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# Probiotics for GI Health in 2012: Issues and Updates


## Learning Objectives

After participating in this educational activity, participants should be better able to

1. Differentiate among probiotics and their utility for specific GI issues
2. Counsel patients in clinical practice regarding probiotics utilizing current guidelines and evidence-based data

## Introduction

Microbiota, often referred to as microflora, in the human gastrointestinal (GI) tract comprise a complex community of microorganisms that contribute to a variety of local and systemic functions vital to development and well-being. There is substantial interest in using probiotics to target the GI microbiota to promote health. Probiotics are defined by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) as "live

microorganisms which when administered in adequate amounts confer a health benefit on the host."[1] Prebiotics are different from probiotics. Prebiotics are not alive, are usually nondigestible carbohydrates present in foods, and provide health benefits indirectly by enhancing the growth or activity of beneficial microorganisms present in the digestive tract. Synbiotics combine a prebiotic and a probiotic.[2]

Over the last decade, probiotic use has grown rapidly.[2] In a recent survey of US physicians (86% of whom were gastroenterologists), 93% of respondents reported that at least some of their patients use probiotics.[3] The most commonly targeted conditions were irritable bowel syndrome (IBS), antibiotic associated diarrhea (AAD), *Clostridium difficile* (*C. difficile*) colitis, pouchitis, and ulcerative colitis.[3]

Moreover, the number of clinical trials assessing probiotics in humans also has increased substantially in recent years. A search for human clinical trials published in English in the PubMed database (http://www.ncbi.nlm.nih.gov/sites/entrez) showed that 240 articles (40 per year) were published from January 2000 through December 2005. During the subsequent five years (January 2006 through December 2010), the number more than doubled to 537 (107.4 per year), and in 2011 alone, there were 132 publications.

To assist patients in making informed decisions regarding the use of probiotics for GI health, clinicians should be aware of the similarities and differences among the growing number of probiotics available, and be knowledgeable regarding the current data and guidelines supporting their use. This review on the efficacy of probiotics in GI disorders is designed to provide guidance to primary care clinicians who wish to provide evidence-based probiotic information to their patients.

## Probiotic Nomenclature and Dosing

**Pre-test Question 1**
Results from clinical trials assessing health benefits for one strain should be assumed to apply to only that strain unless there is evidence to the contrary.

A. True
B. False

Probiotic microbes are categorized by genus and species using standard taxonomy, with an alphanumeric designation to identify specific probiotic microbes to the strain level.[1,4] For example, with the strain *Lactobacillus acidophilus* ATCC4356, the genus is *Lactobacillus*, the species is *acidophilus*, and the strain designation is ATCC4356. Maintaining the strain designation is important since strains even of the same species can have different effects. In some cases, manufacturers use a trademarked name to indicate the strain. The majority of probiotics are strains of the genera *Lactobacillus* and *Bifidobacterium*, but other bacteria are also used (eg, *Streptococcus thermophilus*, *Enterococcus faecium*, *Propionibacterium freudenreichii* and *Bacillus coagulans)*.[4] However, probiotics are not limited to bacteria. A probiotic called "Saccharomyces boulardii," which is actually a variant of *Saccharomyces cerevisiae,* is a commonly used probiotic yeast. Products may contain one or more probiotic microbes. Dosing for probiotics is calculated in colony forming units (CFU), which indicate the number of viable microorganisms able to form a colony on an agar plate, and this is generally expressed in a specified amount of the product (eg, $10^9$ CFU/capsule or 1 billion CFU/gram). Because recommended doses vary depending on the strain or product, it is not possible to state

a "general dose" for probiotics; the dosage used in clinical practice should be based on human studies supporting the intended health benefit.[4]

**Because health benefits of probiotics may be strain-specific, providing the genus, species, and strain for each probiotic organism is imperative in clinical publications as well as on product labels.**

## Regulation of Probiotics in the US

At present, the FDA may regulate a probiotic as a dietary supplement, food ingredient, medical food, or as a drug, depending on its intended use.[2] Currently, no probiotic is marketed as a drug in the US.[2,4]

