Earn CME

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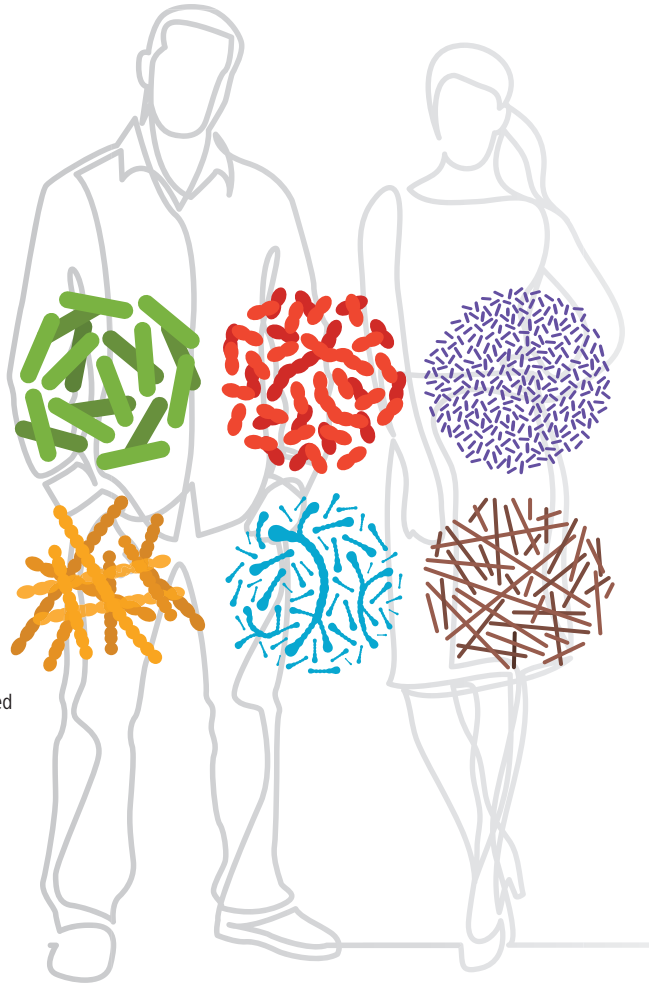
Clinical UPDATE

Probiotics: Facts and Fallacies



ACTIVITY DESCRIPTION

Despite advances in the treatment of gastrointestinal (GI) disorders, many patients continue to experience suboptimal outcomes, persistent symptoms, and/or disease progression, coupled with reduced quality of life. The manipulation of human gut microbiota by way of probiotics may represent a viable therapeutic option. However, widespread misconceptions impede probiotic uptake. This activity reviews key patient inquiries about probiotics and the latest evidence-based answers.

GOAL

The goal of this activity is to facilitate improvements in GI health by educating clinicians on the appropriate use of probiotics.

LEARNING OBJECTIVES

1. Describe the role of microbiota in GI health
2. Evaluate the benefits of probiotic use
3. Review clinical study data on the use of specific probiotic formulations in patients with different conditions and in healthy individuals

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INTENDED AUDIENCES

This activity is designed to meet the educational needs of gastroenterologists; other health care professionals interested in the topic of probiotic use will also find the activity of value.

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Introduction

Gastrointestinal (GI) diseases affect an estimated 60 to 70 million people and drive 48.3 million ambulatory care visits in the United States.[1] Annual spending on these illnesses is estimated at $135.9 billion.[2] Despite the availability of new medications and other advances in treatment, many patients with GI disorders experience suboptimal outcomes, including persistent symptoms, disease progression, and/or reduced quality of life.[2] The microbial ecosystem of the gut may represent an additional viable therapeutic target for these individuals.

