

Gut Reactions: Probiotics and Their Role In Gastrointestinal Care

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GOAL

The goal of this CME initiative is to educate members of the intended audiences about the appropriate use of probiotic therapies in a variety of gastrointestinal (GI) disorders.

LEARNING OBJECTIVES

At the completion of this activity, participants should be better able to:

1. Describe the role of microbiota in GI health
2. Review clinical data for the use of probiotic therapies in irritable bowel syndrome, ulcerative colitis, *Helicobacter pylori* infection, and *Clostridium difficile* infection
3. Understand the effects of probiotics on other aspects of patient health and quality of life
4. Discuss strategies for appropriate patient education and guidance in the use of probiotics

INTENDED AUDIENCE

The activity is designed for primary care physicians, gastroenterologists, nurses, nurse practitioners, physician assistants, retail pharmacists, and other clinicians interested in probiotics and their role in GI care. Credit will be awarded for physicians and pharmacists.

ESTIMATED TIME FOR COMPLETION: 1 hour

COURSE FORMAT: Monograph

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METHOD OF PARTICIPATION

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FEES

None



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SYSTEM REQUIREMENTS

PC

- Microsoft Windows 2000 SE or greater
- Flash Player Plugin (v7.0.1.9 or greater)
- Internet Explorer (v5.5 or greater) or Firefox Adobe Acrobat Reader

MAC

- MAC OS 10.2.8 Flash Player Plugin (v7.0.1.9 or greater)
- Safari Adobe Acrobat Reader
- Internet Explorer is not supported on the Macintosh

Introduction

The intestinal microenvironment, including its endogenous intestinal bacterial flora (microbiota), has a marked effect on gastrointestinal (GI) health and disease. A growing number of studies find that orally ingested preparations of exogenous bacteria (“probiotics”) are useful for the treatment or prevention of various gastroenterological conditions and symptoms.¹ This monograph describes best practices for the safe and effective use of probiotics in maintaining and improving patient health, focusing on irritable bowel syndrome (IBS), ulcerative colitis (UC), *Helicobacter pylori* infection, and *Clostridium difficile* infection (CDI). Special topics, including strain selection and the need for patient education, also will be addressed.

Epidemiology and Burden of Chronic GI Disorders

The burden of GI disease is extensive, affecting 60 to 70 million Americans annually.² An estimated 4.6 million hospitalizations, 72 million ambulatory care visits, and 236,000 deaths are attributable to GI disease.^{2,3} US spending on these diseases has been estimated at \$142 billion per year.²

The leading symptoms and diagnoses for GI disorders in US outpatient clinic visits are summarized in Tables 1A and 1B.² Although not included in the table, a substantial increase in the incidence of CDI has been noted during the past decade (Figure 1).² Indeed, CDI hospitalizations have increased by 237% since 2000 and now account for a proportion of inpatient mortality similar to that of GI hemorrhage.²

Because many GI diseases are chronic with recurrent flares, and because symptoms can be debilitating and interfere with activities of daily living, these conditions have a significant effect on health-related quality of life (HRQoL) compared with many other chronic illnesses.⁴ An extensive analysis of large databases by Peery et al found worse HRQoL and significantly greater impairments in work, school attendance, social activities, and general activity for patients with GI disease and symptoms than other patient populations.²

Overview of Probiotics and Strain Specificity

The human GI system is a diverse and dynamic ecosystem comprising more than 10¹⁵ microorganisms and an estimated 1,000 species.⁵ Major functions of the gut microflora include metabolic activities that help process nutrients and energy, promote intestinal epithelial integrity and immune function, and protect the colonized host against invasion by pathogenic microbes.⁶⁻⁸ Alterations in the intestinal microenvironment can occur for a variety of reasons, including antibiotic use, and can disrupt normal intestinal function, leading to overgrowth of pathogenic microorganisms, GI infection, and subsequent symptoms.⁶⁻⁸

Several studies suggest that GI disorders and symptoms are associated with alteration in the function or composition of endogenous intestinal flora. Indeed, a relative decrease in the population of *Bifidobacteria* is one of the most consistent findings in these studies.^{9,10} Qualitative changes can lead to the proliferation of species that produce more gas and short-chain fatty acids, resulting in the deconjugation of bile acids, with subsequent changes in water and electrolyte transport in the colon and altered colonic motility and/or sensitivity.¹¹

These insights have led to the recognition that oral administration of some types of exogenous bacteria can promote intestinal homeostasis and prevent or treat disorders and symptoms. These beneficial bacterial preparations are known as *probiotics* and are defined by the Food and Agriculture Organization and the World Health Organization as “live microorganisms, which when present in adequate amounts, confer health benefits on the host.”¹²

The mechanisms of action of probiotics are not understood fully and vary by species and strain but likely involve regulation of intestinal microbial homeostasis, interference with the ability of pathogens to colonize and infect the mucosa, modulation of local and systemic immune responses, and stabilization or maintenance of GI barrier function.¹³ Probiotics also produce short-chain fatty acids, an action that decreases luminal pH and increases production of bactericidal proteins.¹⁴ Finally, the DNA of probiotic organisms has been shown to inhibit apoptosis of epithelial cells^{15,16} and improve bowel dysmotility.¹⁷