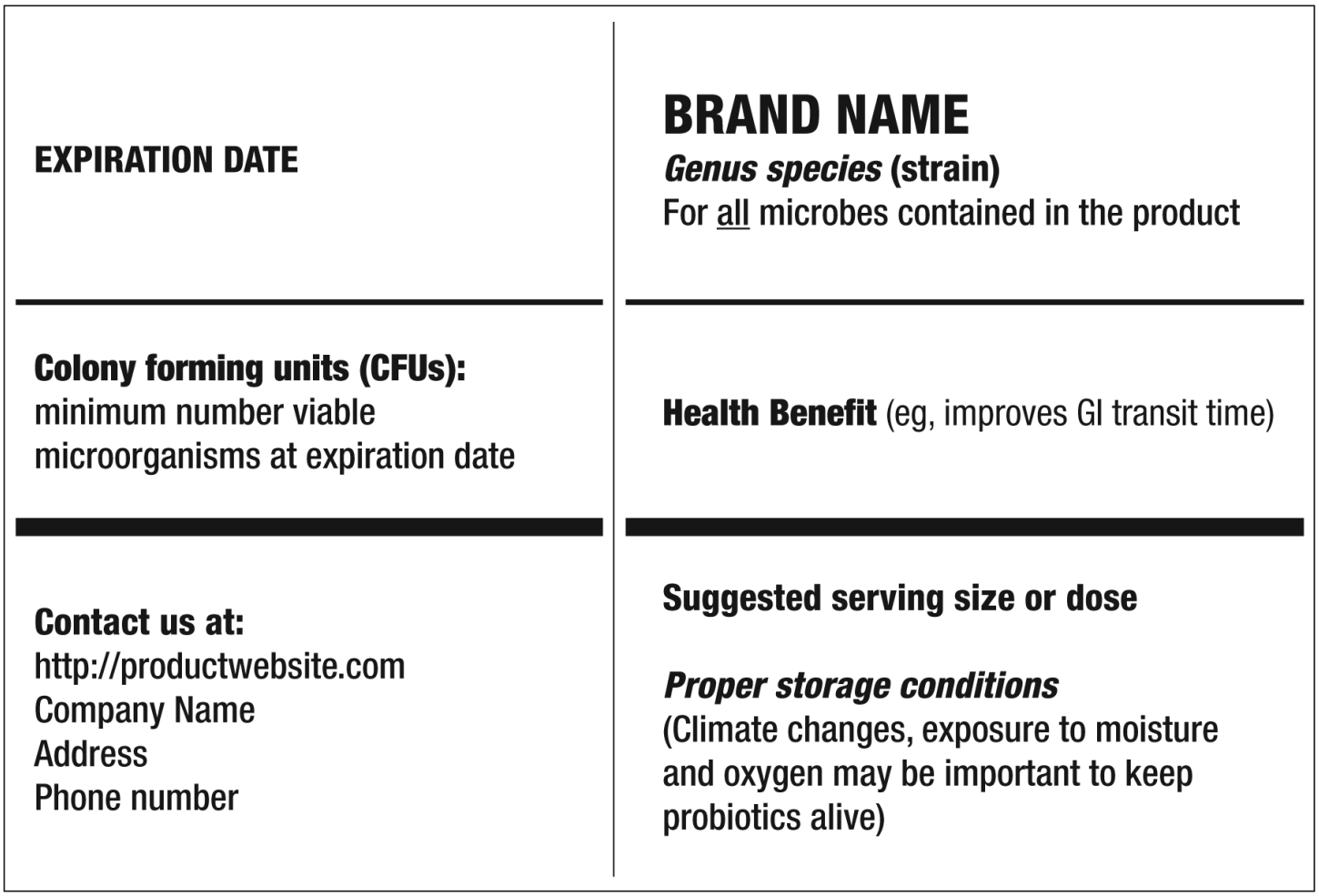
Most probiotics are marketed in the US as dietary supplements or as food ingredients.[2] Probiotic supplements are available as capsules, powders, or drops. Probiotic foods are most commonly yogurts or other fermented milk products (eg, kefir), but other food formats also exist. Labels for foods or dietary supplements may claim how the product affects the structure or function of the body – FDA approval is not required for this type of claim, although the products are required by law to be labeled in a truthful and accurate fashion.[2,5] Claims that relate the probiotic to the cure, treatment, prevention, or mitigation of disease are not allowed in the US for a food or dietary supplement; such claims are limited to drugs.[2,4,6] However, claims that a product can reduce the risk of a disease are allowed with premarket approval.[7] Clinical data showing the efficacy of a probiotic in the treatment or prevention of disease may be available, but food or dietary supplement labels may not communicate that evidence.[6] For example, a manufacturer may state that a product improves transit time through the colon, as this is an effect on a normal body function, but not that the food or dietary supplement treats constipation, which is a disease. As a result, many of the claims cited on probiotic product labels are general and provide patients or clinicians with limited information about their potential use because they do not specifically relate to the studies that have been conducted.

Probiotics can also be marketed in the US as medical foods. The FDA defines a medical food as "a food which is formulated to be consumed or administered enterally under the supervision of a physician, and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."[8] Medical foods are exempt from the labeling requirements for health claims and nutrient content claims.[8]

**A medical food is intended for use under the supervision of a physician, whereas a dietary supplement can be used with or without supervision of a physician.**

(**Figure 1**) illustrates the type of information that experts from the World Health Organization and International Scientific Association for Probiotics and Prebiotics (ISAPP)[1,6] consider to be important on probiotic product labels. Patients should be advised to choose products that provide complete information.

**Figure 1. World Health Organization Recommended Label Information[6]**




## Probiotic Mechanisms of Action

Microbiota are important to the development and maintenance of innate and adaptive immunity, digestive and metabolic actions, intestinal barrier integrity, and discouraging the colonization of pathogens.[9] The microbiota in healthy individuals over the age of 2 are relatively stable[9] but can be perturbed with different lifestyle exposures.[10] Colonization patterns common to humans have been identified, but each individual has a unique microbiota.

