules, tablets, packets, or powders and are contained in various fermented foods, most commonly yogurt or dairy drinks. Probiotic products may contain a single microorganism or a mixture of several species. Table 1 lists common microorganisms used as probiotics. The most widely used probiotics include lactic acid bacteria, specifically *Lactobacillus* and *Bifidobacterium* species. The yeast *Saccharomyces boulardii* also appears to have health benefits. It is noteworthy that probiotic effects tend to be specific to a particular strain, so a health benefit attributed to one strain is not necessarily applicable to another strain, even within one species. Therefore, generalizations about potential health benefits should not be made.[2,5,6,8,9]

Table 1. Microorganisms Used as Probiotics[2,5–7]

Bacteria
Lactobacillus species
L. acidophilus
L. bulgaricus
L. casei
L. crispatus
L. fermentum
L. gasseri
L. johnsonii
L. lactis
L. plantarum
L. reuteri
L. rhamnosus GG
Bifidobacterium species
B. adolescentis
B. animalis
B. bifidum
B. breve
B. infantis
B. lactis
B. longum
Bacillus cereus
Enterococcus faecalisa
Enterococcus faeciuma

Escherichia coli Nissle
Streptococcus thermophilus
Yeast
Saccharomyces boulardii

[a] Concerns exist about using enterococci as probiotics because of possible pathogenicity and vancomycin resistance.

The rationale for using probiotics involves restoring microbial balance. More than 500 different bacterial species reside in the adult gastrointestinal tract.[6,8] Some microbes are considered beneficial to the human host, while others are pathogenic. An appropriate balance of gut flora is generally maintained; however, antibiotics, immunosuppressive medications, surgery, and irradiation can cause an increase in the pathogenic bacteria and disrupt this homeostasis. Probiotics, which contain beneficial bacteria and yeast, may restore the microbial balance in the gastrointestinal tract.[5–7]

In order for probiotics to be successful, they must possess certain characteristics. Probiotic organisms must be able to withstand passage through the gastrointestinal tract (i.e., survive acid and bile degradation), colonize and reproduce in the gut, attach and adhere to the intestinal epithelium, and stabilize the balance of the gut flora. Furthermore, probiotic strains must be safe and effective in humans, remain viable for the shelf life of the product, and not have pathogenic properties.[2,9–11] Products containing more than one organism are particularly appealing for two reasons: colonization in some patients may occur with one strain and not another, and probiotic mixtures may be synergistic in suppressing pathogens.

Uses

Probiotics have been used for the prevention and treatment of various medical conditions and to support general wellness. Some of their beneficial health effects have been validated, while other uses are supported by limited evidence. Not only are probiotic effects strain specific, probiotic products may vary from each other, and greater benefits may be seen with one lot of probiotics versus another due to the complexity of quality control with live microorganisms. Furthermore, combination agents can make it challenging to quantify particular clinical benefits.[2,12,13]

Illnesses associated with the gastrointestinal tract have been a common target of probiotics, mainly due to their ability to restore gut flora. The strongest evidence for the use of probiotics lies in the treatment of certain diarrheal diseases, especially rotaviral diarrhea in children. Clinical studies have also supported the role of probiotics in treating pouchitis.[2,8,9] Data are inconsistent regarding the efficacy of probiotics for antibiotic-associated diarrhea (AAD) and travelers' diarrhea.[2,8] Although clinical trial results are conflicting, probiotic therapy may also be beneficial in the treatment of Crohn's disease, ulcerative colitis (UC), irritable bowel syndrome (IBS), and *Helicobacter pylori* infections.[5,8,14,15] Probiotics have also been shown to decrease the symptoms of lactose intolerance.[11,15–17]

Other illnesses not associated with the gastrointestinal tract or gut microbiota, including various urogenital problems (e.g., bacterial vaginosis, candidal vaginitis, urinary tract infections), may also respond to probiotics.[2,6,8,15] Probiotics have also been studied for their role in treating upper respiratory infections (e.g., acute otitis media); reducing the risk of colon and bladder cancer, allergic diseases, and atopy; boosting immune response; and preventing dental caries.[2,14,15,17,18]

Pharmacology

Although the exact mechanisms of action of probiotics are not known, several have been proposed. As mentioned previously, the most frequently used probiotics include lactic acid bacteria, particularly *Lactobacillus* and *Bifidobacterium* species. These bacteria produce lactic acid, acetic acid, and propionic acid, which lower the intestinal pH and suppress the growth of various pathogenic bacteria, thereby reestablishing the balance of the gut flora.[6,7]

