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Clinical Gastroenterology and Hepatology

A Gastroenterologist's Guide to Probiotics

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Abstract and Introduction

Abstract

The enteric microbiota contribute to gastrointestinal health, and their disruption has been associated with many disease states. Some patients consume probiotic products in attempts to manipulate the intestinal microbiota for health benefit. It is important for gastroenterologists to improve their understanding of the mechanisms of probiotics and the evidence that support their use in practice. Clinical trials have assessed the therapeutic effects of probiotic agents for several disorders, including antibiotic- or *Clostridium difficile*–associated diarrhea, irritable bowel syndrome, and the inflammatory bowel diseases. Although probiotic research is a rapidly evolving field, there are sufficient data to justify a trial of probiotics for treatment or prevention of some of these conditions. However, the capacity of probiotics to modify disease symptoms is likely to be modest and varies among probiotic strains—not all probiotics are right for all diseases. The current review provides condition-specific rationale for using probiotic therapy and literature-based recommendations.

Introduction

For more than a hundred years it has been recognized that certain microorganisms may impart health benefits to the host when administered in adequate amounts. These microorganisms, termed *probiotics*, have recently become a topic of significant focus in basic and clinical investigation. Relevant to the practice of gastroenterology, probiotics are commonly used by patients with gastrointestinal (GI) complaints or diseases. Increasingly, probiotics are also being recommended by the clinicians who treat these conditions.[1]

The goal of this review is to provide clinicians with an overview of the rationale and data which support or refute the role of probiotics for treating commonly encountered GI disorders. The information provided is based on review of primary literature from randomized controlled trials (RCTs), meta-analyses, expert consensus panel recommendations, and society-based practice recommendations. References are provided for more in-depth reading and tables or figures summarize key information.

The Human Microbiome and Probiotic Mechanisms

To understand the role that probiotics may have in influencing health, it is important to have an appreciation of the roles of the normal intestinal microbiome (commensal microbiota). The human GI tract is host to over 500 bacterial species as well as a less well-described virome. These microbiota form a virtual bioreactor facilitating digestion, nutrient provision, and the shaping of our immune system.[2] Our intestinal bacteria weigh up to 1 kg and bacterial cells outnumber human cells by 10:1. The bacterial genome may outnumber the human genome by 100:1. Nutritional factors including several B vitamins, vitamin K, folate, and short-chain fatty acids are produced by these bacteria. Up to 10% of an individual's daily energy needs can be derived from the by-products of bacterial fermentation. Gastrointestinal microbiota are also critical for normal immune system

development.[3] The physiologic impact mediated by our resident microbes is substantial enough to have earned the label of "other organ" from some.[4]

Beyond contributing to or modifying the metabolic and nutritional functions of the commensal microbiota, probiotic bacteria have several putative mechanisms by which they may confer specific beneficial effects. General categories include modulation of immune or sensory-motor function, enhancement of mucosal barrier function, and antipathogen effects (Figure 1).[5–7] Some of these mechanisms have been worked out in animal models and/or in vitro systems only.