The make-up of microbiota may be altered by diet, medications, and illness. However, alterations in the microbiota in response to short-term dietary changes tend to be rapid, transient, and typically do not alter the overall composition of an individual's microbiota.[11] Results of two small studies suggest that antibiotic-associated changes in the human microbiota are not as quickly resolved. Dethlefsen, et al[12,13] followed outcomes in 3 patients through 2 courses of ciprofloxacin treatment. They found that antibiotic-induced changes were evident within 3 to 4 days after initiating ciprofloxacin.[13] While the overall pretreatment microbiota composition was somewhat restored after stopping the antibiotic, there was evidence that recovery was incomplete.[12,13] Some diseases (ie, inflammatory bowel diseases [IBD], metabolic disease, type 1 diabetes, allergy, asthma, neurological and cardiovascular disease)

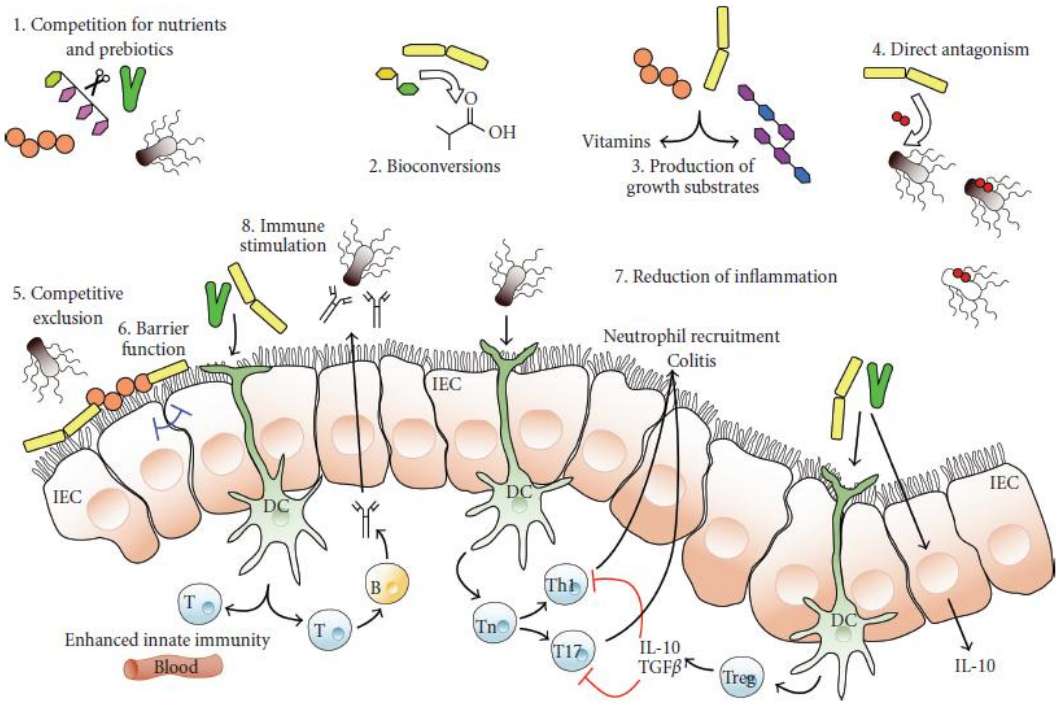
are associated with microbiota that differ from the microbiota of healthy controls. However, it is not clear if these differences cause, or are the result of, the disease.[14]

**Pre-test Question 2**
Probiotics are thought to provide health benefits through all of the following mechanisms EXCEPT:

A. Altering the microbiota through long-term colonization
B. Directly inhibiting growth of pathogenic microorganisms
C. Eliciting elaboration of anti-inflammatory cytokines
D. Exerting neuromodulatory effects

Mechanisms, both established and hypothesized, of probiotic activity are shown in (**Figure 2**).[15] Briefly, probiotics may act directly or indirectly on the colonizing gut microbiota, thereby positively impacting human health. Probiotics have been shown to inhibit the growth of pathogens through the production of antimicrobial substances, and to bolster the epithelial barrier function. They contribute to sustaining the host immune response and have metabolic and digestive functions, such as reducing cholesterol levels and synthesizing folate and vitamin B12.[16] Preclinical data have shown that probiotic microorganisms can have anti-inflammatory effects and may exert neuromodulatory effects that moderate response to stress.[17] In addition, these multiple mechanisms of action provide an explanation for many of the GI benefits observed, but may also explain the potential for numerous extra-intestinal benefits, such as reduction of incidence or duration of some acute respiratory diseases,[18] pain perception,[19] and improved therapeutic efficacy of drugs to treat bacterial vaginosis.[18,20]

**Figure 2. Potential or known mechanisms of action of probiotics in the gut.[15]**

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Mechanisms include (1) competition for dietary ingredients as growth substrates, (2) bioconversion of, for example, sugars into fermentaion products with inhibitory properties, (3) production of growth substrates for other bacteria (ie, vitamins), (4) direct antagonism by bacteriocins, (5) competitive exclusion for binding sites, (6) improved barrier function, (7) reduction of inflammation that alters intestinal proprties for colonization within, and (8) stimulation of innate immune response by unknown mechanisms. IEC, intestinal epithelial cells; DC, dendritic cells; T, T cells; TGF, transforming growth factor; IL, interleukin; B, Bcell; Tn, neutrophil regulating T cell; Th, helper T cell; T17,T cells producing IL17; Treg, regulatory T cell.

The intestines are considered to be the site of most probiotic activity. For probiotics to survive transit into the colon, they need to be resistant to the extreme acidic environment of the stomach and the digestive secretions (bile and enzymes) in the proximal small intestine. Although most probiotics can survive intestinal transit, their effects require regular use because they generally colonize the digestive tract transiently.[17,21]

## Evidence-Based Recommendations: Probiotics for GI Health

Because regulatory requirements for dietary supplements and foods require that products have demonstrated efficacy in the general (not patient) population, some studies of probiotics are designed with physiological, rather than clinical, endpoints. For example, a study may evaluate a probiotic's effects on colonic transit time in healthy people rather than on the relief of constipation. However, numerous examples of studies examining effects in patient populations can also be found in the literature.[22] The quality of these studies ranges broadly, but the literature in recent years comprises a greater number of well-designed, adequately powered, registered clinical trials (RCT).