Advances in sequencing technologies have revealed that a diverse community of microbes (including bacteria, archaea, fungi, microbial eukaryotes, and viruses/phages) inhabit the human gut. This collection of microbes, estimated to number more than 1 trillion, is known as the *microbiota*; the collective genome of microbiota is known as the *microbiome.*[3,4] Bacteria, primarily those belonging to the phylogenetic lineages *Firmicutes*, *Bacteroidetes,* and *Proteobacteria,* are the most populous among the organisms that comprise gut microbiota.[5]

Accumulating evidence points to gut microbiota as an important contributor to the vital bodily processes of nutrition, metabolism, immunomodulation, colonization resistance, and neuroendocrine homeostasis.[6,7] The composition and function of microbiota can be compromised by various environmental factors that overcome resistance and resilience capabilities. These include dietary changes, toxins, medications (particularly antibiotics), and pathogens. The resultant alterations to microbiota, which frequently include a decrease in microbial diversity, are now hypothesized to be etiologic factors in a number of GI and extra-GI disorders.[8,9]

A variety of interventions aimed at modulating and/or restoring the ecology of gut microbiota are being explored, and some are now in common use. Fecal microbiota transplantation (FMT), the process by which stool from a healthy donor is transplanted into the intestine of a diseased patient, results in a cure rate of 90% in patients with *Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI).[10] FMT is also being examined in the setting of ulcerative colitis, metabolic syndrome, type 2 diabetes mellitus, constipation, pouchitis, and irritable bowel syndrome (IBS), among other indications.[11,12] Prebiotics, nonviable dietary substances that function as substrates for bacterial metabolism, have shown promise in the treatment of IBS and may promote blood glucose regulation, calcium homeostasis, weight loss, and improvements in mood and cognition.[12] Probiotics have attracted the widest interest among researchers and consumers and constitute the focus of this review.

Probiotics are available widely and have been the topic of much popular media coverage. As a result, it is now common for patients to ask physicians for recommendations on their use. Although many health care providers do endorse a role for probiotics in patients with GI disorders, the advice they provide is inconsistent. Some have concerns about safety or efficacy.[13] Others fail to specify particular strains.[14] This variability is due in part to the fact that probiotic formulations are regulated as dietary supplements, not as therapeutic agents, and, therefore, their manufacturers are not required by the FDA to provide clinical trial data demonstrating safety and efficacy before making them available in the marketplace.[15,16] Moreover, marketers are not permitted to make claims about the use of probiotics in the treatment, prevention, cure, mitigation, or diagnosis of specific human diseases.[17] This can lead to the omission of probiotics from clinical guidelines and the misconception among some physicians that probiotic use is not supported by evidence. A study exploring physician perceptions of probiotics revealed that "lack of evidence" was the primary reason cited among those who did not recommend probiotics.[13] In a study evaluating patient knowledge, attitudes, and expectations of probiotics, participants frequently reported that gastroenterologists told them that scientific evidence supporting the use of probiotics for disease management is limited.[18]

Microbiota: diverse community of microbes that inhabit the human gut (including bacteria, archaea, fungi, microbial eukaryotes, and viruses/phages)

Microbiome: collective genome of microbiota

In fact, probiotics have been evaluated in numerous clinical trials, meta-analyses, and systematic reviews covering a range of diseases.[19-21] As the results of these studies vary considerably by species, strain, and disease, physicians need guidance on how to advise patients who are interested in probiotic use for GI concerns. In order to assist physicians with this task, frequently asked questions and their answers are summarized in this review.

What exactly is a probiotic?

Labels on an enormous array of products from facial cleansers to pet foods to dietary supplements proclaim that these items contain probiotics. These labels can be misleading. Unlike the regulatory bodies in some European jurisdictions, those in the United States do not restrict the use of the term *probiotics* by manufacturers and distributors.[22] Probiotics (literally, *for life*) are defined by the World Health Organization/Food and Agricultural Organization as "live microorganisms that when administered in adequate amounts confer a health benefit on the host." The International Scientific Association for Probiotics and Prebiotics (ISAPP), an international nonprofit collaboration of scientists dedicated to advancing scientific excellence in probiotics and prebiotics, proposed more exacting criteria for use of the term, stating that a probiotic must (1) be alive when administered; (2) have undergone controlled evaluation to document health benefits in the target host; (3) be a taxonomically defined microbe or combination of microbes (genus, species, and strain level); and (4) be safe for its intended use.[15] Patients should be cautioned that some products in the US marketplace purporting to contain probiotics do not meet these standards.[22,23]

How do probiotics work?