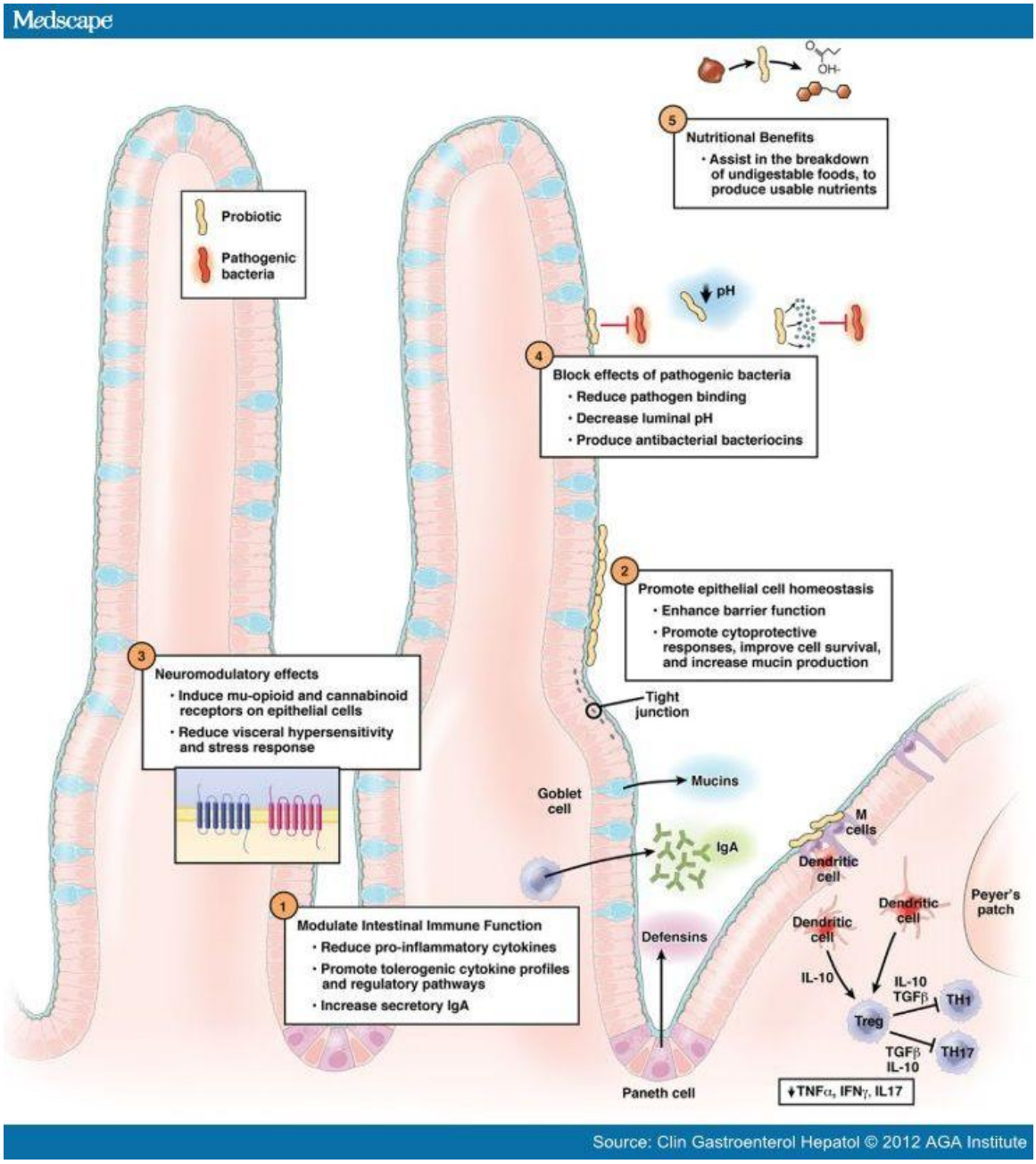

Figure 1. Mechanisms of action of probiotics in the gastrointestinal tract.

Soluble products secreted or shed by probiotics also mediate important physiologic benefits; thus, viable bacteria are not necessarily required for all benefits.[8,9] The mechanisms by which probiotics exert benefit varies by specific probiotic strain and likely depends on the clinical indication.[10,11] Therefore, as with antibiotic prescribing, clinical use of probiotics should focus on matching the probiotic strain and dosage to the condition for which it has shown benefit in clinical trials. In the future, greater understanding of probiotic-specific mechanisms could allow for precise selection of a particular probiotic strain to target a patient's specific pathogenic defect and clinical problem.

Probiotic Concepts for Practice

What Makes a Probiotic a Probiotic?

Definitions of the terms probiotic, prebiotic, and synbiotic are provided in Table 1. This review focuses on probiotics, though some probiotics have been tested as part of a synbiotic product. *Lactobacillus* and *Bifidobacterium* species are the most commonly used probiotics. However, 1 of the first probiotics, which is still in use, is the nonpathogenic *Escherichia coli* Nissle 1917 (ECN). Most probiotics were initially cultured from humans and resemble known commensal gut bacteria. However, the commensal population they resemble typically represents only a fraction of the total luminal bacteria. *Saccharomyces boulardii* is a probiotic yeast strain with the potential advantage of having resistance to most antibiotics.