Table 1A and 1B. Leading GI Symptoms and Diagnoses in Outpatient Clinic Visits (United States, 2009)²

A Rank	Symptom Prompting Outpatient Visit	Estimated Visits, million	B Rank	Physician Diagnosis	Estimated Visits, million
1	Abdominal pain	15.87	1	Gastroesophageal reflux disease	8.86
2	Diarrhea	4.24	2	Abdominal pain	7.17
3	Constipation	3.18	3	Gastroenteritis/dyspepsia	4.01
4	Vomiting	2.86	4	Constipation	3.98
5	Nausea	2.81	5	Abdominal wall hernia	3.56
6	Heartburn/indigestion	1.98	6	Diverticular disease	2.68
7	Rectal bleeding	1.70	7	Diarrhea	2.40
8	Other/unspecified	1.36	8	Inflammatory bowel disease (including ulcerative colitis)	1.89
9	Dysphagia	1.15	9	Colorectal neoplasm	1.74
10	GI bleeding	1.07	10	Nausea/vomiting	1.68
11	Decreased appetite	0.73	11	Rectal bleeding	1.67
12	Bloating/distention	0.70	12	Irritable colon	1.55

GI, gastrointestinal

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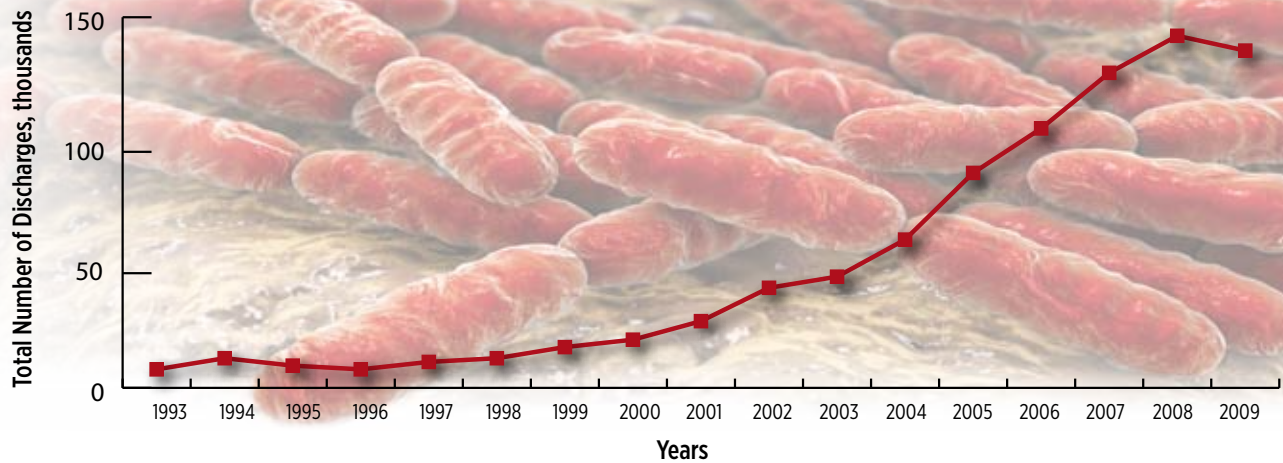


Figure 1. Annual hospital discharges with principal diagnosis of *Clostridium difficile* infection (United States, 1993-2009).²

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The most commonly used probiotics are the gram-positive rods and obligate facultative anaerobes *Lactobacillus* (including *L. acidophilus*, *L. rhamnosus*, *L. bulgaricus*, *L. reuteri*, and *L. casei*) and *Bifidobacterium* (including *B. animalis*, *B. infantis*, *B. lactis*, and *B. longum*) and the yeast *Saccharomyces boulardii*.¹⁸ These organisms produce lactic acid through anaerobic digestion of saccharides. Most can tolerate fluctuations in temperature and low-pH environments, properties that afford them the ability to withstand the acidic milieu of the stomach and transiently colonize the GI tract.^{19,20}

Because probiotics are considered health foods and therefore not regulated by the FDA as drugs, most are available over-the-counter as dietary supplements or fermented products (Table 2).¹⁸ The wide array of formulations can complicate physician-guided therapy. For example, yogurt is a common source of probiotics for patients who self-prescribe such therapy; however, not all live cultures contained in yogurt survive well in an acidic environment, nor do they all colonize the GI tract efficiently.^{21,22} In addition, pasteurization of yogurt, which is common in the United States, can kill the beneficial bacteria in yogurt, and the lactose contained in yogurt can actually increase GI symptoms in some patients.

