Probiotics

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Probiotics are microorganisms with potential health benefits. They may be used to prevent and treat antibiotic-associated diarrhea and acute infectious diarrhea. They may also be effective in relieving symptoms of irritable bowel syndrome, and in treating atopic dermatitis in children. Species commonly used include *Lactobacillus* sp., *Bifidobacterium* sp., *Streptococcus thermophilus*, and *Saccharomyces boulardii*. Typical dosages vary based on the product, but common dosages range from 5 to 10 billion colony-forming units per day for children, and from 10 to 20 billion colony-forming units per day for adults. Significant adverse effects are rare, and there are no known interactions with medications. (*Am Fam Physician*. 2008;78(9):1073-1078. Copyright © 2008 American Academy of Family Physicians.)

Probiotics are live microorganisms that benefit the health of the host when administered in adequate amounts. A large number of organisms are being used in clinical practice for a variety of purposes. The most widely used and thoroughly researched organisms are *Lactobacillus* sp. (e.g., *L. acidophilus*, *L. rhamnosus*, *L. bulgaricus*, *L. reuteri*, *L. casei*), *Bifidobacterium* sp., and *Saccharomyces boulardii*, a nonpathogenic yeast.

**Pharmacology**

Several mechanisms have been proposed to explain the actions of probiotics. In most cases, it is likely that more than one mechanism is at work simultaneously. In the prevention and treatment of gastrointestinal infection, it is likely a combination of direct competition between pathogenic bacteria in the gut, and immune modulation and enhancement. In children with atopic dermatitis, the mechanism is probably related to the effect of probiotics on the early development of immune tolerance during the first year of life. Probiotics may help down-grade the excessive immune responses to foreign antigens that lead to atopy in some children. They may also contribute to systemic down-regulation of inflammatory processes by balancing the generation of pro- and anti-inflammatory cytokines, in addition to reducing the dietary antigen load by degrading and modifying macromolecules in the gut. Probiotics have been shown to reverse the increased intestinal permeability characteristic of children with food allergy, as well as enhance specific serum immunoglobulin A (IgA) responses that are often defective in these children.

To be most effective, a probiotic species must be resistant to acid and bile to survive transit through the upper gastrointestinal (GI) tract. Most probiotics do not colonize the lower GI tract in a durable fashion. Even the most resilient strains generally can be cultured in stool for only one to two weeks after ingestion. To maintain colonization, probiotics must be taken regularly.

**Uses and Effectiveness**

Most of the identified benefits of probiotics relate to GI conditions, including antibiotic-associated diarrhea, acute infectious diarrhea, and irritable bowel syndrome (IBS) (*Table 1*). Some studies indicate a benefit in treating atopic dermatitis in children. Probiotics are also commonly used for conditions in which firm evidence is lacking, including vaginal candidiasis, *Helicobacter pylori* infection of the stomach, inflammatory bowel disease, and upper respiratory infections. These uses are not addressed in this review.
ANTIBiotic-ASSOCIATEd DIARRHEA

A meta-analysis of 19 recent studies showed that probiotics reduced the risk of developing antibiotic-associated diarrhea by 52 percent (95% confidence interval [CI], 0.35 to 0.65; \( P < .001 \)).\(^5\) The benefit was greatest when the probiotics were started within 72 hours of the onset of antibiotic treatment. The species that were evaluated included strains of \textit{L. rhamnosus}, \textit{L. acidophilus}, and \textit{S. boulardii}. The authors found that the magnitude of the effect did not differ significantly among the strains, although a limited number of strains were represented.\(^5\)

In a second meta-analysis of 25 randomized controlled trials (RCTs; \( n = 2,810 \)), various probiotics were given to prevent or treat antibiotic-associated diarrhea.\(^6\) The relative risk (RR) of developing antibiotic-associated diarrhea with probiotics was 0.43 (95% CI, 0.31 to 0.58; \( P < .0001 \)), which was a significant benefit when compared with placebo.\(^6\) This analysis also found that \textit{L. rhamnosus}, \textit{S. boulardii}, and mixtures of two or more probiotic species were equally effective in preventing antibiotic-associated diarrhea. The mean daily dosage of the bacterial species in these studies was 3 billion colony-forming units (CFUs), but studies using more than 10 billion CFUs per day showed that these dosages were significantly more effective. The dosages of \textit{S. boulardii} were 250 mg or 500 mg per day.\(^6\)