### *Safety*

**Pre-test Question 3**
Which of the following adverse events are routinely reported in ≥5% of patients who use probiotics?

A. Nausea and vomiting
B. Diarrhea
C. Flatulence and bloating
D. All of the above
E. None of the above

Given that many probiotic products contain naturally occurring microbes that are widely consumed in foods, historically many investigators did not see the need to track adverse events (AEs).[23] The inconsistent approach to safety reporting was noted in a recent report sponsored by the Agency for Healthcare Research and Quality (AHRQ).[24] They found no reports evaluating the safety of long-term probiotic use. In their review of 622 human short-term studies of probiotics, they found that the relative risk of any AE did not differ among groups that received probiotics versus controls. The analysis found no evidence for an increased risk for serious adverse events with concomitant probiotic and corticosteroid use.[24] The study group identified a total of 8 studies (including 3 case studies) that reported on patients taking both probiotics and immunosuppressive agents.[24] Two case series reported fungicemia and one reported an abscess potentially associated with probiotic use. No strong safety signal was found in the analysis of RCTs.[24] These findings suggest that infections due to probiotic use are low even in this particularly vulnerable patient population.

A systematic review[25] of 72 publications that reported data from patients who required nutritional support found low rates of probiotic blood-stream infections. Risk factors for infections were the presence of a central venous catheter and immunosuppression.[25] Probiotic use in patients at high risk of severe acute pancreatitis was associated with higher mortality in one randomized controlled trial.[26] Therefore, probiotics should be used with caution in seriously ill patients.


**In 622 short-term studies of probiotic administration, the incidence of adverse events in the probiotic groups was statistically similar to that of control groups.[24]**

## Current Recommendations for Use of Probiotics in GI Conditions

Updated guidelines for global probiotic use were issued by the World Gastroenterology Organization (WGO) in 2011.[4] A working group at the *Third Yale Workshop on Probiotic Use* also published recommendations for probiotic use in GI conditions the same year.[27] This review summarizes these recommendations for probiotic products marketed in the US.

WGO levels of evidence are defined as: 1a, systematic review with homogeneity of randomized controlled trials; 1b, individual randomized, controlled trial with narrow confidence interval; or, 2b, individual cohort study, including low-quality RCT.[4,17] Effectiveness ratings assigned by the Yale working group are defined as: A = strong, positive studies in the literature; B = based on positive controlled studies, but presence of some negative studies that did not support the primary outcome; C = some positive studies but clearly inadequate amount of work to establish certainty.[27] For the reader's convenience, a summary of these recommendations, including descriptions of rating scales, will be available for download at the end of this educational activity.

## *Acute Infectious Diarrhea*

**Pre-test Question 4**
Which of the following statements is NOT a widely accepted approach to prevention and treatment of infectious diarrhea?

A. *Lactobacillus* species reduce the risk of traveler's diarrhea
B. *Lactobacillus rhamnosus* GG (Culturelle), *Lactobacillus reuteri* DSM 17938 (BioGaia) or *Lactobacillus casei* DN-114 001 (DanActive) taken routinely may reduce the risk of infectious diarrhea, especially in children
C. Use of products containing *Lactobacillus rhamnosus* GG (Culturelle) or *Saccharomyces cerevisiae* boulardii (Florastor) may shorten the duration of acute infectious diarrhea in children and adults

Prevention of infectious diarrhea with probiotics has been evaluated in children. Studies show modest benefits from the use of *Lactobacillus rhamnosus* GG (LGG; Culturelle), *Lactobacillus reuteri* (*L. reuteri*) DSM 17938 (BioGaia) or *Lactobacillus casei* (*L. casei*) DN-114 001 (DanActive) to prevent pediatric acute infectious diarrhea.[17] The Yale group cites moderate support for prophylaxis with LGG (Culturelle) or *Saccharomyces cerevisiae* var. boulardii (S. boulardii; Florastor).[27] However, WGO guidelines state that additional studies are needed to confirm the benefit of these microorganisms for prevention of infectious diarrhea in children.[4] Whether results in children will translate to efficacy in adults remains to be determined, as fewer data are available regarding probiotics for the prevention of acute infectious diarrhea in adults.

Based on consistent data from several meta-analyses, the WGO recommends the use of LGG (Culturelle) and S. boulardii (Florastor) for the treatment of acute infectious diarrhea in children.[4] In addition to LGG (Culturelle) and S. boulardii (Floraster), the Yale group assigned an A effectiveness rating to *L. reuteri* DSM 17938 (BioGaia) for treatment of pediatric infectious diarrhea.[26] The American Academy of Pediatrics recommends starting children on LGG (Culturelle) early in the course of acute infectious diarrhea.[28] WGO recommendations support the use of S. boulardii (Florastor) to treat adult diarrhea.[4]