Importantly, the therapeutic effects of a particular probiotic species or strain cannot be generalized to others.¹⁸ Current US regulations do not mandate that probiotic labeling indicates strain designations, and quality-assurance testing (viable cell counts, shelf-life, appropriate storage conditions, etc) is left to the discretion of individual manufacturers; this can result in marked variations in efficacy.¹⁸ Interpretation of the scientific literature also is complicated by the use of many different strains in studies. In the sections that follow, efforts have been made to describe data with as much specificity as possible.

Probiotic Use in GI Disorders and Symptoms

In an effort to support the selection of appropriate probiotic therapy, the World Gastroenterology Organization has summarized high-quality clinical trials of specific probiotic strains in various chronic GI conditions (Table 3).²³

Irritable Bowel Syndrome

Among the most common functional GI disorders in clinical practice,²⁴ IBS can present with a variety of GI and extra-intestinal indicators typically revolving around a symptom complex of chronic abdominal pain and altered bowel habits including diarrhea, constipation, or a mix of diarrhea and constipation.²⁵

Among more recent advances in the characterization of the pathophysiology of IBS are the concept of “brain-gut interaction” and the role of endogenous gut flora. Indeed, the central nervous system and gut enjoy bidirectional communication via neural pathways and immunologic and endocrinological mechanisms that can contribute to the development of IBS.^{26,27} Furthermore, IBS may result from a dysfunctional interaction between the endogenous flora and the intestinal mucosa that leads to immune activation in the colonic mucosa.²⁸ Some investigators propose a role for bacterial overgrowth as a causative factor in the pathogenesis of symptoms in IBS, whereas others suggest that qualitative changes in the colonic flora may be more relevant.^{29,30}

These observations led to the investigation of the therapeutic utility of probiotics in patients with IBS. A randomized controlled trial (RCT) by Whorwell et al evaluated different doses of *Bifidobacterium infantis* 35624 in 362 women diagnosed with IBS.³¹ Participants were randomized to *B. infantis* 35624 or placebo and followed for 4 weeks. In the treatment group, a significant decrease in abdominal pain/discomfort (the primary end point) was observed at 4 weeks, along with improvement in the secondary end points of bloating/distension, sensation of incomplete evacuation, passage of gas, straining, bowel habit satisfaction, and a reduction in composite symptom score.

A more recent RCT (N=49) demonstrated greater relief of IBS-related abdominal pain/discomfort with multispecies probiotics (mixture of *B. longum*, *B. bifidum*, *B. lactis*, *L. acidophilus*, *L. rhamnosus*, and *Streptococcus thermophilus*) for 4 weeks compared with placebo (68.0% vs 37.5%; $P<0.05$).³² Fecal analysis revealed that *B. lactis*, *L. rhamnosus*, and *S. thermophilus* increased significantly in the probiotics group, whereas only *B. lactis* increased in the placebo group. Numerous other RCTs have examined the effects of various probiotic formulations on IBS symptoms, with several summarized here (all data for probiotic versus control):

- *L. plantarum* 299V in liquid suspension was associated with greater resolution of abdominal pain (100% vs 55%; $P=0.0012$) and reduction in overall IBS symptoms (95% vs 15%; $P<0.0001$; N=40).³³
- A drink containing 5×10^7 colony-forming units (CFU)/mL of *L. plantarum* DSM 9843 led to significant reduction in flatulence (N=60).³⁴ The same strain, provided as a capsule, led to reduced pain severity (0.68 ± 0.53 on VAS vs 0.92 ± 0.57 ; $P<0.05$) and daily bowel frequency (1.01 ± 0.77 vs 1.71 ± 0.93 ; $P<0.05$), with similar results for bloating (N=214).³⁵
- VSL# 3, a mixture of 4 strains of *Lactobacillus* (*L. casei*, *L. plantarum*,

L. acidophilus and *L. delbrueckii* subsp. *bulgaricus*), 3 strains of *Bifidobacterium* (*B. longum*, *B. breve* and *B. infantis*), and 1 strain of *Streptococcus* (*S. salivarius* subsp. *thermophilus*), was associated with lower flatulence scores (29.7±2.6 vs 39.5±2.6; $P=0.011$; $N=48$)³⁶; and lower bloating scores (-13.7; $P=0.046$ vs -1.7; $P=0.54$; $N=25$)³⁷

- Fermented milk containing *B. animalis* DN-173 010 led to greater response on HRQoL discomfort (65.2% vs 47.7%; $P<0.005$) and bloating scores (0.56±1.01 vs 0.31±0.87; $P=0.03$) and with increased stool frequency in patients with fewer than 3 stools per week at baseline ($P<0.001$; $N=267$)³⁸
- A preparation containing *L. acidophilus* CUL-60 (NCIMB 30157), *L. acidophilus* CUL-21 (NCIMB 30156), *B. bifidum* CUL-20 (NCIMB 30153), and *B. lactis* CUL-34 (NCIMB 30172) was associated with significantly greater improvement in symptom severity ($P=0.0217$), QoL ($P=0.0068$), days with pain ($P=0.0448$), and bowel habit satisfaction ($P=0.0422$; $N=52$)³⁹
- *Saccharomyces cerevisiae* ($n=86$) led to a significantly greater response, defined as reduction in abdominal pain/discomfort (63% vs 47%; odds ratio [OR], 1.88; 95% confidence interval [CI], 0.99-3.57; $P=0.04$) without stool modification ($N=179$)⁴⁰