In the early days of probiotic research, the benefits of probiotics were presumed to result from recolonization, correction, and restoration of disordered or disrupted gut microbiota.[22] Recent studies suggest that this hypothesis was incorrect; probiotics have not been shown to facilitate sustained changes in the composition of gut microbiota.[22] The beneficial effects of probiotics may instead be achieved through many mechanisms,[24] including enhancement of the epithelial barrier, adhesion to intestinal mucosa, inhibition of pathogen adhesion, competitive exclusion of pathogenic microorganisms, and production of anti-microorganism substances **(Figure 1)**.[24]

Are probiotics effective?

According to an expert consensus statement from ISAPP on the scope and appropriate use of the term *probiotic*, probiotics as a class may be generally expected to support a healthy digestive tract via their beneficial effects on gut microbiota.[15] Studies in the laboratory as well as in patients with various GI and extra-GI disorders have revealed the potential of probiotics as therapeutic agents.[25] Differences in study size, power, design, strain selection, dosage, and use of concomitant drug therapy also make interpretation of these studies challenging. Meta-analyses have pooled these studies but provide limited additional insight into the roles of individual strains.[26] In general, probiotics should be considered as complementary therapies and not be substituted for proven therapies in the management of GI diseases.[27]

Checklist for Choosing a Probiotic

- ✔ Select a product certified by reputable third-party certification services
- ✔ Select dose based on clinicals trials relevant to patient's concerns
- ✔ Select genus, species, and strain(s) based on clinical trials relevant to patient's concerns
- ✔ Analyze risk vs benefit in:
  - Immunocompromised individuals
  - Premature infants
  - Patients with short-bowel syndrome
  - Patients with central venous catheters
  - Patients with cardiac valve disease

Which probiotic should I use?

Similar to the principles of antibiotic use, doses and strains of probiotics intended to improve outcomes in specific GI or extra-GI disorders should be selected based on evidence from clinical trials. Studies demonstrating the benefits of probiotics for such conditions typically employ specific doses, strains, and species; therefore, recommendations for using "probiotics" need to be very precise.[28] Although some probiotic formulations deliver in the range of 1 to 10 billion colony-forming units (CFUs) per dose, it should not be presumed that higher concentrations are more efficacious.[29] Other factors that clinicians should consider when selecting a probiotic include formulation, source, manufacturing quality control, shelf-life, and dose.[30,31] Seals of approval from organizations offering third-party certification services can facilitate the selection of probiotics that have undergone independent testing, have been demonstrated to meet their label claims, and in some cases, ensure that the product was manufactured under stringent conditions.[32]

Lactic acid-producing bacteria primarily belonging to the *Lactobacillus* and *Bifidobacterium* species together with the yeast *Saccharomyces boulardii* are the microorganisms most commonly used as probiotics.[11] Strains of *Bacillus coagulans* have also been commercialized as probiotics, but these are less common. *Lactobacilli* comprise a significant portion of microbiota and have been investigated for health benefits since the early part of the 20th century.

Characterized by the formation of lactic acid as the product of carbohydrate fermentation, these organisms (particularly *L. acidophilus*, *L. casei*, *L. rhamnosus*, and *L helveticus*) are widely employed in the production of fermented foods such as yogurt, cheese, sausage, rice wine, pickles, and soy sauce. Applications of *lactobacillus*-based probiotics include the improvement of lipid profiles and the treatment and/or prevention of inflammation-associated disease, allergy, infectious diarrhea, respiratory infections, and oral diseases.[11,33,34]