Table 1. Definitions

Probiotics	Live microorganisms that confer a health benefit on the host when administered in adequate amounts
Prebiotic	Dietary substances that nurture specific changes in the composition and/or activity of the GI microbiota (favoring beneficial bacteria), thus conferring benefit(s) upon host health
Synbiotics	Products that contain both probiotics and prebiotics
NOTE. Adapted from Guarner F, Khan AG, Garisch J, et al. Probiotics and prebiotics: world gastroenterology organisation global guidelines, 2011. Available at: http://www.worldgastroenterology.org/probiotics-prebiotics.html.[48]	

According to current definitions, probiotics should survive both gastric acid and bile to reach the small intestine and colon where they exert their effects. Clinical and basic investigations on probiotics have used a multitude of probiotic species, both as single strains and multispecies products. Many of these probiotics are available in a lyophilized (freeze-dried) pill form, though some are available in yogurt or as packets (sachets) which can be mixed into noncarbonated drinks. Whether synergism or antagonism exists between probiotic species when offered together has not been examined in clinical studies, though both scenarios are theoretically possible. Though not exhaustive, Table 2 lists several of the more commonly available probiotic preparations which have shown benefit in human trials. Probiotics are considered dietary supplements; thus, they are not covered by medical insurance and their production is not regulated by the Food and Drug Administration. As such, product quality, purity, and viability have been reported to be variable.[12] However, several clinically tested probiotic products with quality-controlled production are now marketed by reputable companies.

Table 2. Available Probiotic Products Specifically Tested for Gastrointestinal Disorders

Brand name (Company)	Bacterial species	Clinical condition	Effectiveness[32,42,a]	Practice guidelines[15,48,84,b]	Bacteria count/dosing	Cost/quantity
Activia (Dannon,	*B lactis* DN-173010 (plus	IBS	C	1b[c]	4 oz/cup, 1–4 qd	$10–$18/24 count

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White Plains, NY)	yogurt starters *L bulgaricus, L lactis*, and *Streptococcus thermophilus)*					
Align (Proctor and Gamble, Cincinnati, OH)	*B infantis* 35624	IBS	B	1b[c]	1 Billion/1 qd	$29.99/28 count
BioGaia (Everidis Health Sciences, St Louis, MO)	*L reuteri Protectis* SD2112 (ATCC 55730)	Infectious diarrhea treatment IBS	A C	1a[d] 1b[d]	100 Million qd	$22–$30/5 mL (29 servings)
Bio-K+ (Bio-K Plus International, Inc, Laval, QC, Canada)	*L acidophilus* CL1285 and *L casei* LBC80R	AAD prevention CDAD prevention		1b[c] 1b[c]	50 Billion/capsule bid	$29.99/15 count
Culturelle (Valio, Helsinki, Finland/i-Health, Inc, Cromwell, CT)	LGG (LGG also included in Danimals yogurt; Dannon)	AAD prevention Infectious diarrhea treatment Infectious diarrhea prevention CDAD prevention CDAD prevention of recurrence Crohn's disease IBS	A A B B/C B/C C B/C (children)	AAP, 1b[c], 1b[d] AAP, 1a[d], 2b[c] 1b[c], 1b[d] 1a[d],1bc,e	10 Billion/1 qd	$18–$25/30 count
Danactive (Dannon)	*L casei* DN-114001	AAD prevention Infectious diarrhea prevention CDAD prevention	A	1b[c] 1b[d] 1b[c]	3.1 oz/cup; 10 billion/cup	$5.00/8 count
Florastor (Biocodex, Inc, Creswell, OR)	*Saccharomyces boulardii* (yeast)	AAD prevention Infectious diarrhea treatment Infectious diarrhea prevention CDAD prevention CDAD prevention of recurrenceCrohn's disease	A A B B/C B/C C	AAP, 1a[d], 1b[c] 1a[d], 1b[c] 1b[c]	250 mg/1 bid	$19.99/20 count
Mutaflor (Ardeypharm,	ECN	UC induction UC maintenance	B A	1b[c], BSG "A"	100 mg/capsule	$62–$81/60Can