Finally, the American College of Gastroenterology Task Force on the Management of Functional Bowel Disorders published a meta-analysis and systematic review of therapies for IBS and chronic idiopathic constipation.⁴¹ Aggregated data for 3,452 patients in 35 RCTs indicated a benefit for probiotics (*Saccharomyces*, *Lactobacillus*, *Bifidobacterium*, *Escherichia coli*), particularly in bloating and flatulence, with benefits extending to global symptoms and

abdominal pain. Significant heterogeneity among studies, species, and strains complicates the interpretation of this result. Other meta-analyses have shown benefit with probiotics in IBS^{42,43} but also can be difficult to extrapolate.

H. Pylori-Related Gastritis

H. pylori infection induces chronic gastritis with potentially severe consequences including peptic ulcers, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma.⁴⁴ Triple therapy with 2 antibiotics and a proton pump inhibitor, long the mainstay of treatment, has lost efficacy (currently 71%-81%) due to increasingly prevalent antibiotic resistance. Sequential and quadruple therapy with an additional antibiotic or bismuth subcitrate improves efficacy (to 85%-92%) but also increases rates of adverse events (AEs).⁴⁴

With mechanisms including inhibition of *H. pylori* attachment to mucosal cells, regulation of immune response to *H. pylori*, and direct physiologic effects, probiotics may be useful adjuncts in the treatment of *H. pylori*-related gastritis.⁴⁴ For example, in an open-label trial, 234 *H. pylori*-positive patients with gastritis were randomized to 1 week of standard triple therapy (omeprazole, clarithromycin, and amoxicillin); 2 weeks of pretreatment with 3×10^7 CFU of *L. acidophilus* per day plus 1 week of triple therapy; or 1 week of triple therapy then 2 weeks of the same probiotics.⁴⁵ *H. pylori* eradication rates were significantly greater in both probiotics groups (81.6% and 82.4%) than in the group that did not receive probiotics (61.5%).⁴⁵

In a review of 19 RCTs examining adjunctive use of probiotics in *H. pylori* eradication ($N=2,730$), McFarland et al found that 4 of the 6 probiotic mixtures studied were significantly effective (Figure 2).⁴⁴ In addition, 5 mixtures significantly reduced the incidence of AEs associated with standard therapies: *L. Helveticus/L. rhamnosus* (relative risk [RR], 0.12), the 8-strain combination *L. acidophilus/L. casei rhamnosus/L. plantarum/L. reuteri/L. salivarius/L. sporogenes/B. infantis/B. longum* (RR, 0.24), *L. acidophilus/B. longum/E. faecalis* (RR, 0.25), *L. acidophilus/B. animalis* (RR, 0.31), and *L. acidophilus/B. bifidum* (RR, 0.67).⁴⁴

Other studies support the use of *L. reuteri* ATCC 55730,⁴⁶ *L. rhamnosus* GG,⁴⁷ and *S. boulardii* lyo⁴⁸ in reducing the symptoms of *H. pylori*; and for *S. boulardii* lyo in enhancing eradication of *H. pylori*.⁴⁹

Ulcerative Colitis

UC is a chronic relapsing inflammatory disorder of the GI tract. Clinical features include hemorrhagic diarrhea, abdominal pain, weight loss, and/or fatigue. Some patients develop extra-intestinal manifestations, such as primary sclerosing cholangitis, skin lesions, or joint problems.⁵⁰

Current strategies for the treatment of UC involve the induction and maintenance of remission, usually via immunosuppressant and immunomodulatory strategies.⁵⁰ Although existing therapies can be highly effective, they sometimes fall short in achieving remission, and some patients nonetheless require surgical intervention.⁵⁰ This emphasizes the need for alternative therapeutic options to supplement existing modalities.

A role for the intestinal flora in UC is supported by the finding that intestinal inflammation often occurs in anatomical areas with high bacterial numbers.⁵⁰ Furthermore, many of the genetic loci for UC are associated with the innate immunity responsible for the primary defense against enteric bacteria, further underscoring the interaction between the gut flora and mucosal inflammation.⁵⁰

Based on these observations, many studies have investigated the therapeutic efficacy of probiotics in UC. In patients with active disease, VSL#3 and *E. coli* Nissle 1917 have shown the most benefit among probiotic strains.⁵¹⁻⁵⁷ For example, a 3-arm RCT including 90 patients with moderately active UC compared VSL#3 plus balsalazide with balsalazide or mesalazine alone for 8 weeks and found significantly more patients entering clinical remission, as well as faster induction of remission in the probiotic combination group.⁵⁸ Two other large RCTs saw significantly more patients with mild to moderately active UC