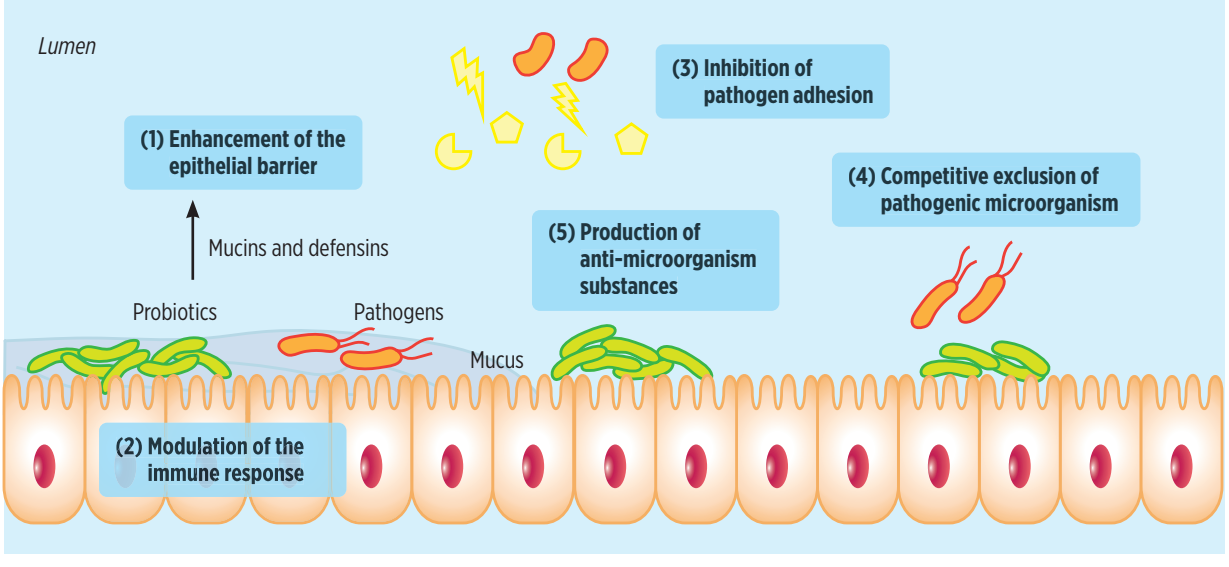

Figure 1. Key mechanisms of action of probiotics in the gut.

With permission from: Bermudez-Brito M, et al. Probiotic mechanisms of action. *Ann Nutr Metab*. 2012;61:160-174.

Bifidobacteria have a long history of use in fermented milks. In the GI tract, these anaerobic, nonmotile, non–spore-forming, and non–gas-producing microorganisms are mainly located in the colon.[35]

As probiotic agents, bifidobacteria (particularly *B. animalis* spp. *animalis*, *B. animalis* spp. *lactis*, *B. breve*, *B. longum* spp. *infantis*, and *B. longum* spp. *longum*) have been investigated for the prevention and treatment of a range of disorders including colonic transit disorders, intestinal infections, colonic adenomas, and cancer.[11,35] *S. boulardii* has been used for the past 4 decades in the prevention and treatment of bacterial diarrhea. Like other fungal probiotics, *S. boulardii* differs from bacterial probiotics based on its physiologic structures, larger size, and natural resistance to antibiotics. *S. boulardii* has demonstrated efficacy in clinical trials for the treatment of acute pediatric diarrhea, prevention of antibiotic-associated diarrhea, and reduction of the adverse effects of *Helicobacter pylori*–eradication regimens. In addition, promising clinical applications for *S. boulardii*, although less well studied, include the treatment of inflammatory bowel disease, prevention of diarrhea in enterally fed patients, and prevention of traveler's diarrhea.[36,37] Commonly used probiotic species are listed in **Table 1**.

Can I get the same benefits from cultured/fermented foods?

A large variety of cultured and fermented foods such as yogurt, kefir, miso, sauerkraut, and kimchi have a long history of safe consumption in the human diet. The process of fermentation can extend a food's shelf-life and safety by killing or inhibiting food-borne pathogens, promoting digestibility, and increasing the bioavailability of vitamins and minerals.[38,39] However, in the absence of head-to-head studies, cultured and fermented foods cannot be equated to probiotics. Many cultured and fermented foods are traditionally associated with health benefits, but they do not necessarily convey probiotic effects. Many have not been tested for their health effects.[40] Moreover, the fermentation process does not guarantee the presence of live microorganisms.[38] In the absence of documented evidence of a health benefit, labels that do claim the presence of live or active cultures do not necessarily mean that the food possesses probiotic activity.[15] **Table 2** delineates the differences between fermented foods and probiotics.