Herdecke, Germany)					bid	ada[f]
VSL*3 (Sigma-Tau Pharmaceuticals, Inc, Towson, MA)	Combination probiotic product (*Streptococcus thermophilus, B breve, B longum, B infantis, L acidophilus, L plantarum, L paracasei, L delbreuckii/bulgaricus*)	IBS UC induction UC maintenancePouchitis: prevention and maintaining remission	B/C B A A	1b[c] 1b[c], BSG "B"	122.5 Billion/capsule; 450 billion/sachet; IBS: ½–1 sachet/d; Pouchitis: 2–4 sachets/d; UC: 1–8 sachets/d	$86/30 sachets $52/60 count

[a]Effectiveness based on expert panel recommendations where: A = strong, positive, well-conducted, controlled studies in the primary literature; B = some positive, controlled studies but presence of some negative studies or inadequate amount of work to establish the certainty; C = some positive studies but clearly inadequate amount of work to establish the certainty.
[b]Practice guidelines include those of (1) World Gastroenterology Organisation's global guidelines evidence level assignment[48] where 1a = systematic review with homogeneity of RCTs; 1b = individual RCT with narrow confidence interval; and 2b = individual cohort study (including low quality RCT)[85]; (2) American Academy of Pediatrics recommended (AAP)[15]; (3) British Society of Gastroenterology guidelines Grade of Evidence (BSG)[84]: grade A indicates consistent results among RCTs, grade B indicates consistent cohort studies or smaller RCTs.
[c]Adult.
[d]Pediatric.
[e]As part of a multispecies probiotic product.
[f]ECN is currently removed from the US market respecting the FDA's decision on the classification of the product as a "biologic" instead of its former status as a "medical food."

Does Any Yogurt Work Just like a Probiotic?

Lactic acid–producing bacteria have been used for centuries in food fermentation. Many yogurts contain live-active *lactobacillus* cultures and are considered functional food products; however, most are not considered probiotics per se. This term is reserved for products with an adequate number of microorganisms at time of consumption specifically shown to confer health benefits in controlled human trials. Yogurts fortified with an adequate number of viable bacteria shown to exert benefit in controlled trials are classified as probiotics. Given this information, and the knowledge that probiotic benefits appear species-specific, expected clinical end points may not be achieved by generically recommending yogurt to patients in whom a purported probiotic benefit is desired. It should be noted, however, that yogurt consumption has other benefits including improved lactose tolerance and the provision of protein, vitamin D, and calcium.

How Long Does One Have to Take a Probiotic?

As viable microorganisms, probiotics can survive in the human gut and impact microbes which colonize the gut. Probiotics are often detectable in the stool by culture or gene-based assays during periods of consumption. However, many probiotic strains do not colonize the gut and are no longer recoverable in stool 1 to 4 weeks after stopping consumption.[13] For example, McNulty and colleagues recently evaluated a fermented milk product with probiotic strains matching the commercially available Activia (Dannon, White Plains, New York). The investigators showed that the probiotic product did not change the gut's overall bacterial composition, but instead altered gene expression patterns relevant to carbohydrate metabolism in the host's resident gut

microbes.[14] These changes in the human fecal "metatranscriptome" were transient, confined only to the time of the probiotic consumption. Thus, if sustained benefit from a probiotic is desired, continued consumption is likely required.

Where Can Probiotics Fit into a Therapeutic Algorithm?

Data for probiotic use in several GI disorders are reviewed in the following section. For AAD and viral gastroenteritis, supporting data are strong and probiotics are among the only treatment modalities available. However, the duration of symptoms in these conditions is typically short regardless of probiotic use. In ulcerative colitis (UC), pouchitis, and irritable bowel syndrome (IBS), adequate data exist for clinicians to consider recommending a therapeutic trial of specific probiotic strains or preparations in selected patients. In these conditions probiotics are usually administered as adjunctive therapy, rather than primary or first-line therapy. The decision to recommend probiotic therapy ultimately depends on the clinical scenario, patient interest, and clinician preference. In hepatic encephalopathy, Crohn's disease (CD), and *Clostridium difficile*–associated diarrhea (CDAD), conventional medical therapies remain the gold standard. Practice relevant probiotic concepts are summarized in Table 3.