Another mechanism of bacterial interference involves the production of various substances, such as hydrogen peroxide, organic acids, bacteriocins, and biosurfactants, that are toxic to pathogenic microorganisms.[7,10,14] One probiotic with this ability is *Lactobacillus* species strain GG, which has been shown to secrete a low-molecular-weight compound that inhibits a broad spectrum of gram-positive, gram-negative, and anaerobic bacteria.[19] In addition, *S. boulardii*, a nonpathogenic yeast, may have a role in *Clostridium difficile* infection by producing a protease that decreases the toxicity of *C. difficile* toxins A and B.[20]

Probiotics also decrease colonization of pathogenic organisms in the urinary and intestinal tracts by competitively blocking their adhesion to the epithelium.[14] Lactobacilli have been shown to inhibit the attachment of *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* to uroepithelial cells and intestinal epithelial cells.[21,22] This inhibition may occur because lactobacilli cause steric hindrance and upregulate intestinal mucins, which are high-molecular-weight glycoproteins produced by epithelial cells; the result is the formation of a protective barrier. In addition, lactobacilli strengthen the gut mucosal barrier by stabilizing tight junctions between epithelial cells and decreasing intestinal permeability.[7]

Another proposed mechanism of action of probiotics involves immunomodulation. Animal studies have found that some probiotic strains augment the immune response by stimulating the phagocytic activity of lymphocytes and macrophages.[18] Probiotics also increase immunoglobulin A (IgA) and stimulate cytokine production by mononuclear cells.[15,18] Kaila et al.[23] found that children with acute rotaviral diarrhea who were given *Lactobacillus rhamnosus* strain GG (LGG) had an increased IgA, immunoglobulin G, and immunoglobulin M response, resulting in a shortened duration of gastroenteritis symptoms.

Numerous health effects are associated with probiotic use. While some of these indications are well documented, probiotics are often used to treat conditions for which data regarding the efficacy of probiotics are lacking or conflicting.[3,9,24] This article focuses on the more-common uses of probiotics.

Acute Diarrhea

There is convincing evidence from multiple studies supporting the efficacy of probiotics in the treatment of acute diarrhea, especially in children with rotavirus infection. The probiotics most frequently studied for treating acute diarrhea include LGG and *Lactobacillus reuteri*.[2,7,15,17] The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition conducted a double-blind, placebo-controlled, multicenter study involving 287 children age 1–36 months from 10 countries who were admitted to the hospital with moderate-to-severe diarrhea, most commonly due to rotavirus or an unknown pathogen.[25] The patients were randomized to receive oral re-hydration solution plus placebo or oral rehydration solution plus a live preparation of LGG. Patients who were given LGG versus placebo had a shorter mean ±S.D. duration of diarrhea (58.3 ± 27.6 hours versus 71.9 ± 35.8 hours, $p = 0.03$) and a shorter hospital stay (78.8 ± 22.2 hours versus 96.3 ± 21.4 hours, $p = 0.04$). In addition, patients treated with LGG were less likely to have persistent diarrhea (i.e., diarrhea lasting longer than seven days) (2.7% versus 10.7% of those receiving placebo, $p < 0.01$).

Van Niel et al.[26] conducted a meta-analysis of nine clinical trials ($n = 765$) involving children younger than three years with acute infectious diarrhea who received *Lactobacillus* species, most frequently LGG. The studies examined were randomized, blinded, controlled trials that measured diarrhea duration and the frequency of diarrheal stools on the

second day of treatment. The meta-analysis revealed a reduced mean duration of diarrhea by 0.7 day (95% confidence interval [CI], 0.3–1.2 days) and a decrease in diarrhea frequency by a mean of 1.6 stools per day on day 2 of treatment (95% CI, 0.7–2.6 fewer stools) in children who received probiotics.

All probiotics are not equally effective in treating acute diarrhea in children. Canani et al.[27] illustrated this point and emphasized that the particular probiotic preparation should be chosen based on solid efficacy data. In their study, 571 children age 3–36 months with acute diarrhea were randomized to one of six different treatment groups: oral rehydration solution alone (control group) or one of five probiotic preparations, which were prescribed for five days. Only two preparations—LGG and a mixture of four bacterial strains (*Lactobacillus delbrueckii* var *bulgaricus*, *Streptococcus thermophilus*, *Lactobacillus acidophilus*, and *Bifidobacterium bifidum*)—were associated with a significantly shorter median duration of diarrhea (78.5 and 70 hours, respectively; $p < 0.001$) compared with children who received oral rehydration solution alone (115.5 hours). One day after initiation of probiotics, children who were given LGG or the probiotic mixture also had a significantly lower daily stool output compared with the other groups ($p < 0.001$). The other three preparations (*S. boulardii*, *Bacillus clausii*, and *Enterococcus faecium* SF 68) did not significantly affect the duration and severity of diarrhea.