Table 1. Commonly Used Probiotics

Kingdom	Genus	Species
Bacteria	*Lactobacillus*	*L. acidophilus* *L. rhamnosus* *L. gasseri* *L. reuteri* *L. bulgaricus* *L. plantarum* *L. johnsonii* *L. paracasei* *L. casei* *L. salivarius* *L. lactis* *L. fermentum*
	Bifidobacterium	*B. bifidum* *B. longum* *B. breve* *B. infantis* *B. lactis* *B. adolescentis*
	Escherichia coli	*E. nissle*
Fungus (yeasts)	*Saccharomyces*	*S. boulardii* *S. cerevisiae*

Can probiotics prevent or reduce my …

… antibiotic-associated diarrhea?

The term *antibiotic-associated diarrhea* refers to diarrhea occurring in connection with antibiotic administration that is otherwise clinically unexplained.[41] Up to 49% of patients who receive antibiotic therapy experience antibiotic-associated diarrhea, which arises from the propensity of antibiotics to disturb the ecological balance of the gut microbiota.[37,42,43] This dysbiosis can impair the metabolism of key nutrients, resulting in osmotic diarrhea. It can also decrease colonization resistance, leaving the host vulnerable to infection with pathogenic bacteria such as *C. difficile*.

A wide range of probiotic formulations has been evaluated for the prevention and treatment of antibiotic-associated diarrhea in adults and children, including *S. boulardii*, *Lactobacillus GG*, other lactobacilli, and various probiotic combinations.[44] In a survey of health care professionals who reported regularly prescribing probiotic supplements or probiotic-containing foods, the prevention of antibiotic side effects was the most common clinical indication (79% of prescribers). *Lactobacillus rhamnosus GG* was the probiotic most frequently recommended for this indication.[14] A recent systematic review of data from 82 randomized controlled trials (RCTs) revealed that probiotics were associated with a statistically significant reduction in antibiotic-associated diarrhea.[45] A Cochrane

Table 2. Differences Between Probiotics and Fermented Foods

Probiotics	Fermented Foods
• Must be a taxonomically defined microbe or combination of microbes • Must confer health benefits when administered in adequate amounts • Must be safe for intended use • Must have documented health benefits • Commonly evaluated in clinical trials	• Encompasses any food that has gone through the fermentation process • May have extended shelf-life based on inhibition of pathogens • May or may not contain live organisms • May or may not exhibit probiotic activity • May or may not confer health benefits • Traditionally used microorganisms are generally recognized as safe • Rarely evaluated in clinical trials

Collaboration review designed to evaluate the safety and efficacy of probiotics used to prevent *C. difficile*-associated disease (CDAD) in adults and children receiving antibiotic therapy, concluded with moderate certainty that probiotics were effective for this use in patients with a baseline risk greater than 5% for developing CDAD, and that the short-term use of probiotics appeared safe and effective in conjunction with antibiotic treatment in patients who were not immunocompromised or severely debilitated.[46]

... infectious diarrhea?

Diarrhea due to GI infection is a leading cause of morbidity and mortality worldwide. Infants and very young children are most vulnerable. The highest mortality rates are in developing countries, but infectious diarrhea remains the second-leading cause of all infectious-disease mortality in the United States, behind lower respiratory infections such as pneumonia and bronchitis.[47] A Cochrane Collaboration review of 63 RCTs investigating the use of probiotics in patients with acute infectious diarrhea concluded that probiotics, when used in conjunction with rehydration therapy, shortened the duration of diarrhea and reduced stool frequency. *Lactobacillus casei strain GG (LGG)*, *S. boulardii,* and *Enterococcus* lactic acid bacteria were the microorganisms most commonly evaluated for infectious diarrhea.[48] A 2014 guideline issued by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommended that the use of *S. boulardii* or *LGG* be considered as an adjunct to rehydration therapy in the treatment of acute infectious diarrhea in previously healthy infants and children. ESPGHAN also stated that *L. reuteri DSM 17938* and heat-inactivated *L. acidophilus LB* may be considered for this indication, although their use was supported by weaker evidence.[49] Heat-inactivated *L. acidophilus* is not a true probiotic, based on the definition requirement that probiotics contain live microorganisms.[15]

... inflammatory bowel disease (IBD)?