Table 3. Practical Considerations Relevant to Probiotics in Practice

Common side effects of probiotics are typically transient but include gas and bloating
Different probiotic strains possess unique properties for benefiting host physiology
One probiotic does not fit all GI illnesses; probiotic selection should be based on the clinical indication and take into consideration the strain and dosage used in clinical trials
Symptomatic benefits offered by probiotics are likely to be modest; thus, probiotic therapies may best be used to supplement rather than replace conventional therapies
Continuous consumption throughout the period of desired effect appears required for probiotics
Avoid probiotics in the critically ill and those with severe immune compromise

Probiotic Therapy for Gastrointestinal Conditions

Acute Onset Infectious Diarrhea

Several RCTs have evaluated the use of probiotics in acute infectious diarrhea. The data are largely from pediatric studies where both prevention and treatment were examined. Trials were conducted across the world with durations of up to 1 year. In the pediatric population, rotavirus has been the most common cause of infectious diarrhea. Data suggest that the benefit of probiotics in *preventing* acute infectious diarrhea is modest.[15,16] *Lactobacillus rhamnosus* GG (LGG), *Lactobacillus reuteri* and *Lactobacillus casei* all have shown benefit, with an approximate number needed-to-treat (NNT) of 7 children to prevent 1 case of rotavirus in the child care center setting.[17,18,19] With the currently available rotavirus vaccine in consideration, the American Academy of Pediatrics states that probiotics for *preventing* acute infectious diarrhea are not universally endorsed, but acknowledges that they may have a role in special circumstances.[15] According to the US Center for Disease Control, data are not sufficient to support the use of probiotics such as LGG to prevent *traveler*'s *diarrhea* of bacterial origin.

The data supporting *treatment* of acute infectious diarrhea with probiotics are stronger. LGG is the most effective probiotic reported to date, reducing both severity and duration of diarrhea by approximately 1 day.[20,21] The American Academy of Pediatrics supports the recommendation of LGG early in the course of acute infectious diarrhea to reduce symptom duration.[15]

Antibiotic Associated Diarrhea

Antibiotic use is common in children, and diarrhea develops in approximately 20% of those taking antibiotics. Prevention of non–*C difficile*-related antibiotic-associated diarrhea (AAD) with probiotics has been assessed in RCTs. A 2011 Cochrane Review evaluating more than 3400 patients from 16 studies concluded that the overall evidence suggests a protective effect of probiotics in preventing AAD.[22] Studies using LGG and *S boulardii* produced the most convincing results.[23] The NNT to prevent 1 case of AAD was approximately 7 in the Cochrane Review. The American Academy of Pediatrics supports the recommendation of probiotics for prevention of, but not treatment of, AAD.[15]

In the adult population probiotics also appear effective in limiting AAD. A meta-analysis evaluating studies on various probiotics and antibiotic regimens published between 1977 and 2005 found that both LGG and *S boulardii* offered a reduction in risk of AAD development (combined RR 0.31 and 0.37, respectively).[24] Two recent placebo-controlled RCTs evaluated combination probiotic products for the prevention of AAD as their primary end point. Hickson et al used the probiotic mixture currently marketed as DanActive (Dannon) in the United States and found that it significantly reduced AAD (12% vs 34%) in an older cohort of hospitalized patients.[25] A second study evaluated a combination probiotic containing both *L casei* and *Lactobacillus acidophilus* (Bio-K+; Bio-K Plus International, Laval, Quebec, Canada) in 255 patients. Patients given the higher dose of probiotic concurrent with antibiotics (and for 5 days afterward) had fewer occurrences of AAD (15.5% vs 44.1%).[26] As a secondary end point, both of these studies also showed a reduction in development of CDAD (discussed below).