## Travelers' Diarrhea

Travelers' diarrhea (TD) is a form of infectious diarrhea that may be caused by bacteria, viruses, or parasites.[29] Neither the WGO or the Yale Group specifically addresses probiotics for preventing traveler's diarrhea, and others have concluded that the evidence is insufficient for use of probiotics for this indication.[30] However, a 2007 meta-analysis of data from 12 studies showed a significant 15% reduction in risk of TD among probiotic users (RR=0.85, 95% CI 0.79 to 0.91).[31] Both S. boulardii (Florastor) and a mixture of *Lactobacillus acidophilus* (*L. acidophilus*) and *Bifidobacterium bifidum* (*B. bifidum*) were found to be beneficial in this analysis.[31] The mixture of *L. acidophilus* and *B. bifidum* is not marketed in the US. A separate analysis of two studies with S. boulardii (Florastor) found a lower risk of TD in subjects who started probiotic use 5 days before travel.[29]

## *Antibiotic-Associated Diarrhea*

**Pre-test Question 5**

A 2 year old girl presents with irritability, fevers, and ear pain. You diagnose her with recurrent otitis media, and place her on amoxicillin and clavulanate for 10 days. The patient's mother is worried because she developed diarrhea the last time you put her on antibiotics. Which of the following options are evidence-based approaches?

A. Start the antibiotic and have her consume regular yogurt
B. Start the antibiotic and have the patient take S. boulardii (Florastor)
C. Start the antibiotic and have the patient take a supplement with LGG (Culturelle)
D. A and B
E. B and C

According to the WGO Guidelines LGG (Culturelle) and S. boulardii (Florastor) are the most widely studied probiotics for the prevention and treatment of AAD and the overall results of those studies support their use in this setting.[4] However, *L. casei* DN-114 001 (DanActive) and the combination of *L. acidophilus* CL1285 and *L. casei* LBC80 (BioK+) also are recommended for adults.[4] A meta-analysis[32] published after the WGO guidelines were released confirmed these recommendations. Pooled results from 63 RCT (39 in outpatients) that included 11, 811 patients showed that patients who used adjunctive probiotics had a 42% lower risk of developing AAD (P<.001). This translates to a number-needed-to treat of 13. The analysis showed similar efficacy across all age groups (infants, children, and adults).[32]

**The number of adults or children needed to treat with adjunctive probiotics to avoid one case of antibiotic-associated diarrhea is 13.[31]**

Evidence of the benefit of probiotics for prevention of the most severe form of AAD, *C. difficile* diarrhea (CDD), remains equivocal. The WGO considered the evidence of benefit to be modest (1b) for *L. casei* DN-114 001(DanActive), S. boulardii (Florastor), and a combination of *L. acidophilus* CL1285 and *L. casei* LBC80R (BioK+) for prevention of CDD.[4] The Yale group rated the effectiveness of S. boulardii (Florastor) as B/C. In a comprehensive review of studies evaluating individual probiotic products, Na and Kelly[33] concluded that studies from larger,

higher-quality trials are needed to determine efficacy in primary or secondary prevention of *C. difficile* infections.

## *Inflammatory Bowel Diseases*

**Pre-test Question 6**

Current evidence does NOT support the use of any probiotic strains for:

A. Crohn's disease
B. Pouchitis
C. Ulcerative colitis
D. All of the above
E. None of the above

### Ulcerative Colitis

VSL#3 is the only probiotic currently marketed in the US that has been widely studied for the treatment or prevention of relapse in ulcerative colitis (UC). In two studies, patients with relapsing UC showed greater improvement in UC disease activity indices compared to placebo after treatment with high-dose VSL#3 (3.6 trillion CFU per day) added to standard therapy.[34,35] A small study (N=29) in children showed improved rates of response or remission with VSL#3 administration added to standard therapy compared to standard therapy alone.[36] Although a Cochrane review concluded there was not sufficient evidence to draw conclusions about the efficacy of probiotics for maintenance of remission of UC,[37] this review did not consider data for VSL#3 separately. The effectiveness of VSL#3 in maintaining remission of ulcerative colitis is rated A by the Yale group.[27] Studies of E coli Nissle 1917 have shown efficacy in maintaining remission of UC. However, this probiotic is no longer marketed in the US based on an FDA decision that this product did not meet the definition of a medical food but would have to be marketed as a biologic drug, a distinct category that must meet regulatory requirements for drugs.[17]

### Pouchitis

Pouchitis is a post-surgical complication of ulcerative colitis. Both WGO guidelines and Yale group reports concur that VSL#3 is effective in the prevention of onset and relapse of pouchitis after induction of antibiotic therapy.[4,17] A single study found that LGG (Culturelle) treatment was effective in the prevention of first-onset pouchitis.[38]

### Crohn's Disease

Several systematic reviews and meta-analyses have found no benefit of probiotics in the maintenance of remission for Crohn's disease.[39-42] Moreover, results from one meta-analysis suggested that administration of LGG (Culturelle) as maintenance therapy may increase the relapse rates of Crohn's disease.[41]


**Several systematic reviews and meta-analyses found no benefit for probiotics in the maintenance of remission of Crohn's disease.[39-42]**

## *Irritable Bowel Syndrome*

Irritable bowel syndrome (IBS) is a functional GI disorder that may be associated predominantly with symptoms of diarrhea (IBS-D), constipation (IBS-C), or alternating. The WGO and Yale working group found the strongest support for the use of *Bifidobacterium infantis (B. infantis*) 35624 *(*Align) for the treatment of irritable bowel syndrome (IBS) in adults based on data from two randomized, double-blind, multicenter, placebo-controlled clinical trials.[43,44] A post-hoc analysis of data from one of these trials was undertaken to determine the impact of treatment with *B. infantis* 35624 on sub-types IBS-D or IBS-C. The analysis showed that satisfaction with bowel habits in subjects who took *B. infantis* 35624 was significantly improved compared to placebo.[44] This finding was true in both IBS-D and IBS-C patients. In patients with IBS-D, scores for overall symptom relief and the IBS composite score were significantly better with *B. infantis* 35624 (Align) treatment compared to placebo. Patients with IBS-C reported a statistically significant reduction in baseline abdominal pain/discomfort scores with treatment compared to placebo (-0.58, P=.036).[44]