The same meta-analysis examined the prevention and treatment of \textit{Clostridium difficile} disease.\(^6\) Six RCTs were analyzed and revealed a prevention benefit for participants.
The authors found that *S. boulardii* significantly reduced the duration of diarrhea when compared with the control group, for a mean difference of −1.1 days (95% CI, −1.3 to −0.8). However, a large trial (n = 571) comparing several probiotic preparations to oral rehydration solution concluded that *L. rhamnosus* GG or a combination of *Lactobacillus delbrueckii* subsp. *bulgaricus*, *S. thermophilus*, *L. acidophilus*, and *Bifidobacterium bifidum* was more effective than *S. boulardii* or oral rehydration therapy alone in reducing the duration and severity of acute diarrhea in children.12

Another trial examined the prophylactic benefits of probiotics in preventing GI infections in children.13 In a double-blind, placebo-controlled RCT at 14 child care centers, infants four to 10 months of age (n = 201) were fed formula supplemented with *L. reuteri* SD2112, *B. lactis* Bb-12, or no probiotic for 12 weeks. Both probiotic groups had fewer and shorter episodes of diarrheal illness, with no change in respiratory illness. Effects were more prominent in the *L. reuteri* group, which had fewer absences, clinic visits, and antibiotic prescriptions during the study.

Therapeutic yogurts have also been studied in the prevention and treatment of community-acquired diarrhea in children.14,15 Although a benefit is suggested, more confirmatory studies are indicated.

A meta-analysis of 12 studies (n = 4,709) found a modest decrease in the risk of traveler’s diarrhea, with an RR of 0.85 (95% CI, 0.79 to 0.91; *P* < .0001) in patients taking probiotics.16 No difference was found among organisms, including *S. boulardii* or mixtures of *Lactobacillus* sp. and *Bifidobacterium* sp.

**IRRITABLE BOWEL SYNDROME**

Although definitive evidence is still lacking, several studies have found probiotics to be effective in relieving symptoms of IBS, particularly abdominal pain and bloating.17,19 One study found a 20 percent reduction in symptoms of IBS with *Bifidobacterium infantis* 35624 at a dose of $1 \times 10^9$ CFUs compared with placebo in 362 patients.17 In another study, 50 children fulfilling the Rome II definitions of diarrhea and specific outcomes varied. The reviewers concluded that probiotics significantly reduced the risk of diarrhea at three days (RR = 0.66; 95% CI, 0.55 to 0.77; *P* = .02). The mean duration of diarrhea was also reduced by 30.48 hours (95% CI, 18.51 to 42.46 hours; *P* < .00001). This analysis included all causes of infectious diarrhea (e.g., viral diarrhea, traveler’s diarrhea). The authors concluded that probiotics appear to be a useful adjunct to rehydration therapy in treating acute infectious diarrhea in adults and children.

A meta-analysis examining *S. boulardii* for treatment of acute diarrhea in children combined data from four RCTs (n = 619).11

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criteria for IBS were given L. rhamnosus GG or placebo for six weeks. L. rhamnosus GG was not superior to placebo in relieving abdominal pain, but there was a lower incidence of perceived abdominal distention (P = .02).

IBS symptoms may also be managed by adding components to patients’ diets. One yogurt (Activia), which contains Bifidobacterium animals DN-173 010, improved health-related quality of life scores and decreased bloating symptoms in patients with IBS.

**ATOPIC DERMATITIS**

There may be a role for probiotics as prophylaxis in the development of atopic dermatitis in high-risk infants. One double-blind, placebo-controlled RCT (n = 132) of children with a strong family history of atopic disease administered L. rhamnosus GG (1 × 10^9 CFUs) or placebo to mothers for two to four weeks prenatally and then to infants postnatally for six months. The incidence of diagnosis of eczema by two years of age was reduced by one half (23 percent in the probiotic group versus 46 percent in the placebo group [RR = 0.51; 95% CI, 0.32 to 0.84]). Follow-up visits at four and seven years of age showed no reduction in asthma, food allergy, or allergic rhinitis, suggesting that this intervention will not prevent other manifestations of atopy.

A larger study (n = 925) using L. rhamnosus GG combined with L. rhamnosus LC705, Bifidobacterium breve Bb99, Propionibacterium freudenreichii subsp. shermanii JS, and 0.8 g of galacto-oligosaccharides (newborns only) showed similar effectiveness for atopic dermatitis at two years of age. A placebo-controlled study using L. acidophilus LAVRI-A1 administered to 231 newborns at high risk of atopic dermatitis failed to replicate this finding, possibly because of a different strain or dosage.

Several small RCTs have shown some benefit in children with established atopic dermatitis treated with probiotics. In another study, 56 children six to 18 months of age with moderate or severe atopic dermatitis were recruited into a randomized, double-blind, placebo-controlled trial. The children were given a probiotic (1 × 10^9 Lactobacillus fermentum VRI-033) or an equivalent volume of placebo twice daily for eight weeks. A final assessment at 16 weeks showed a significant reduction in the Severity Scoring of Atopic Dermatitis (SCORAD) index over time in the probiotic group (P = .03) but not in the placebo group. Significantly more children receiving probiotics (92 percent) had a SCORAD index that was better than baseline at week 16, compared with the placebo group (63 percent; P = .01).