IBD comprises chronic, progressive, relapsing conditions characterized by inflammation of the GI tract.[50] Ulcerative colitis (UC) and Crohn's disease (CD) are the most common types of IBD and affect an estimated 3 million adults in the United States.[51] A widely held hypothesis of IBD pathogenesis is that, in genetically susceptible hosts, environmental factors trigger an aberrant immune response against gut microbiota.[52] Indeed, ample evidence shows that the microbiota in patients with IBD differs from that in healthy controls (particularly with regard to microbial diversity). It remains unclear, however, whether perturbations in gut microbiota represent an etiologic factor in IBD or whether they result from IBD-associated intestinal inflammation.[53]

UC and CD have demonstrated differing responses to treatment with probiotics. In some studies and meta-analyses, probiotic administration resulted in improved outcomes in patients with UC, but the generalizability of these results is uncertain due to deficits in study design, availability of effective strains, and problems with quality control of probiotic products.[54]

Strong evidence supports the efficacy of probiotics in the prevention of pouchitis in patients with UC.[54,55] VSL#3, a combination of bacteria from the *Lactobacillus*, *Bifidobacterium,* and *Streptococcus* genera, was demonstrated to be more effective than placebo in eliciting a clinical response in patients with relapsing, mild to moderate UC despite treatment with mesalamine and/or immunosuppressants.[56] As other formulations carrying the name VSL#3 also have been marketed, it is important to specify that the aforementioned positive studies were obtained with what is now referred to as the "De Simone Formulation."

According to a technical review on the management of mild to moderate UC from the American Gastroenterological (AGA), the benefit of probiotics over placebo or mesalamine for induction and maintenance of remission in mild to moderate UC is uncertain. The AGA makes no recommendation for the use of probiotics in patients with mild to moderate UC.[57] In contrast, the European Society for Clinical Nutrition and Metabolism guideline on clinical nutrition in IBD recommends probiotics as an adjuvant treatment for the induction and maintenance of remission in patients with UC.[58]

... irritable bowel syndrome?

IBS is a chronic, functional bowel disorder affecting approximately 11% of the global population. It is associated with abdominal pain and altered bowel habits, with diarrhea (IBS-D), constipation (IBS-C), or both (IBS-M) being the predominant bowel habit in individual patients.[59] The etiology of IBS is not understood completely. Proposed mechanisms include visceral hypersensitivity, dysfunction along the gut–brain axis, disturbances in epithelial barrier integrity causing abnormal intestinal permeability, altered GI motility, immune activation, abnormal enteroendocrine signaling, and alterations in the composition of the gut microbiota (although a distinctive signature and causation have not as yet been identified).[60] Numerous studies and meta-analyses have shown that probiotic administration is associated with reductions in global symptoms, abdominal pain, bloating, and flatulence.[61-64] Although the particular species and strains that are the most beneficial in IBS remain to be elucidated because of a lack of head-to-head comparisons, a 2020 meta-analysis incorporating evidence from 35 RCTs concluded that supplementation with a multistrain probiotic had greater potential to improve IBS symptoms than any single strain.[64] However, these probiotic cocktails involved many different combinations; in their meta-analysis Ford et al. noted positive trends for *Bifidobacteria* (3 studies), *Escherichia* (2 studies), and *Streptococcus* (1 study).[63] Proposed mechanisms for the beneficial effects of probiotics in patients with IBS include regulation of the intestinal inflammatory response via improvement in the balance of pro- and anti-inflammatory cytokines; reduction in the adherence of pathogenic bacteria on epithelial cells and pathogenic bacterial translocation; modulation of intestinal transit and motility; reinforcement of the intestinal mucosal barrier; beneficial changes in the intra-luminal milieu; and analgesic effects resulting from the induction of the expression of μ-opioid and cannabinoid receptors in the intestinal epithelium.[61,63]