The effects of consuming yogurt containing *Bifidobacterium animalis* subsp. *lactis* (*B. lactis*) DN-173 010 (Activia) was evaluated in two randomized controlled trials in adults with IBS-C. One 4-week study (n=34) reported a significantly greater reduction in overall IBS severity and abdominal pain in IBS-C subjects compared with control subjects.[45] A second study assessed efficacy using a Health Quality of Life Discomfort score in 274 IBS-C adults.[46] The *B. lactis* group was more likely to achieve a 10% decrease in baseline discomfort scores over 3 weeks compared with controls.[46] Although the WGO rated the evidence for *B. lactis* DN-173 010 (Activia) as 1b, the Yale group rated the effectiveness as C.[4,27]

Additional studies are needed to better elucidate the role of specific strains in treating IBS. However, since so few traditional treatment options exist for IBS, and probiotics have low rates of adverse events, a 3- to 4-week course of a specific probiotic product for managing IBS symptoms may be beneficial. If symptoms do not improve, it would be prudent to have a washout period for a few weeks and then try another probiotic strain.

## *Functional Bowel Disorders in Children*

Of the products marketed in the US, the WGO found reasonably strong evidence to support the use of LGG (Culturelle) for symptomatic relief of functional bowel disorders in children.[4] This position is consistent with findings of a meta-analysis of data from three randomized controlled trials of children.[47] The pooled results showed that among children with IBS, those who received LGG (Culturelle) were significantly more likely to achieve response (no pain or a decrease in pain intensity) than those who received placebo.[47]

## *Lactose Intolerance*

Eating yogurt containing live cultures may be beneficial for individuals who do not effectively digest lactose. Based on the findings of the European Food Safety Authority (EFSA),[48] WGO guidelines recommend consumption of yogurt containing $10^8$ CFU per gram of *Lactobacillus delbruekii* subsp. *bulgaricus* (*L. bulgaricus*) and *Streptococcus thermophilus* (*S. thermophilus*) to reduce symptoms of lactose maldigestion.[4] *L. bulgaricus* and *S. thermophilus* are the standard starter cultures used for yogurt in the US, and the National Yogurt Association certifies that refrigerated products that carry their Live & Active Cultures seal contain $10^8$ CFU of these two starter cultures per gram at the time of manufacture.[49]

### *Necrotizing Enterocolitis (NEC)*

Necrotizing enterocolitis is a serious condition that sometimes develops in preterm infants. The WGO guidelines and the Yale group recommendations indicate that probiotic administration significantly reduces the incidence of NEC and mortality in preterm infants (level of evidence 1b/effectiveness B), albeit for probiotics not marketed in the US.[4,27] Mihatsch et al conducted a meta-analysis of data from 15 studies of *Lactobacillus* and *Bifidobacterium* species for prevention of NEC and sepsis.[50] The 2012 analysis concluded that although there is promising evidence of benefit in the setting of NEC, more studies are needed to clarify effective strains and doses before a general recommendation can be made.[50] Use of a live biotherapeutic in the highly susceptible premature infant is a concern for some practitioners.[51]

## Future Directions in Probiotic Use

As the understanding of how probiotics interact with GI microbiota in health and disease continues to develop, there is hope that probiotics can be targeted to the patients and conditions that will benefit most. In addition to improving outcomes for individuals with difficult-to-treat GI symptoms, promising benefits beyond the gut may be realized. The metabolic and neuromodulatory effects of gut microorganisms may expand probiotic use in managing general immune-associated conditions such as common infectious diseases and allergy, as well as systemic conditions such as diabetes and obesity.[14] Animal studies, supported by some small human pilot trials, show that the microbiota have a profound effect on anxiety and stress.[10,52] Abdominal pain experienced by patients with IBS is attributed to visceral hypersensitivity. The heightened pain response is thought to be mediated by components of both the peripheral and central nervous systems.[53]

## Conclusions

In the US, there is growing interest in the use of probiotics, and this review is designed to provide physicians with useful information to guide patient decisions about using probiotics for GI heath. Currently probiotic products are marketed as dietary supplements and yogurts containing live cultures, as well as other foods. A combination of microorganisms (VSL#3) is sold as a medical food for use under the supervision of a physician. Although it is important for patients to read product labels, patients need to know that, legally, manufacturers of foods or supplements are not allowed to cite clinical evidence of efficacy for any disease. Claims of efficacy to cure or prevent a disease are limited to drugs. Patients who decide to use probiotics should be advised to use products that provide complete label information (**Figure 1**) including the genus, species, and strain for each organism the product contains. Moreover, they need to know that sustained use of probiotics is needed for chronic conditions; probiotics have not been shown to colonize the human gut.

The role of probiotics in managing a broad range of GI conditions has been supported by current evidence. Based on updated clinical guidelines, there is convincing evidence that probiotics available in the US may improve patient outcomes in treating infectious diarrhea, particularly in children, and preventing AAD. Further studies are needed to confirm the promise for other disorders, and strain-specific effects are important to consider. Short-term clinical trials have reported few serious adverse events associated with currently marketed probiotics.