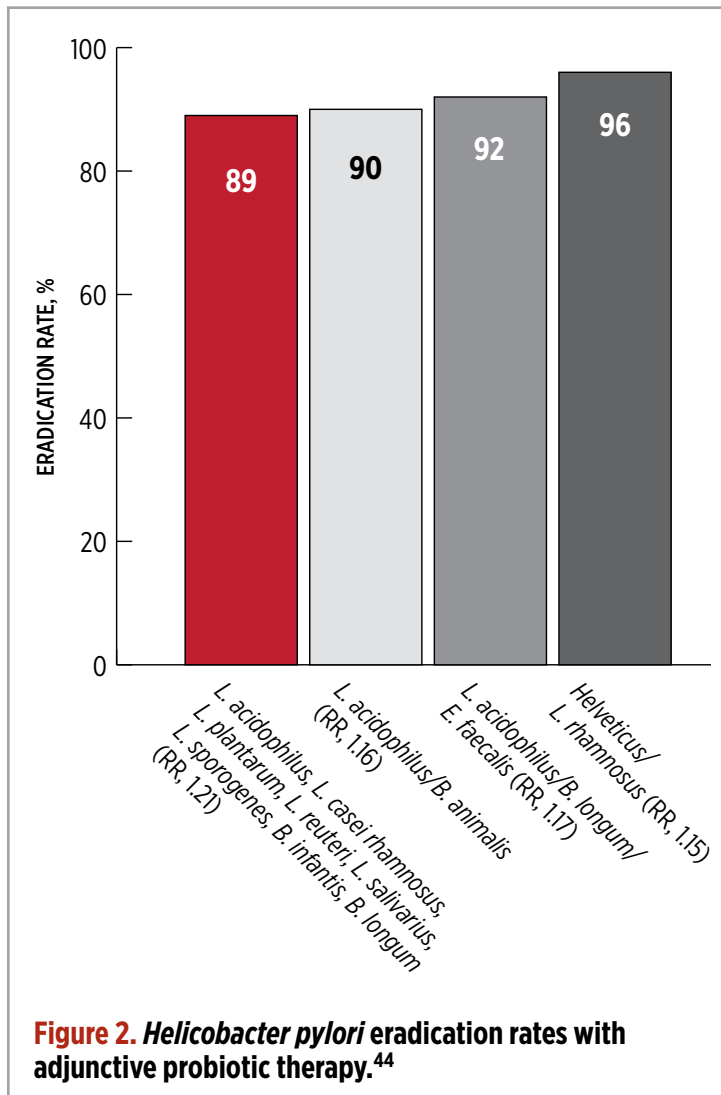


Figure 2. *Helicobacter pylori* eradication rates with adjunctive probiotic therapy.⁴⁴

reach at least 50% reduction in clinical activity after VSL#3 versus placebo for 12 (n=147)⁵⁹ and 8 weeks (n=144).⁶⁰ Remission rates increased significantly⁵⁹ and insignificantly⁶⁰ in these trials. A meta-analysis of all 3 studies showed that VSL#3 use was associated with an RR of 1.69 (95% CI, 1.17-2.43), indicating a significant benefit versus controls.⁶¹

Another meta-analysis found that VSL#3 3.6×10¹² CFU per day plus conventional therapy was more effective than conventional therapy alone in achieving at least 50% reduction in clinical activity (44.6% vs 25.1%; P=0008; OR, 2.793; 95% CI, 1.375-5.676), response (53.4% vs 29.3%; P<0.0001; OR, 3.03; 95% CI, 1.89-4.83) and remission (43.8% vs 24.8%; P=0007; OR, 2.4; 95% CI, 1.48-3.88) in patients with mild to moderately active UC (N=441).⁶²

Finally, a 12-month trial in 337 patients established *E. coli* Nissle 1917 200 mg once daily to be equally effective as established therapy with mesalazine 500 mg 3 times daily.⁵⁷ Relapse rates were 36.4% in the probiotic group and 33.9% in the mesalazine group (significant equivalence P=0.003), underscoring the pathogenic significance of the enteric flora in UC.

C. difficile Infection and Antibiotic-Associated Diarrhea

C. difficile is an anaerobic, gram-positive, sporulating, toxin-producing bacillus that causes a spectrum of clinical conditions ranging from an asymptomatic carrier state to fulminant disease.⁶³ Disruption of the structure and/or function of an individual’s normal intestinal flora (eg, after exposure to antibiotics) enables colonization by *C. difficile*, and in the absence of an effective immune response, the bacteria may lead to a spectrum of colonic pathologies ranging from diarrhea to toxic megacolon and death.⁶³ Despite purported clinical

resolution of CDI in response to metronidazole or vancomycin, a significant proportion of patients experience recurrence.⁶³

Lactobacillus-containing probiotic mixtures and *S. boulardii* may be effective in the prevention of CDI in high-risk antibiotic recipients^{64,65} as well as the prevention of recurrent CDI.⁶⁶ In a double-blind RCT, the addition of *S. boulardii* 1 g per day to a standard antibiotic (vancomycin hydrochloride or metronidazole) in patients with active CDI-associated diarrhea (CDAD) or a history of CDAD led to a significantly lower rate of recurrence versus placebo in recurrent CDAD (34.6% vs 64.7%; P=0.04).