AAD and *C. Difficile* Infection

There is evidence that probiotics can prevent AAD and treat *C. difficile* infection (CDI); however, data are conflicting or inconclusive.[2,5,13,14,17] The most common probiotic microorganisms used for these diseases include lactobacilli and *S. boulardii*.[5] Two meta-analyses of studies examining the use of probiotics to prevent AAD suggested that concurrent administration of probiotics (most commonly lactobacilli and *S. boulardii*) with antibiotics resulted in a reduced frequency of diarrhea.[28,29] The first meta-analysis, which examined 7 trials ($n = 881$), revealed a combined relative risk (RR) of 0.3966 (95% CI, 0.27–0.57) in favor of a beneficial effect of probiotics for reducing the risk of AAD.[28] The other meta-analysis yielded a combined odds ratio of 0.37 (95% CI, 0.26–0.53; $p < 0.001$) for pooled data from all 9 trials ($n = 1214$), supporting probiotic treatment over placebo in the prevention of AAD.[29]

A third meta-analysis reviewed 25 randomized controlled trials ($n = 2810$) examining the use of probiotics for the prevention of AAD and 6 randomized controlled trials ($n = 354$) of probiotic therapy for the treatment or prevention of CDI.[30] The meta-analysis revealed that LGG, *S. boulardii*, and various mixtures of two probiotic strains significantly reduced the frequency of AAD. However, only *S. boulardii* in combination with oral vancomycin or metronidazole or both significantly decreased the recurrence of CDI. Other probiotics tested, including LGG and *Lactobacillus plantarum* 299v in combination with oral vancomycin or metronidazole, were not effective in decreasing CDI recurrence rates. On the other hand, a recent study found that the rate of *C. difficile* colonization in 44 critically ill patients receiving antibiotics was significantly reduced by enteral administration of *L. plantarum* 299v ($p < 0.05$).[31] It is important to note that this study was stopped prematurely due to the low rate of enrollment and reduced funding.

In contrast to the previous studies that found that probiotics reduced the rate of CDI, a systematic review of 8 randomized controlled trials did not find sufficient evidence for routine probiotic use in CDI.[32] A Cochrane Library review also concluded that there was inadequate evidence to support the adjunctive use of probiotics for CDI.[33] While results have been inconsistent, some studies have indicated that probiotics, especially *S. boulardii*, may prevent *C. difficile* overgrowth and decrease CDI recurrence.

Travelers' Diarrhea

Results of studies evaluating the effectiveness of probiotics for preventing travelers' diarrhea have been inconsistent, possibly due to the probiotic strain used and the various trip destinations. Similar to AAD and CDI, the most commonly studied probiotics for travelers' diarrhea include lactobacilli and *S. boulardii*.[5,8] Hilton et al.[34] randomized 245

American tourists traveling to various developing countries to receive LGG or placebo. Those travelers who ingested LGG had a mean daily risk of developing diarrhea of 3.9%, compared with 7.4% for travelers taking placebo (p = 0.05). In contrast, Katelaris et al.[35] found that ingestion of *L. acidophilus* or *Lactobacillus fermentum* strain KLD did not reduce the frequency of diarrhea among 282 British soldiers deployed to Belize. McFarland[36] conducted a meta-analysis of 12 studies (n = 4709), which included the two above-mentioned studies,[34,35] on the role of probiotics in the prevention of travelers' diarrhea. The types of probiotics in the meta-analysis included *S. boulardii* (4 studies), various types of lactobacilli (6 studies), and probiotic mixtures (2 studies). The meta-analysis revealed that probiotics significantly prevented travelers' diarrhea (pooled relative risk [RR_{pooled}], 0.85; 95% CI, 0.79–0.91; $p < 0.001$).