... H. pylori *infection?*

H. pylori is a highly prevalent bacterial species recognized as an etiologic factor in gastritis, gastroduodenal ulcers, and gastric cancer. *H. pylori* eradication has been shown to reduce the recurrence rate of gastroduodenal ulcers, protect against gastric cancer, and cure certain gastric

lymphomas. Current guidelines recommend bismuth quadruple therapy as first-line treatment.[65] However, despite a 90% success rate with this intervention, effectiveness in eradicating *H. pylori* infection has been hampered by sharp increases in rates of antibiotic resistance. In addition, frequent adverse effects of treatment such as antibiotic-associated diarrhea, nausea, abdominal pain, and vomiting can reduce medication compliance and lead to treatment failure.[66] Numerous studies and meta-analyses have provided evidence that probiotic administration in conjunction with guideline-based antibiotics enhances the eradication of *H. pylori* and reduces adverse effects. *Lactobacilli* and *Bifidobacteria* species, as well as *S. boulardii*, have demonstrated efficacy in this indication.[65] In addition, results from a 2018 meta-analysis showed that probiotic monotherapy eradicated *H. pylori* in 14% of cases. *Lactobacilli*, *S. boulardii*, and multistrain combinations eradicated the bacterium at rates of 16%, 12%, and 14%, respectively.[67]

... hepatic encephalopathy?

Hepatic encephalopathy (HE) comprises a broad range of neurocognitive abnormalities in patients with fulminant acute liver failure or chronic liver disease.[68,69] Management of HE is complex but might also incorporate modulation of gut microbiota.[70] A variety of probiotics, including strains from the *Lactobacillus*, *Bifdobacterium*, and *Streptococcus* genera and VSL#3 have demonstrated efficacy in patients with the earliest form of HE, referred to as minimal hepatic encephalopathy.[71] A Cochrane review of 21 trials involving 1,420 participants concluded that probiotic use may reduce the development of overt HE and improve quality of life and plasma ammonia concentrations but have little or no effect on mortality.[72] In addition to preventing bacterial translocation, reducing inflammation, and modulating intestinal permeability, probiotics may improve outcomes in patients with HE by decreasing ammonia levels.[72]

... necrotizing enterocolitis?

Necrotizing enterocolitis (NEC) is a serious form of intestinal inflammation that occurs in premature, low–birth-weights infants. The sequelae of NEC can include ischemic damage to colonic mucosa and bacterial sepsis. An abnormal inflammatory response to the microbiome from the incompletely developed gut immune system has been proposed as an etiologic factor. Beneficial effects of probiotics for NEC were evinced in meta-analyses of both RCTs and observational studies.[73] A 2017 meta-analysis suggested that multistrain probiotics may represent the most feasible and effective strategy for the prevention of NEC and reduction of mortality in preterm neonates.[74] The authors of a 2014 Cochrane review concluded that enteral supplementation with probiotics prevents severe NEC and all-cause mortality in preterm infants and strongly supported the adoption of probiotic prophylaxis in the management of these infants.[75]

... psychiatric and neurodegenerative disorders?

The gut microbiota is viewed as a key regulator of the *gut–brain axis*, a term used to describe the bidirectional communication that takes place between the GI tract and the central nervous system. A growing body of literature links perturbations in the microbiome with numerous psychiatric and neurodegenerative disorders such as Parkinson's disease, autism, mood and anxiety disorders, and Alzheimer's disease. It has not yet been determined whether the altered microbiome represents a causal factor in the development of these conditions or is a result of disease processes.[76] A recent meta-analysis of clinical trials evaluating the efficacy of prebiotics and probiotics for treating depression and anxiety demonstrated modest evidence for antidepressant and anxiolytic efficacy.[77] Another meta-analysis designed to determine whether probiotic consumption affects psychological symptoms in healthy individuals concluded that it may reduce symptoms of depression, anxiety, and stress.[78]

Can probiotics help me lose weight?

Obesity causes or exacerbates many other medical disorders. Preventable consequences include diabetes, dyslipidemia, hypertension, cardiovascular disease, obstructive sleep apnea, asthma, and fatty liver disease. Over the past 3 decades, the incidence of obesity has increased by more than 70% in adults and 85% in children.[79] Given ongoing concerns about the safety and efficacy of anti-obesity drugs, probiotics have garnered considerable interest for their potential role. Some strains have been hypothesized to decrease weight gain and insulin resistance by favorably altering the composition of the microbiota and enhancing the secretion of glucagon-like peptide-1 (GLP-1), a hormone that promotes satiety, slows gastric emptying, and improves glucose tolerance. Probiotics also may reduce low-grade chronic inflammation, which is increasingly implicated as an etiologic factor in obesity.[80,81] Other anti-obesogenic mechanisms proposed for probiotics include the prevention of pathogen colonization, competitive adherence to the mucosa and epithelium, strengthening of the gut epithelial barrier, and modulation of the immune system.[82] *Akkermansia muciniphila*, a bacterium that resides in the mucus layer of its host, and strains belonging to the *Lactobacillus* and *Bifidobacterium* genera have the strongest evidence base for efficacy in promoting weight loss. However, the improved obesity outcomes seen with the use of *Lactobacillus* and *Bifidobacterium*-based probiotics occur only with certain specific strains. Other strains may have negative effects.[80]