Critically ill patients often are treated with antibiotics and are at high risk for developing CDAD. In a study of 22 such patients, fecal sample analysis showed that *C. difficile* colonization was prevented with enteral administration of *L. plantarum* 299v via a fermented oatmeal.⁶⁷

A Cochrane meta-analysis examining whether concurrent use of probiotics and antibiotics prevented CDI (23 RCTs, N=4,213) found the incidence of CDI to be 2.0% in the probiotic cohort and 5.5% in the control cohort (RR, 0.36; 95% CI, 0.26-0.51), with a number needed to treat for benefit of 29 (95% CI, 22-43).⁶⁸

Diarrhea also can occur in a significant proportion of patients receiving antibiotics in the absence of CDI. This condition is known as antibiotic-associated diarrhea (AAD).⁶⁹ A review of the literature supports the efficacy of *S. boulardii* in the prevention of AAD.⁶⁵

The risks associated with CDAD and AAD may be greater in older patients. In an RCT including 135 hospitalized patients (mean age 74 years) who were taking antibiotics, consumption of a probiotic drink containing *L. casei*, *L. bulgaricus*, and *S. thermophilus* twice daily or placebo was associated with reduced

Table 2. Probiotic Products and Their Compositions¹⁸

Product	Composition	
Activia yogurt	<i>Bifidobacterium lactis</i>	100 million bacteria/g
Align	<i>B. infantis</i> 35624	4 mg per capsule (1 billion CFU)
Culturelle	<i>Lactobacillus rhamnosus</i>	10 billion bacteria + insulin 200 mg per capsule
Culturelle Kids	<i>L. rhamnosus</i>	1.5 billion bacteria per packet
Florajen	<i>L. acidophilus</i>	20 billion bacteria per capsule
Florastor	<i>Saccharomyces boulardii</i> lyo	250 mg per capsule
Howaru	<i>L. acidophilus</i> , <i>B. lactis</i>	10 billion bacteria per capsule
Kefir	<i>L. lactis</i> , <i>L. rhamnosus</i> , <i>L. plantarum</i> , <i>L. casei</i> , <i>L. acidophilus</i> , <i>L. reuteri</i> , <i>Leuconostoc cremoris</i> , <i>Streptococcus diacetylactis</i> , <i>Saccharomyces florentinus</i> , <i>B. longum</i> , <i>B. breve</i> , <i>B. lactis</i>	7-10 billion CFU per cup
Lactinex	<i>L. acidophilus</i> , <i>L. bulgaricus</i>	10 ⁶ CFU per tablet, 10 ⁹ CFU per packet
RepHresh Pro-B	<i>L. rhamnosus</i> , <i>L. reuteri</i>	5 billion CFU per capsule (vaginal use)
VSL#3	<i>L. acidophilus</i> , <i>L. plantarum</i> , <i>L. paracasei</i> , <i>L. bulgaricus</i> , <i>B. breve</i> , <i>B. infantis</i> , <i>B. longum</i> , <i>Streptococcus thermophilus</i>	225 billion bacteria per 2 capsules
Yakult	<i>L. casei</i>	8 billion bacteria per 80-mL bottle

CFU, colony-forming unit

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Table 3. Evidence-Based Indications for Probiotics in Gastroenterology (Adults)²³