C Difficile-associated Diarrhea

C *difficile*–associated diarrhea is a common nosocomial and community-based medical condition. Typically linked to antibiotic-induced disturbance of the intestinal microbiota, CDAD is now increasingly identified in patients without recent antibiotic exposure.[27] Antibiotic therapy with metronidazole, oral vancomycin, and now fidaxomicin make up the current treatment paradigm.[28] Recurrence of CDAD remains a clinical problem. In 1994, a trial reported that *S boulardii* (500 mg twice a day) offered for 4 weeks after antibiotic therapy reduced overall CDAD recurrence rates.[29] However, the finding was only significant for those with a history of recurrent CDAD. A follow-up study, designed to be confirmatory, did not find *S boulardii* to significantly reduce CDAD recurrence after standard therapy.[30] Though a favorable trend was found in patients treated with high-dose vancomycin (2 g/d) in the latter study, the clinical significance of this is less clear. Lactobacillus probiotics have been tested as single species and as combination probiotic products for preventing CDAD recurrence. While some results have been promising, most studies are underpowered, have methodological flaws, or have not been reproduced.[31]

Probiotic-based primary prevention still may be an approach to the current scourge of *C difficile*. The 2 recent probiotic trials discussed previously in the AAD section suggest that this may be feasible. The Hickson study reported that DanActive (Dannon) supplementation in older hospitalized adults reduced AAD, but also CDAD (0% vs 17% placebo).[25] The study evaluating the combination probiotic Bio-K+ (Bio-K Plus International) also showed a reduction in CDAD in the treated cohort (1.2% vs 23.8% placebo).[26] The high incidence rate of *C difficile* positivity in the placebo groups (17% and 23.8%) is a criticism for both of these studies. Nonetheless, if confirmatory studies show similar results, these intriguing findings may lead to a paradigm shift in managing older adults requiring antibiotic therapy.

While controversy exists, current society guidelines and expert opinion panels state that existing data are not sufficient to justify recommending available probiotics for preventing primary or recurrent CDAD.[31,32,33]

Irritable Bowel Syndrome

Irritable bowel syndrome is characterized by symptoms of abdominal pain and altered bowel habits which occur over at least 3 months. This common disorder is managed with varying clinical styles as no dominant

therapeutic strategy has emerged.[34] The pathophysiology of IBS remains unknown, but several lines of evidence link symptomatic expression of this disorder with the intestinal microbiota. IBS patients may have subtle differences in their luminal and mucosal-associated intestinal microbiota compared with controls.[35,36] New-onset IBS symptoms can develop in up to a third of individuals after recovery from a self-limited episode of infectious gastroenteritis.[37,38] Small-bowel bacterial overgrowth has been reported in a proportion of IBS patients, and antibiotics offer relief of IBS symptoms in some individuals.[39,40] Although controversy exists, bacteria likely contribute to at least some symptoms of IBS.[41]

Several clinical trials have investigated the potential for probiotics as therapy in IBS. These trials are the subject of several single-topic reviews.[42–44] Systematic summarization of these results is complicated by the inclusion of several probiotic strains/species, single or combination preparations, dosing regimens, and unique study designs. Several studies included end points which were not clinically applicable, or demonstrated improvement over baseline, but not compared with placebo.[42] Most studies were short-term only; data on long-term efficacy are still lacking.

A meta-analysis of 3 RCTs suggests that LGG moderately improves pain symptoms in children with IBS (NNT = 4).[45] Traditional IBS treatment end points have not been adequately met in studies of other single strain *lactobacillus* species in adults.[42] A *Bifidobacterium infantis* strain (*B infantis*;[35624] Align, Proctor and Gamble, Cincinnati, Ohio) was evaluated in 2 clinical trials. One study found significant reductions in pain, bloating, bowel movement difficulty, and composite symptom score vs placebo and a *lactobacillus* species.[46] In a larger follow-up study, reduction in pain and global relief of IBS symptoms were significantly greater in the *B infantis*–treated group compared with placebo.[47]

General recommendations from the American College of Gastroenterology as well as expert consensus panels from both the United States and in Europe are similar.[32,34,48] There is reasonable rationale for why probiotics may work as treatment for IBS. There are at least some positive controlled studies showing that probiotic supplementation reduces IBS symptoms in some patients. The evidence of benefit is not sufficiently strong to support the general recommendation of probiotics for IBS; however, the benefit appears greatest for *bifidobacteria* species and certain combinations of probiotics which include *bifidobacteria* species rather than single species *lactobacillus* probiotics.