**Table 1.** World Gastroenterology Organization (WGO)[1] and Yale Probiotic Working Group[2] Recommendations Regarding Probiotics Marketed in the United States: Uses for GI Conditions. Probiotic use is not recommended for seriously ill patients.

| INDICATION | GENUS/SPECIES/ STRAIN | PATIENT POPULATION: STRENGTH OF EVIDENCE[A]/ EFFECTIVENESS[B] (Evidence-based dose) | COMMERCIAL PRODUCT/ PROPRIETARY MICROBE NAME/ MANUFACTURER'S RECOMMENDED DOSE | MANUFACTURER'S WEBSITE | COST/QUANTITY[c] |
|---|---|---|---|---|---|
| **Prevention of Acute Infectious Diarrhea** | *Lactobacillus rhamnosus* (GG) | **Pediatrics: B** | **Culturelle**<br>$10x10^9$ CFU/ day<br>To support digestive health and immune function<br>$10x10^9$ CFU twice per day for digestive upset | http://www.culturelle.com/ | $18.52/30 capsules ($1 x 10^{10}$ CFU/capsule); $15.82/30 powder packets ($1.5 x10^9$ CFU/packet) |
| | *Saccharomyces cerevisiae* var. boulardii | **Pediatrics: B** | **Florastor**<br>Saccharomyces boulardii (lyophilized [lyo])<br>250 mg<br>*Contraindicated with central venous catheter* | http://florastor.com/ | $35.50/50 capsules (250 mg/capsule); $19/10 powder packets (250 mg/packet) |
| **Treatment of Acute Infectious Diarrhea** | *Lactobacillus reuteri* (DSM 17938) | **Pediatrics: A**<br>($10^8$ CFU twice daily) | **BioGaia**<br>*Lactobacillus reuteri* protectis<br>$1x10^8$ CFU/dose | http://www.childrenspro-biotics.com/ | $39.50/ 50 mL; $25.39/ 30 chewable tablets; $29.99/30 straws |
| | *Lactobacillus rhamnosus* (GG) | **Pediatrics: 1a/A**<br>($10^{10}$-$10^{11}$ CFU twice daily)<br><br>**Adults 2b**<br>($10^9$ CFU twice daily) | **Culturelle**<br>$10x10^9$ CFU/ day<br>To support digestive health and immune function<br>Twice per day for digestive upset | http://www.culturelle.com/ | $18.52/30 capsules ($1 x 10^{10}$ CFU/capsule); $15.82/30 powder packets ($1.5 x10^9$ CFU/packet) |
| | *Saccharomyces cerevisiae* var. boulardii | **Pediatrics: 1a/A**<br>(200 mg three times daily)<br><br>**Adults: 1b**<br>($10^9$ CFU per capsule of 250 mg, 2-6 capsules per day) | **Florastor**<br>Saccharomyces boulardii (lyophilized [lyo])<br>250 mg<br>*Contraindicated with central venous catheter* | http://florastor.com/ | $35.50/50 capsules (250 mg/capsule); $19/10 powder packets (250 mg/packet) |
| **Prevention of Antibiotic-associated Diarrhea** | *Lactobacillus acidophilus* (CL1285) and *Lactobacillus casei* (LBC80R) | **Adult: 1b**<br>($5x10^{10}$ CFU once or twice daily) | **BioK+**<br>Cultured food or capsules | https://www.biokplus.com/en-us/home | Capsules available<br>$12.00/15 capsules (12.5 $x10^9$ CFU/capsule); $20.00/15 capsules (25 $x10^9$ CFU/capsule); $31.50/15 capsules (50 $x10^9$ CFU/capsule) |
| | *Lactobacillus casei* (DN-114 001) | **Adult: 1b/A**<br>($10^{10}$ CFU twice daily) | **DanActive**<br>Lactobacillus immunitas<br>Plus starter cultures<br>Yogurt or cultured food[d] | http://www.dannon.com/ourproducts.aspx | Price varies by store |
| | *Lactobacillus rhamnosus* (GG) | **Pediatrics: 1b/A**<br>($10^{10}$ CFU once or twice daily)<br><br>**Adult: 1b**<br>($10^{10}$ - $10^{11}$ CFU twice daily) | **Culturelle**<br>$10x10^9$ CFU/day<br>To support digestive health and immune function<br>$10x10^9$ CFU/twice per day for digestive upset | http://www.culturelle.com/ | $18.52/30 capsules ($1 x 10^{10}$ CFU/capsule); $15.82/30 powder packets ($1.5 x10^9$ CFU/packet) |
| | *Saccharomyces cerevisiae* var. boulardii | **Pediatrics: 1a/A**<br>(250 mg twice daily)<br><br>**Adults: 1b**<br>(1 g or $4x10^9$ CFU daily) | **Florastor**<br>Saccharomyces boulardii (lyophilized [lyo])<br>250 mg<br>*Contraindicated with central venous catheter* | http://florastor.com/ | $35.50/50 capsules (250 mg/capsule); $19/10 powder packets (250 mg/packet) |