IBS

IBS is characterized by abdominal pain, bloating, flatulence, and altered bowel habits. These symptoms may be due to bacterial overgrowth in the small intestine, causing increased fermentation activities and gas production.[37] Some studies suggest that probiotics may be beneficial in reducing bloating and flatulence associated with IBS. The probiotics used most frequently in the treatment of IBS include lactobacilli and bifidobacteria. In addition, a combination product (VSL#3, VSL Pharmaceuticals, Inc., Towson, MD) has reduced abdominal bloating and flatulence. This preparation contains eight bacterial organisms in large numbers: three bifidobacteria (*Bifidobacterium longum*, *Bifidobacterium infantis*, and *Bifidobacterium breve*), four lactobacilli (*L. acidophilus*, *Lactobacillus casei*, *L. bulgaricus*, and *L. plantarum*), and *S. thermophilus*.[12,24]

A recent meta-analysis involving 20 trials (n = 1404) found that probiotics (most commonly lactobacilli and bifidobacteria) improved global IBS symptoms (RR_{pooled}, 0.77; 95% CI, 0.62–0.94) and reduced abdominal pain (RR_{pooled}, 0.78; 95% CI, 0.69–0.88) compared with placebo.[38] This meta-analysis was not able to examine other types of individual IBS symptoms (e.g., bloating or distension, flatulence, stool frequency) or the effectiveness of specific probiotic strains due to insufficient data. A review of 14 clinical trials also revealed that probiotics (most commonly lactobacilli, bifidobacteria, and VSL#3) improved overall symptoms associated with IBS compared with placebo; however, the contributing studies had methodological limitations.[37] Although probiotics may be beneficial in treating IBS symptoms, limitations exist in interpreting trial results due to the lack of standardization of strains, dosages, treatment durations, and assessment of clinical outcomes. More data are needed before probiotics can be recommended as typical care in the treatment of IBS.[37,38]

Inflammatory Bowel Disease

Inflammatory diseases of the digestive tract include UC, Crohn's disease, and pouchitis. An imbalance of intestinal microflora, specifically high numbers of enteroadhesive and enterohemorrhagic *E. coli* with UC and reduced levels of bifidobacteria with Crohn's disease, may contribute to the inflammation seen with these diseases. Probiotics may improve the microbial balance of the indigenous flora. Although studies have been conflicting, probiotics seem to be an attractive option in the treatment and prevention of inflammatory bowel disease, providing an appealing alternative to the use of antibiotics.[5,7]

Several studies examining the role of probiotics in UC have suggested that they can induce or maintain disease remission. Three controlled trials compared the probiotic *E. coli* Nissle 1917 with mesalamine in UC and found that the two therapies were similar in preventing disease relapse, suggesting that the probiotic was equivalent to standard therapy with mesalamine in maintaining remission.[39–41] Two of the studies had notable limitations—diverse patient population[39] and short study duration[40]—but the more recent study was methodologically more sound and confirmed the results of the other two studies.[41] The particular nonpathogenic *E. coli* probiotic strain used in these three studies has been shown to colonize the intestine and antagonize the pathogenic bacteria seen with UC.[40] Another study

investigated the use of *S. boulardii* in 25 patients who developed a mild-to-moderate clinical flare-up of UC while taking standard maintenance therapy with mesalamine.[42] For various reasons, treatment with corticosteroids was not suitable for these patients. Clinical remission, confirmed endoscopically, was attained in 68% of patients after adding a four-week course of *S. boulardii* to mesalamine treatment. This study was limited by its small sample size, lack of a control group, and open-label design. Bibiloni et al.[43] noted that a six-week course of VSL#3 was also effective in inducing remission or causing a response in 77% of patients with active mild-to-moderate UC that was unresponsive to conventional therapy. This open-label trial also lacked a control group and involved only 34 patients.

Studies have also investigated the role of probiotics in maintaining remission of Crohn's disease. Guslandi et al.[44] noted that patients with inactive Crohn's disease had a significantly lower clinical relapse rate when receiving a six-month regimen of *S. boulardii* plus mesalamine versus treatment with mesalamine alone (6.25% versus 37.5%, $p = 0.04$), suggesting that the probiotic yeast may be beneficial in the maintenance treatment of Crohn's disease. In contrast, Marteau et al.[45] found that a six-month regimen of *Lactobacillus johnsonii* LA1 was not effective in preventing endoscopic recurrence of Crohn's disease after surgical resection.