However, other interventions to improve allergic symptoms have not been successful.

**Contraindications, Adverse Effects, and Interactions**

There are no absolute contraindications to probiotics comprised of Lactobacillus sp., Bifidobacterium sp., S. thermophilus, or S. boulardii. There are typically few or no adverse effects; flatulence or mild abdominal discomfort, usually self-limited, are reported occasionally. There have been reports of pathologic infection, including bacteremia with probiotic species following oral administration. These are rare, occurring in severely ill or immunocompromised hosts, or in children with short-gut syndrome. It is prudent to avoid probiotics in these patients, or to be aware of the risk of sepsis. A recent systematic review examined the safety of L. rhamnosus GG and Bifidobacterium sp. and concluded that the risk of sepsis is low, with no cases reported in any prospective clinical trial. There are no reports of sepsis or other pathologic colonization in healthy patients. There are also no known interactions with medications or other supplements.

**Dosages**

A wide range of dosages for Lactobacillus sp. and other probiotics have been studied in clinical trials, ranging from 100 million to 1.8 trillion CFUs per day, with larger dosages used to reduce the risk of pouchitis relapse. Most studies examined dosages in the range of 1 to 20 billion CFUs per day, although exact dosages for specific indications varied within this range. Generally, higher dosages of probiotics (i.e., more than 5 billion CFUs per day in children and more
than 10 billion CFUs per day in adults) were associated with a more significant study outcome. There is no evidence that higher dosages are unsafe; however, they may be more expensive and unnecessary. The dosages of *S. boulardii* in most studies range between 250 mg and 500 mg per day.

Probiotics are generally sold as capsules, powder, tablets, liquid, or are incorporated into food. The specific number of CFUs contained in a given dose or serving of food can vary between brands. Patients should be advised to read product labels carefully to make sure they are getting the proper dose.

A recent study analyzed a range of brands of probiotics and found that of the 19 brands examined, five did not contain the number of live microorganisms stated on the label. Because some labels are unreliable, physicians should recommend specific brands known to be of reasonable quality or encourage patients to research brands before purchasing a specific product (Table 2). Guidance on probiotics can be found at [http://www.usprobiotics.org](http://www.usprobiotics.org) and at the National Center for Complementary and Alternative Medicine's Web site, [http://nccam.nih.gov/health/probiotics/](http://nccam.nih.gov/health/probiotics/).

For patients who dislike taking pills or powder, therapeutic yogurt preparations may be preferred option. Traditional yogurts likely do not contain sufficient concentrations of probiotics to deliver the type of CFU doses studied in the clinical trials. Therapeutic fermented dairy products such as Danactive, which contains 10 billion CFUs of *L. casei* DN-114 001 per serving, and Activia, which contains about 5 to 10 billion CFUs of *B. animalis* DN-173 010 per 4-oz. container, are currently available. Yo-Plus and Stonyfield yogurts contain well-studied probiotic strains *B. lactis* Bb-12 and *L. reuteri* ATCC 55730, respectively, but at undisclosed levels. Danimals, a drinkable yogurt marketed for children, contains 1 billion live *L. rhamnosus* GG. More studies are warranted on many food sources of probiotics to provide confidence in effectiveness and dose recommendations.

### The Authors

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Author disclosure: Nothing to disclose.

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**Table 2. Probiotic Strains and Preparations**

<table>
<thead>
<tr>
<th>Probiotic strain</th>
<th>Recommended daily dosage</th>
<th>Preparations*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Lactobacillus rhamnosus GG</em></td>
<td>10 billion CFUs</td>
<td>Capsules (Culturelle)</td>
</tr>
<tr>
<td><em>Lactobacillus sp./Bifidobacterium sp.</em></td>
<td>100 million to 35 billion CFUs, depending on preparation</td>
<td>Capsules (Align, Primadophilus) Powder (Primal Defense) Capsules or powder (Fem-Dophilus, Jarro-Dophilus) Therapeutic yogurts and fermented milks (Activia, Danactive, Yo-Plus)</td>
</tr>
<tr>
<td><em>Saccharomyces boulardii</em></td>
<td>250 mg to 500 mg</td>
<td>Capsules (Florastor)</td>
</tr>
</tbody>
</table>

*CFU = colony-forming unit.

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*---This is not a complete list of commercially available preparations.

†—Most commercial brands contain a mixture of strains that may include *Lactobacillus acidophilus*, *L. rhamnosus*, *Lactobacillus bulgaricus*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, and others. Exact combinations of strains vary among brands.

Information from references 30 and 31.
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REFERENCES