With probiotics, patients might experience a global improvement in symptomatology rather than specific improvement in bowel function. Because treatment options for IBS remain limited in both number and efficacy, a therapeutic trial of probiotics is reasonable for patients interested in this approach.

Inflammatory Bowel Diseases

Evidence points to the intestinal microbiome being a key player in the development and perpetuation of the inflammatory bowel diseases.[49] Defects in the innate immune response to commensal intestinal bacteria resulting in an exaggerated adaptive immune response to these organisms are implicated in the pathogenesis of CD.[50] Several key CD risk genes have functions related to bacterial killing, and antibiotics have therapeutic efficacy in CD and pouchitis.[51,52] Compared with CD, a central role for gut bacteria is less strongly implicated in the pathogenesis of UC.[53] However, the evidence supporting probiotics in patient management is better for UC and pouchitis than for CD.

Several limitations exist with trials which have evaluated probiotic therapy in the inflammatory bowel diseases. These include small cohort sizes, use of different probiotic doses and strains, varied treatment durations, and differences in concurrent conventional treatments. Regardless, patients with inflammatory bowel disease often take or consider taking probiotics and appreciate their clinician having knowledge of the topic.

Crohn's Disease

Probiotic use in the management of CD is not supported by currently available RCT data. Trials have found LGG and other *lactobacilli* not superior to placebo as an additive to standard care for inducing or maintaining remission in CD or for preventing postoperative relapse.[54–56] There are also no solid data to support the use of ECN or *S boulardii* in CD.[57]

Ulcerative Colitis

Several published RCTs have shown benefit of probiotics in the management of UC. These studies have examined *induction of remission* and *maintenance of remission* typically by comparing the probiotic with oral mesalamine or adding the probiotic to standard therapy. ECN at 200 mg/d was similar in efficacy to 1500 mg of mesalamine for maintaining UC in remission.[58]

High dose VSL#3 (3.6 trillion colony-forming units per day; Sigma-Tau Pharmaceuticals, Inc, Towson, MA) has shown therapeutic efficacy in 2 RCTs evaluating patients with mild-to-moderately active UC. When offered to UC patients having a flare while taking mesalamine or an immunomodulator, the probiotic cohort demonstrated improved symptom-based disease activity indexes and rectal bleeding, but not endoscopic scores, compared with the placebo group.[59] A study conducted in India included 144 adults with relapsing UC and showed the VSL#3 group to have significantly higher remission rates (42.9% vs 15.9%) and endoscopic healing (32% vs 14.7%).[60] Most patients in both groups remained taking a stable dose of mesalamine therapy. A high dropout rate in both groups (29% VSL#3, 59% placebo) was a limitation of the latter study. VSL#3 was also shown to improve rates of induction and maintenance of remission in children with UC (n = 29 total).[61] Recent Cochrane reviews conclude that there are insufficient data to demonstrate that probiotics have efficacy in maintaining remission in UC; however, they have not recently addressed induction of remission in UC.[62] Single strain *Lactobacillus* and *Bifidobacterium* (*infantis*,35624 Align, Proctor and Gamble) probiotics did not show efficacy for maintaining UC remission in clinical trials.[63,64]

In summary, the overall evidence suggests that ECN and VSL#3 have modest efficacy, similar to and perhaps complementary to mesalamine, in inducing and maintaining remission for mild-to-moderately active UC.

Pouchitis

Chronic or recurrent pouchitis is an important complication occurring in approximately 10% to 20% of UC patients after ileal anal pouch formation surgery. VSL#3 (Sigma-Tau Pharmaceuticals, Inc) was shown beneficial in prophylaxis against pouchitis onset after surgical take-down[65] and in maintaining clinical remission after antibiotic induction.[66,67] These trials were conducted in Europe and included approximately 20 patients per group. A practice-based report from the Cleveland Clinic found only 19% of patients (6 of 31) who started taking VSL#3 after treatment with antibiotics to still be taking the probiotic at 8 months.[68] A single study from the Netherlands found that compared with a historical cohort, patients taking LGG had a delayed onset of pouchitis at 3 years (7% vs 29%).[69]