Various studies support the use of probiotics, particularly VSL#3, in reducing relapse rates and maintaining remission of pouchitis. Pouchitis is a nonspecific inflammation of the ileal reservoir, which is formed surgically after an ileal pouch–anal anastomosis from a proctocolectomy. It is characterized by increased stool frequency and abdominal cramping.[46–48] Although the etiology of pouchitis is unknown, it may be associated with decreased lactobacilli and bifidobacteria counts as well as increased concentrations of other bacteria.[46] In addition to modifying the endogenous flora, VSL#3 alters the immune response in pouchitis by raising tissue levels of the antiinflammatory cytokine interleukin 10 and reducing tissue levels of tumor necrosis factor, interferon, and matrix metalloproteinase activity.[47,48]

In a randomized, double-blind, placebo-controlled trial involving 40 patients with chronic relapsing pouchitis, Gionchetti et al.[46] found that VSL#3 was significantly more effective than placebo in maintaining remission after nine months. All 20 placebo-treated patients experienced a relapse within four months, while 17 of the 20 patients treated with VSL#3 remained in remission after nine months ($p < 0.001$). When the probiotic was discontinued at the study's end, these 17 patients also experienced relapse within four months. In addition, fecal concentrations of lactobacilli, bifidobacteria, and *S. thermophilus* increased significantly from baseline in patients treated with VSL#3 ($p < 0.001$). Mimura et al.[48] confirmed the efficacy of VSL#3 in maintaining remission in patients with recurrent or refractory pouchitis. In this study, 36 patients whose pouchitis was in remission were randomized to receive VSL#3 or placebo for one year or until relapse. Similar to the previous study, 17 of the 20 patients treated with VSL#3 remained in remission at one year versus only 1 of 16 patients who received placebo ($p < 0.0001$). In addition to preventing relapses, Gionchetti et al.[47] showed that the probiotic mixture VSL#3 was significantly more effective than placebo in preventing the occurrence of pouchitis ($p < 0.05$) during the first year after pouch formation in this randomized, double-blind, placebo-controlled study involving 40 patients.

In contrast to those studies with encouraging results using VSL#3 in pouchitis, a three-month trial involving LGG did not show any benefit as primary therapy for ileal pouch inflammation.[49] This trial did not show differences in the mean pouchitis disease activity index scores between treatment with LGG and placebo, and only 40% of patients who received the probiotic had LGG recovered in their fecal flora.

Allergy

Several studies have found that probiotics have a beneficial effect on atopic eczema. Kalliomaki et al.[50] conducted a double-blind, randomized, placebo-controlled trial in which 159 pregnant women with a family history of atopic disease were given LGG or placebo daily for two to four weeks before their expected delivery date, followed by administration of the probiotic or placebo to the newborn infant for 6 months; 132 participants completed the trial. There was a 50%

reduction in the frequency of atopic eczema during the first two years of the children's lives in those given probiotics compared with placebo (23% [15 of 64] versus 46% [31 of 68]; RR, 0.51; 95% CI, 0.32–0.84; p = 0.008). This cohort was reexamined after four years, and significantly fewer children who had previously received LGG were diagnosed with atopic eczema compared with placebo (26% [14 of 53] versus 46% [25 of 54]; RR, 0.57; 95% CI, 0.33–0.97), suggesting that the protective effect of this probiotic on atopic eczema in at-risk children continues beyond infancy.[51] In another randomized double-blind study, 27 infants (mean age, 4.6 months) with atopic eczema received formula supplemented with probiotics (either LGG or *Bifidobacterium lactis* Bb-12) or the same formula without probiotics.[52] After 2 months, the Scoring Atopic Dermatitis index, which reflects the extent and severity of atopic eczema, was reduced significantly in the infants given probiotic-supplemented formulas compared with those who did not receive probiotic supplementation (p = 0.002).

Genitourinary Infections

Abnormal vaginal microbiota may lead to symptomatic infections, including vulvovaginal candidiasis (VVC). Lactobacilli, especially *Lactobacillus crispatus* and *Lactobacillus iners*, are the predominant vaginal microorganisms in healthy premenopausal women. When the normal vaginal microflora is disrupted, such as with use of broad-spectrum antibiotics, overgrowth of *Candida albicans* may occur, causing VVC. Restoring the normal flora with lactobacilli may help treat this genital infection.[53] Hilton et al.[54] conducted a study involving 28 women with a history of recurrent VVC who also had signs and symptoms of active VVC. After the administration of vaginal suppositories containing LGG twice daily for seven days, all of the women reported an improvement in vaginal symptoms and reduced vaginal erythema and discharge. Reid et al.[55] investigated the ability of an orally administered solution containing *L. rhamnosus* GR-1 and *L. fermentum* RC-14 to colonize the vagina in 10 women who were asymptomatic for infection but who had a history of recurrent urogenital infections, primarily recurrent VVC. The probiotic solution was administered twice daily for 14 days. Within one week, one or both of the *Lactobaccillus* strains were recovered from the vaginas of all 10 women, and no VVC occurred during the study. Hilton et al.[56] found that consumption of 8 oz of yogurt containing *L. acidophilus* daily for six months reduced vaginal colonization and infection by *Candida* species in a crossover trial involving 33 women with recurrent VVC, 13 of whom completed the protocol. The mean number of candidal infections of the vagina and candidal colonization in the vagina and rectum were significantly lower in the women who consumed yogurt versus the control group (0.38 versus 2.54, p = 0.001 and 0.84 versus 3.23, p = 0.001, respectively). However, these three studies had important methodological limitations, including small sample sizes, inadequate controls, and lack of blinding. Two of the studies lacked detailed statistical analyses,[54,55] one study had a high attrition rate,[56] and more than half of the women in one study had recently completed treatment with antifungal medications.[54] Therefore, it is difficult to reliably conclude whether probiotics can prevent recurrent VVC.