| INDICATION | GENUS/SPECIES/ STRAIN | PATIENT POPULATION: STRENGTH OF EVIDENCE[A]/ EFFECTIVENESS[B] (Evidence-based dose) | COMMERCIAL PRODUCT/ PROPRIETARY MICROBE NAME/ MANUFACTURER'S RECOMMENDED DOSE | MANUFACTURER'S WEBSITE | COST/QUANTITY[c] |
|---|---|---|---|---|---|
| **Prevention of *C. difficile* diarrhea** | *Lactobacillus acidophilus* (CL1285) and *Lactobacillus casei* (LBC80R) | **Adult: 1b** ($5x10^9$ CFU once or twice daily) | **BioK+** Cultured food or capsules | https://www.biokplus.com/en-us/home | \$12.00/15 capsules ($12.5 x10^9$ CFU/capsule); \$20.00/15 capsules ($25 x10^9$ CFU/capsule); \$31.50/15 capsules ($50 x10^9$ CFU/capsule) |
| | *Lactobacillus casei* (DN-114 001) | **Adult: 1b** ($10^{10}$ CFU twice daily) | **DanActive** Lactobacillus immunitas Yogurt or cultured food[d] | http://www.dannon.com/ourproducts.aspx | Price varies by store |
| | *Lactobacillus rhamnosus* (GG) | **Adult: B/C** | **Culturelle** $10x10^9$ CFU/ day To support digestive health and immune function $10x10^9$ CFU/ twice per day for digestive upset | http://www.culturelle.com/ | \$18.52/30 capsules ($1 x 10^{10}$ CFU/capsule); \$15.82/30 powder packets ($1.5 x10^9$ CFU/packet) |
| | *Saccharomyces cerevisiae* var. boulardii | **Adult: 1b/B/C** ($2\text{-}3 x10^9$ CFU daily for 28 days, followed for another 4 weeks) | **Florastor** Saccharomyces boulardii (lyophilized [lyo]) 250 mg *Contraindicated with central venous catheter* | http://florastor.com/ | \$35.50/50 capsules (250 mg/capsule); \$19/10 powder packets (250 mg/packet) |
| **Inflammatory Bowel Diseases (IBD)** Treatment of mildly active UC or pouchitis | *Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus bulgaricus, Streptococcus thermophilus* | **Pediatrics: 1b** ($4\text{-}9x10^{11}$ CFU twice daily) **Adults: 1b** ($2\text{-}9x10^{11}$ CFU twice daily) | **VSL#3** *For use under the supervision of a physician* (Strains not indicated on product) | http://www.vsl3.com/ | Capsules that contain 112.5 billion live bacteria \$54/60 capsules (\$7.20/2x $9x10^{11}$ CFU dose); Packets that contain 450 billion live bacteria \$86/ 30 packets (\$5.73/2x$9x10^{11}$ CFU dose); Double Strength (DS) packets that contain 900 billion live bacteria. Price not given |
| **IBD** Induction of remission | | **Pouchitis: C** **UC: B** | | | |
| **IBD** Prevention and maintenance of remission of pouchitis | | **Adults: 1b/A** ($9x10^{11}$ CFU twice daily) | | | |
| **IBD** Maintenance of remission of ulcerative colitis | | **Adults: A** | | | |
| **Irritable Bowel Syndrome** Symptomatic relief | *Bifidobacterium infantis* (35624) | **Adults: 1b/B** ($10^8$ CFU once daily) | **Align** Bifantis $1x10^9$ CFU/ day As 1 capsule | http://www.alignGi.com/ | \$44.99/42 capsules (\$1.07/capsule) |
| | *Bifidobacterium animalis* subsp. *lactis* (DN-173 010) + starter cultures | **Adults: 1b/C** ($10^{10}$ CFU twice daily) | **Activia** Bifidobacterium regularis Yogurt[d] | http://activia.us.com/ | Price varies by store |
| **Pediatric functional bowel disorders-** Symptomatic relief | *Lactobacillus reuteri* DSM 17938 | **Pediatrics: 1b** ($10^8$ CFU twice daily) | **BioGaia** *Lactobacillus reuteri* protectis $1x10^8$ CFU/dose | http://www.childrensprobiotics.com/ | \$39.50/50 mL (107 CFU/5 drops); \$25.39/30 chewable tablets (107 CFU/tablet); \$29.99/30 straws (107 CFU/straw) |
| | *Lactobacillus rhamnosus* (GG) | **Pediatrics: 1a** ($10^{10}\text{-}10^{11}$ CFU twice daily) | **Culturelle** $10x10^9$ CFU/day To support digestive health and immune function $10x10^9$ CFU twice per day for digestive upset | http://www.culturelle.com/ | \$18.52/30 capsules ($1 x 10^{10}$ CFU/capsule); \$15.82/30 powder packets ($1.5 x10^9$ CFU/packet) |

[a]World Gastroenterology Organization (WGO) levels of evidence are defined as: 1a, systematic review with homogeneity of randomized controlled trials; 1b = individual randomized, controlled trial with narrow confidence interval; or 2b, individual cohort study, including low-quality RCT

[b]Effectiveness ratings assigned by the Yale working group are defined as: A = strong, positive studies in the literature; B = based on positive controlled studies, but presence of some negative studies that did not support the primary outcome; C = some positive studies but clearly inadequate amount of work to establish certainty

[c]Prices were taken from various websites for US distributors on August 16, 2012

[d]The CFU/per serving is not available for some yogurts and fermented milk preparations. Patients may wish to try consuming 2 to 3 servings a day and adjust their dose as needed

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