Clinical expert-generated guidelines concur that probiotics (VSL#3) can be effective for preventing recurrence of pouchitis.[32,70,71]

Complications of Chronic Liver Disease/Hepatic Encephalopathy

Luminal microbiota play an important role in the pathogenesis of both spontaneous bacterial peritonitis and hepatic encephalopathy. Ammonia produced by gut bacteria is believed to play a key role in hepatic encephalopathy. Antibiotics are employed in clinical practice to reduce severity or frequency of both these chronic liver disease complications. Lactulose, a mainstay of therapy, is a prebiotic for *lactobacilli* which can limit bacterial ureases.

The role for probiotics in these disorders is an area of ongoing investigation.[72]
Treatment of hepatic encephalopathy with *L acidophilus* was studied as early as 1965.[73] More recently, Liu and colleagues offered a probiotic and prebiotic mixture to 97 patients with minimal hepatic encephalopathy and observed a reduction in ammonia levels and improvement in encephalopathy.[74] Another group found that a yogurt-based probiotic supplement significantly improved quantitative measurements of minimal hepatic encephalopathy in patients with nonalcoholic cirrhosis.[75] The latter group is now completing a more comprehensive trial using the probiotic LGG in a similar patient cohort.[76]

Society guidelines and expert consensus panels do not currently support a recommendation of probiotic use for any chronic liver disease–associated condition.

Safety of Probiotics

For most populations, probiotic consumption is considered safe and complications rare. A review on the safety of probiotics by Snydman points out that although case reports of bacteremia and endocarditis (LGG) as well as cases of fungemia (*S boulardii*) exist, epidemiologic evidence suggests that there is no overall increase in population risk based on usage data.[77] This position is substantiated by a recent US government commissioned review panel report.[78] As a caveat, however, a high profile multicenter placebo controlled Dutch RCT examining probiotic supplementation in severe acute pancreatitis found a higher incidence of mesenteric ischemia and death in the treatment group.[79] This is the only trial to date to infer such a relationship, but supports the concept that probiotics should be avoided in critically ill patients. Indwelling central vein catheters and perhaps cardiac valvular disease may be relative contraindications.[80]

What Lies Ahead for Probiotics in Digestive Diseases

Inspired investigators and technical advances in genomics are facilitating in-depth scientific investigation of the human microbiome and the functional capacities of probiotics. These advances are sure to bring paradigmatic changes to our fundamental understanding of how microbiota influence health and how they can be manipulated to combat disease and improve quality of life. Future indications and therapeutic directions for probiotics may include conditions as diverse as mood disorders, obesity, autism, and diabetes. Recent clinical trials and translational studies suggest that lactobacillus probiotics may offer epithelial cytoprotection to limit symptoms of radiation enteritis, a dose-limiting side effect for patients receiving abdominal radiation therapy for malignancy.[8,81,82] Promise is held for confirmative testing of helminth-based therapy and "turbo-probiotics" designed to secrete human cytokines. Gene-based bacterial profiling studies from disease affected humans have identified what may be novel "probiotics" such as *Faecalibacterium prausnitizii* and *Clostridium* species IV and XIVa. Finally, the identification, purification, and repackaging of probiotic-derived soluble factors possessing proven capacity to modify biological function may allow us to harness the power of probiotics while averting the potential risks associated with live bacteria. As these advances progress to the clinic, the term *pharmabiotic* has been proposed by some investigators in an effort to encompass both beneficial microbes and their products.[83]

Conclusions

Evidence supports a role for considering the recommendation of conventional probiotics for some clinical conditions. Probiotic strain selection should focus on quality-tested products with clinically demonstrated benefit for the given disorder. Patients and physicians should expect modest effects and consider using probiotics as a supplement to, rather than a replacement for, conventional therapy. Though challenges exist, ongoing investigations offer great promise for the future. Perhaps one day clinicians will have the opportunity to use directed selection of a probiotic or probiotic-derived product to specifically address a patient's unique disease-causing physiologic or genetic defect. **References** Williams MD, Ha CY, Ciorba MA