Dosages and Product Selection

Probiotics are available as supplements (i.e., tablets, capsules, or powders) and as fermented dairy products (i.e., yogurt and milk). Their efficacy relies on their ability to survive passage through the gastrointestinal tract and colonize a tissue section. To prevent destruction by gastric acid and intestinal bile salts, some probiotic preparations may be enteric coated or microencapsulated. For colonization to occur, probiotics must contain living, viable organisms and must be ingested on a regular basis in order to maintain effective concentrations.[57–60] Unfortunately, the manufacturing process may cause living organisms to become nonviable, thus reducing probiotic effectiveness.[32] The quantity, quality, and purity of the bacteria or yeast in probiotics can vary among products due to the complexity of quality control with live microorganisms and the lack of universal quality-assurance programs.[13,38,57] One study analyzed 18 commercially available probiotic products available in the United States and found that 7 (39%) had differences between the stated and actual concentrations of bacteria.[61]

Probiotic dosing varies depending on the product and specific indication. No consensus exists about the minimum

number of microorganisms that must be ingested to obtain a beneficial effect.[16] Typically, a probiotic should contain several billion microorganisms to increase the likelihood of adequate gut colonization.[28] For lactobacilli, typical doses used in studies ranged from 1–20 billion colony-forming units per day. For *S. boulardii*, most studies examined daily doses ranging from 250 to 500 mg.[57] Table 2 summarizes dosing for various probiotic strains based on doses found to be efficacious in human studies. Products should be stored according to the manufacturer's recommendations, since some may require refrigeration. In addition, preparations may have a limited shelf life, and many preparations contain several different species, so dosing may vary depending on the product.

Table 2. Probiotic Species and Dosing[a]

Indication and Probiotic	Recommended Dosage Regimen
Acute infectious diarrhea in infants and children	
Lactobacillus rhamnosus GG (LGG)	At least 10^{10} CFU in 250 mL of oral rehydration solution;[25] 10^{10}–10^{11} CFU twice daily for 2–5 days[26]
Lactobacillus reuteri	10^{10}–10^{11} CFU daily up to 5 days[26]
Antibiotic-associated diarrhea	
Saccharomyces boulardii	4×10^9–2×10^{10} CFU daily for 1–4 wk[30]
LGG	6×10^9–4×10^{10} CFU daily for 1–2 wk[30]
Lactobacillus acidophilus and *Lactobacillus bulgaricus*	2×10^9 CFU daily for 5–10 days[30]
L. acidophilus and *Bifidobacterium longum*	5×10^9 CFU daily for 7 days[30]
L. acidophilus and *Bifidobacterium lactis*	1×10^{11} CFU daily for 21 days[30]
Clostridium difficile infection	
S. boulardii	2×10^{10} CFU (1 g) daily for 4 wk plus vancomycin and/or metronidazole[30]
Travelers' diarrhea	
LGG	2×10^9 bacteria daily starting 2 days before departure and continued throughout trip[34]
S. boulardii	5×10^9–2×10^{10} CFU daily starting 5 days before departure and continued throughout trip[36]
Irritable bowel syndrome	
VSL#3[b]	9×10^{11} CFU daily for 8 wk[38]
Bifidobacterium infantis 35624	10^6–10^{10} CFU daily for 4 wk[38]
LGG and other	