Disorder/Action	Strain	Recommended Dose	Evidence Level ^a	Comments
Treatment of acute diarrhea	<i>Enterococcus faecium</i> LAB SF68	10 ⁸ CFU tid	1b	
	<i>Lactobacillus paracasei</i> B 21060 or <i>L. rhamnosus</i> GG	10 ⁹ CFU bid	2b	
	<i>Saccharomyces boulardii</i> , strain of <i>S. cerevisiae</i>	10 ⁹ CFU per 250-mg capsule; 2-6 capsules/d	1b	
Prevention of antibiotic-associated diarrhea	<i>E. faecium</i> LAB SF68	10 ⁸ CFU bid	1b	
	<i>S. boulardii</i> , strain of <i>S. cerevisiae</i>	1 g or 4×10 ⁹ CFU/d	1b	
	<i>L. rhamnosus</i> GG	10 ¹⁰ -10 ¹¹ CFU bid	1b	
	<i>L. casei</i> DN-114 001 in fermented milk	10 ¹⁰ CFU bid	1b	
	<i>Bacillus clausii</i> (<i>Enterogermina</i> strains)	2×10 ⁹ spores tid	1b	
	<i>L. acidophilus</i> CL1285 + <i>L. casei</i> LBC80R	5×10 ¹⁰ CFU qd/bid	1b	Strains administered in capsules or fermented milk vehicle
Prevention of <i>Clostridium difficile</i> diarrhea	<i>L. casei</i> DN-114 001 in fermented milk	10 ¹⁰ CFU bid	1b	
	<i>L. acidophilus</i> + <i>Bifidobacterium bifidum</i> (Cultech strains)	2×10 ¹⁰ CFU each strain qd	1b	Strain designations not provided
	Oligofructose	4 g tid	1b	
	<i>L. rhamnosus</i> HN001 + <i>L. acidophilus</i> NCFM	10 ⁹ CFU each qd	2b	Probiotic administration reduced fecal counts of <i>C. difficile</i> in elderly patients without diarrhea
	<i>L. acidophilus</i> CL1285 + <i>L. casei</i> LBC80R	5×10 ⁹ CFU qd/bid	1b	
	<i>S. boulardii</i> , strain of <i>S. cerevisiae</i>	2-3×10 ⁹ for 28 d; patients followed for another 4 wk	1b	
Coadjuvant therapy for <i>Helicobacter pylori</i> eradication	<i>L. rhamnosus</i> GG	6×10 ⁹ CFU bid	1b	
	<i>Bacillus clausii</i> (<i>Enterogermina</i> strains)	2×10 ⁹ spores tid	1b	
	<i>S. boulardii</i> , strain of <i>S. cerevisiae</i>	500 mg-1 g or 2-4×10 ⁹ CFU/d	1b	
	Kefir	250 mL bid	2b	Improved eradication rates (78% vs 50%)
	<i>L. reuteri</i> ATCC 55730	10 ⁸ CFU/d	1b	
Reduction of symptoms associated with lactose maldigestion	Yogurt with live cultures of <i>L. delbrueckii</i> ssp. <i>Bulgarius</i> + <i>Streptococcus thermophilus</i>	≥10 ⁸ CFU of each strain/g	1a	Systematic review of RCTs
Alleviation of some symptoms of IBS	<i>B. infantis</i> 35624	10 ⁸ CFU qd	1b	
	<i>B. animalis</i> DN-173 010 in fermented milk	10 ¹⁰ CFU bid	1b	
	<i>L. acidophilus</i> SDC 2012, 2013	10 ¹⁰ CFU/d	2b	
	<i>L. rhamnosus</i> GG, <i>Lactobacillus rhamnosus</i> LC705, <i>B. breve</i> Bb99 + <i>Propionibacterium freudenreichii</i> ssp. <i>shermanii</i>	10 ¹⁰ CFU qd	1b	
	<i>B. longum</i> 101 (29%), <i>L. acidophilus</i> 102 (29%), <i>Lactococcus lactis</i> 103 (29%), + <i>Streptococcus thermophilus</i> 104 (13%)	10 ¹⁰ CFU qd	1b	
	Short-chain fructooligosaccharides	5 g/d	2b	
	Galactooligosaccharides	3.5 g/d	2b	
	<i>Bacillus coagulans</i> GBI-30, 6086	2×10 ⁹ CFU qd	2b	
	Maintenance of remission in UC	<i>Escherichia coli</i> Nissle 1917	5×10 ¹⁰ viable bac bid	1b

Table 3. Evidence-Based Indications for Probiotics in Gastroenterology (Adults), continued²³

Disorder/Action	Strain	Recommended Dose	Evidence Level ^a	Comments
Treatment of mildly active UC or pouchitis	VSL# 3 mixture of 8 strains (1 <i>S. thermophilus</i> , 4 <i>Lactobacillus</i> , + 3 <i>Bifidobacterium</i>)	2×9×10 ¹¹ CFU bid	1b	
Prevention and maintenance of remission in pouchitis	VSL# 3 mixture of 8 strains (1 <i>S. thermophilus</i> , 4 <i>Lactobacillus</i> , + 3 <i>Bifidobacterium</i>)	2×4.5×10 ¹¹ CFU bid	1b	
Treatment of constipation	Lactulose	20-40 g/d	1a	Review of cohort studies
	Oligofructose	>20 g/d	2a	Review of cohort studies
Treatment of hepatic encephalopathy	Lactulose	45-90 g/d	1a	Systematic review of RCTs
Prevention of common infections in athletes	<i>L. casei Shirota</i> in fermented milk	10 ¹⁰ CFU qd	1b	

CFU, colony-forming unit; IBS, irritable bowel syndrome; RCT, randomized clinical trial; UC, ulcerative colitis

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^a Evidence levels: 1a, systematic review of RCTs; 1b, individual RCT; 2a, systematic review of cohort studies; 2b, individual cohort study (Oxford Centre for Evidence-based Medicine – Levels of Evidence; March 2009).

incidence of both AAD (12% vs 34%; $P=0.007$; OR, 0.25; 95% CI, 0.07–0.85; absolute risk reduction 21.6%) and CDAD (0% vs 17%; $P=0.001$; absolute risk reduction, 17%).⁷⁰

In a double-blind RCT (N=255) 2 doses of combination *Lactobacillus acidophilus* CL1285-*Lactobacillus casei* LBC80R were effective for the prophylaxis of AAD and CDAD in hospitalized adults.⁷¹ A dose-ranging effect was seen, with 100 billion CFU per day yielding superior outcomes and fewer GI events than 50 billion CFU or placebo (respectively, AAD incidence 15.5%, 28.2%, and 44.1%; symptom duration 2.8, 4.1, and 6.4 days; CDAD incidence 1.2%, 9.4%, 23.8%).⁷¹