Can probiotics improve my general health?

The majority of research on probiotics has evaluated safety and efficacy in the treatment of patients with specific disorders. However, according to the ISAPP, some probiotic strains (*Bifidobacterium* [*adolescentis*, *animalis*, *bifidum*, *breve*, and *longum*] and *Lactobacillus* [*acidophilus*, *casei*, *fermentum*, *gasseri*, *johnsonii*, *paracasei*, *plantarum*, *rhamnosus*, and *salivarius*] may be expected to provide benefits in healthy adults.[15] Probiotics have been suggested to improve markers of immunity, bolster immunity against the common cold, improve lipid profiles, and normalize bowel habits.[83]

Are probiotics safe?

Remarkably few adverse effects been reported despite decades of consumption of probiotic supplements and centuries of consumption of *Lactobacillus* and *Bifidobacterium* strains in foods. Although clinical trials demonstrating safety are not mandated by the FDA for dietary

supplements, many probiotic microorganisms and microbial-derived ingredients have received the FDA designation "Generally Regarded as Safe" (GRAS). GRAS acknowledges a "general recognition of safety through experience based on common use in foods." This designation requires, among other things, a substantial history of consumption of a substance for food use by a significant number of consumers.[84]

Mild, transient GI symptoms may occur with probiotic use. Very rare adverse effects, including fungemia or bacteremia caused by organisms consistent with consumed probiotic strains, have been reported, as have deleterious metabolic events in critically ill patients.[85] A highly publicized study linked probiotic use, small intestinal bacterial overgrowth, and metabolic acidosis to a syndrome involving self-reported brain fogginess, gas, and bloating in a cohort of 30 patients; however, due to the observational design of the study and numerous methodological limitations, probiotic consumption could not be conclusively linked the described symptoms.[86,87] Theoretical concerns have been raised about the potential for the transfer of antibiotic resistance genes between probiotic organisms and other organisms in the GI tract, but, to date, this has not emerged as a clinical problem.[85] In addition, issues with quality control, including procedures allowing for the inclusion of microorganisms not indicated on the label, suggest a need for higher industry standards.[32] Quality control for probiotic products should involve the full description of their genomes, thereby, facilitating the identification of pathogenicity islands as well as transferrable antibiotic resistance genes and also providing the ultimate template for confirmation of batch contents. Probiotics should be used cautiously in immunocompromised individuals; premature infants; and patients with short-bowel syndrome, central venous catheters, or cardiac valve disease or artificial valves.[85]

Conclusion

Given the incontrovertible and growing evidence of gut microbiota as a significant factor in health and disease, interest among clinicians and patients on the role of probiotics as a treatment or preventative strategy for various GI and extra-GI disorders is timely and warranted. Although clinical and laboratory evidence suggests numerous benefits for probiotics, methodological limitations in clinical trials and meta-analyses designed to determine their efficacy have led to conflicting conclusions and doubts surrounding the generalizability of their conclusions. Unfortunately, this state of affairs has largely precluded the development of evidence-based algorithms for probiotic prescription. When faced with questions from patients, clinicians should make recommendations for probiotic formulations based on safety and benefit for the health condition in question. Referrals to specific probiotic products should be reserved for those with evidence of efficacy and high manufacturing standards and rigorous quality control. Clinicians should advocate for improvements in the regulatory landscape and for rigorous clinical trials of probiotics in patients with various diseases. Only when these improvements are accomplished will clinicians be able to precisely and with confidence select probiotics for specific indications and diagnoses.

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