LGG and other organisms	8–9 × 10^9 CFU daily for 6 mo[24,38]
Ulcerative colitis (UC)	
Escherichia coli Nissle 1917	Active UC: 5 × 10^{10} bacteria twice daily until remission (maximum of 12 wk), followed by 5 × 10^{10} bacteria daily for a maximum of 12 mo39; inactive UC: 5 × 10^{10} bacteria daily (study duration was 12 wk)[40]
S. boulardii	Active UC: 250 mg 3 times daily for 4 wk plus mesalamine[42]
VSL#3[b]	Active UC: 1.8 × 10^{12} bacteria (two 3-g sachets) twice daily for 6 wk plus conventional therapy[43]
Crohn's disease	
S. boulardii	Maintenance therapy: 1 g daily for 6 mo plus mesalamine[44]
Pouchitis	
VSL#3[b]	Maintenance therapy: 1.8 × 10^{12} bacteria daily, given as 3-g sachets twice daily (study duration was 9 mo)46; maintenance therapy: 1.8 × 10^{12} bacteria daily, given as two 3-g sachets once daily (study duration was 12 mo)[48]
Atopic disease prevention	
LGG	10^{10} CFU daily for 2–4 wk before expected delivery in pregnant women, followed by infant administration for 6 mo[50]
Vulvovaginal candidiasis	
LGG	10^9 bacteria per suppository inserted twice daily for 7 days[54]
L. rhamnosus GR-1 and *Lactobacillus fermentum* RC-14	At least 10^9 bacteria suspended in skim milk given orally twice daily for 14 days[55]

[a] CFU = colony-forming units.
[b] VSL#3 is a mixture of eight probiotic organisms (*Lactobacillus casei*, *L. plantarum*, *L. acidophilus*, *L. bulgaricus*, *B. longum*, *Bifidobacterium breve*, *B. infantis*, and *Streptococcus thermophilus*).

Various probiotics are available in the United States; however, only those products that have been evaluated in controlled human studies should be recommended. Some examples of these commercially available preparations include LGG (Culturelle, Amerifit Brands, Fairfield, NJ), *S. boulardii* (Florastor, Biocodex, Inc., Beauvais, France), *B. infantis* 35624 (Align, JB Laboratories, Holland, MI), and VSL#3.[62] Yogurt products fermented with probiotics should be labeled with a "Live and Active Cultures" seal, specifying that the preparation contains a minimum of 100 million viable bacteria per gram at the time of manufacture. An example is Activia yogurt (Dannon/Danone, Paris, France), which contains *B. animalis* DN-173 010, marketed by Dannon/Danone as "Bifidus regularis."[57,62,63]

Adverse Effects and Safety

When ingested orally, probiotics are generally considered safe and well tolerated. The most common adverse effects include bloating and flatulence; however, these are typically mild and subside with continued use.[24,57,58] Constipation

and increased thirst have also rarely been associated with *S. boulardii*.[64] One theoretical concern associated with probiotics includes the potential for these viable organisms to move from the gastointestinal tract and cause systemic infections. Although rare, probiotic-related bacteremia and fungemia have been reported.[65] It is estimated that the risk of developing bacteremia from ingested lactobacilli probiotics is less than 1 per 1 million users,[66] and the risk of developing fungemia from *S. boulardii* is estimated at 1 per 5.6 million users.[64] Another theoretical risk associated with probiotics involves the possible transfer of antibiotic resistance from probiotic strains to pathogenic bacteria; however, this has not yet been observed.[65,66]

Although no serious adverse events have been described in clinical trials, systemic infections associated with specific probiotics have been noted in isolated reports. These include sepsis or endocarditis with lactobacilli, fungemia with *S. boulardii*, and liver abscess with LGG.[24,65] Bacteremia due to lactobacilli rarely occurs, but predisposing factors include immunosuppression, prior hospitalization, severe underlying comorbidities, previous antibiotic therapy, and prior surgical interventions.[67] There have been several documented cases of fungemia associated with use of *S. boulardii*. Those at greatest risk include critically ill or highly immunocompromised patients or those with central venous catheters in place. When *S. boulardii* capsules are opened at the bedside for administration through the nasogastric tube, central venous catheters may become contaminated and serve as the source of entry for the organism.[68] Although there have been infrequent reports of lactobacillemia and fungemia, to date there have been no reports of bifidobacterial sepsis associated with the use of a probiotic, supporting the low pathogenicity of bifidobacteria species.[69] Fortunately, most cases of probiotic bacteremia or fungemia have responded well to appropriate antibiotic or antifungal therapy.