Patient Education and Safety

The studies described here suggest the potential to decrease morbidity, health care costs, and mortality with appropriate administration of specific probiotic strains; however, large, well-designed, RCTs, dose-ranging trials, comparative trials, and cost-benefit analyses are necessary. As with any therapy, patient education about issues around efficacy studies is necessary. Patient resources from reputable organizations are available to help guide this process:

- American Gastroenterological Association: www.gastro.org/patient-center/diet-medications/probiotics

- American College of Gastroenterology: <http://patients.gi.org/topics/probiotics-for-the-treatment-ofadultgastrointestinal-disorders/>
- International Scientific Association for Probiotics and Prebiotics: www.isapp.net/docs/Consumer_Guidelines_final.pdf

Probiotics are generally safe but should be used with caution during pregnancy and in infants and should not be used in critically ill or immunocompromised patients.¹⁸ Rare cases of sepsis, endocarditis, and liver abscess have been reported with the use of *Lactobacillus*, and rare cases of fungemia have been reported with the use of *S. boulardii*, primarily in the context of immunosuppression or other severe comorbidities.¹⁸

Conclusions

Chronic GI diseases are common and associated with significant burdens for patients and the health care system. Probiotic therapy may serve as an effective and safe adjunct in the treatment of many chronic GI conditions, with support from clinical trials and medical society guidelines. Clinicians should familiarize themselves with the specific therapies available and be prepared to educate their patients with GI disorders and symptoms about the utility of this approach for symptomatic relief and improved HRQoL.

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CME Post-Test

1. **After participating in this activity, how confident are you in your ability to describe the role of microbiota in gastrointestinal (GI) health?**
 - a. Very confident
 - b. Moderately confident
 - c. Only a little confident
 - d. Not at all confident
2. **After participating in this activity, how often do you plan to discuss strategies for appropriate use of probiotic therapy with patients who present with GI disorders?**
 - a. Always or most of the time
 - b. Sometimes
 - c. Rarely
 - d. Never
3. **A relative decrease in the population of _____ is among the most consistent findings in studies of alterations in the function and composition of endogenous intestinal flora among patients with GI disorders.**
 - a. *Lactobacillus*
 - b. *Bifidobacteria*
 - c. *Helicobacter pylori*
 - d. *Saccharomyces*
4. **The therapeutic mechanisms of probiotics include all of the following except _____.**
 - a. interference with the ability of pathogens to colonize and infect the mucosa
 - b. modulation of local and systemic immune responses
 - c. increasing luminal pH and decreasing production of bactericidal proteins
 - d. inhibition of epithelial cell apoptosis
5. **In a study by Whorwell et al, _____ was associated with a significant decrease in abdominal pain/discomfort (primary end point) and decreases in bloating/distension, sensation of incomplete evacuation, passage of gas, straining, and bowel habit satisfaction (secondary end points)**
 - a. *B. infantis* 35624
 - b. butyric acid and fiber supplementation
 - c. *Escherichia coli* Nissle 1917
 - d. *L. rhamnosus*
6. **In a meta-analysis and systematic review on probiotics, the American College of Gastroenterology Task Force on irritable bowel syndrome found that probiotics were beneficial in reducing _____.**
 - a. flatulence
 - b. abdominal pain
 - c. bloating
 - d. all of the above
7. **In a recent review of 19 randomized controlled trials examining adjunctive use of 6 different probiotic mixtures in *H. pylori* eradication therapy, McFarland et al recently found that _____ most significantly improved eradication rates, reaching 96%.**
 - a. *Helveticus/L. rhamnosus*
 - b. *L. acidophilus/B. animalis*
 - c. *B. bifidum*
 - d. *L. plantarum/L. reuteri*
8. **Which of the following statements about ulcerative colitis is true?**
 - a. It induces chronic gastritis with potentially severe consequences including peptic ulcers, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma.
 - b. Intestinal inflammation often occurs in anatomical areas with low bacterial numbers.
 - c. Studies have demonstrated a role for probiotics in maintaining but not inducing remission.
 - d. In patients with active disease, VSL #3 and *E. coli* Nissle 1917 have shown the most benefit among probiotic strains.
9. **Colonization by *Clostridium difficile* infection can arise from _____.**
 - a. treatment with probiotics that normally are not present in the gut
 - b. disruption of normal intestinal flora by antibiotics
 - c. *Lactobacillus*-containing probiotic mixtures
 - d. toxic megacolon
10. **Which of the following is true of yogurt-based probiotics?**
 - a. They are regulated by the FDA as drugs.
 - b. Pasteurization encourages increased bacteria growth.
 - c. Not all of the live cultures contained in yogurt survive well in an acidic environment.
 - d. Current US regulations mandate that labeling indicates strain designations.