In a review of the literature, Boyle et al.[69] identified major and minor risk factors for probiotic-associated sepsis. Major risk factors included immunosuppression (including a debilitated state or malignancy) and prematurity in infants. Minor risk factors were the presence of a central venous catheter, impairment of the intestinal epithelial barrier (such as with diarrheal illness), cardiac valvular disease (*Lactobacillus* probiotics only), concurrent administration with broad-spectrum antibiotics to which the probiotic is resistant, and administration of probiotics via a jejunostomy tube (this method of delivery could increase the number of viable probiotic organisms reaching the intestine by bypassing the acidic contents of the stomach). The authors recommended that probiotics be used cautiously in patients with one major risk factor or more than one minor risk factor.

It is important to remember that the overall risk of developing an infection from ingested probiotics is very low, particularly when used by generally healthy individuals. In Finland, LGG has been routinely added to dairy products since 1990.[70] Despite a substantial increase in the consumption of LGG-containing products from 1995 through 2000, there was no significant change in the incidence of *Lactobacillus*-associated bacteremia observed during the surveillance period of 1990–2000.

A recent study found an increased risk of mortality when probiotics were used to prevent infectious complications in patients with predicted severe acute pancreatitis.[71] These patients had acute pancreatitis and an elevated Acute Physiology and Chronic Health Evaluation (APACHE) II score, Imrie/modified Glasgow score, or C-reactive protein value, predicting a severe disease course and putting them at risk for developing infectious complications, including infected pancreatic necrosis. This multicenter, randomized, double-blind, placebo-controlled trial involved 298 patients who received a multispecies probiotic preparation (*L. acidophilus*, *L. casei*, *Lactobacillus salivarius*, *Lactobacillus lactis*, *B. bifidum*, and *B. lactis*) or placebo, administered enterally twice daily for a maximum of 28 days. The study found that this combination of six probiotic strains did not decrease infectious complications in patients with predicted severe acute pancreatitis but rather was associated with significantly more deaths than was placebo (24 versus 9, $p = 0.01$) and an increased risk of bowel ischemia in the probiotics group compared with placebo (9 versus 0, $p = 0.004$). The authors stated that probiotics should not be routinely given to patients with predicted severe acute pancreatitis and should be used cautiously in critically ill patients or those at risk for nonocclusive mesenteric ischemia.

Drug Interactions

Since probiotics contain live microorganisms, concurrent administration of antibiotics could kill a large number of the organisms, reducing the efficacy of the *Lactobacillus* and *Bifidobacterium* species. Patients should be instructed to separate administration of antibiotics from these bacteria-derived probiotics by at least two hours.[58,72] Similarly, *S. boulardii* might interact with antifungals, reducing the efficacy of this probiotic.[73] According to the manufacturer, Florastor, which contains *S. boulardii*, should not be taken with any oral systemic antifungal products.[74] Probiotics should also be used cautiously in patients taking immunosuppressants, such as cyclosporine, tacrolimus, azathioprine, and chemotherapeutic agents, since probiotics could cause an infection or pathogenic colonization in immunocompromised patients.[58,72,73]

Precautions and Contraindications

Since probiotics contain live microorganisms, there is a slight chance that these preparations might cause pathological infection, particularly in critically ill or severely immunocompromised patients. Probiotic strains of *Lactobacillus* have also been reported to cause bacteremia in patients with short-bowel syndrome, possibly due to altered gut integrity.[57,58,72,73] Caution is also warranted in patients with central venous catheters, since contamination leading to fungemia has been reported when *Saccharomyces* capsules were opened and administered at the bedside.[68,73]

Lactobacillus preparations are contraindicated in persons with a hypersensitivity to lactose or milk.[75] *S. boulardii* is contraindicated in patients with a yeast allergy.[73,76] No contraindications are listed for bifidobacteria, since most species are considered nonpathogenic and nontoxigenic.[57,72]

Limitations

Probiotics are regulated as dietary supplements and not subjected to the same rigorous standards as medications. A challenge with these products involves the complexity of quality control with live microorganisms. As a result, individuals may obtain a product that is ineffective or that contains varying quantities of bacteria or yeast. Published studies involving probiotics have often utilized small sample sizes and lacked appropriate randomization, blinding, or control groups. Therefore, the results from many probiotic studies should be interpreted cautiously due to methodological limitations. There is also heterogeneity among studies, since different probiotic doses, strains, treatment durations, and patient populations may have been used. Since probiotic effects are specific to a particular strain, this may have important implications when interpreting meta-analyses, particularly if strain designations were not provided. Future research needs to encompass more well-designed clinical trials in larger populations and for longer durations to better evaluate the efficacy of probiotics.

Conclusion

Probiotics have demonstrated efficacy in preventing and treating various medical conditions, particularly those involving the gastrointestinal tract. Data supporting their role in other conditions are often conflicting.

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