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Targeting gut flora to treat and prevent disease

There's evidence to suggest that probiotics, prebiotics, and a high-fiber diet can help manage various illnesses. Here's how to translate gut flora research into practice.

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PRACTICE RECOMMENDATIONS

› *Encourage patients to eat a healthy diet that includes an adequate amount of soluble fiber to maintain a healthy, diverse microbiome.* (B)

› *Recommend combination probiotics to treat symptoms of irritable bowel syndrome.* (A)

› *Encourage patients to take probiotics containing* Lactobacillus *species to prevent antibiotic-associated diarrhea and* Saccharomyces *to prevent* Clostridium difficile *infection.* (A)

› *Recommend probiotics containing* Lactobacillus *species and/or* Saccharomyces *to treat acute infectious diarrhea.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE 1 ▶ Sheila S, age 27, has irritable bowel syndrome (IBS) and comes to your office for a follow-up visit. Over the past 6 months she has started taking a fiber supplement, drinking more water, and looking for links between stress and her symptoms. She has read about probiotics and wonders if you would consider recommending them in her situation.

CASE 2 ▶ Mark M, age 45, has type 2 diabetes and is overweight. He is motivated to change his diet and has started to exercise more. He is taking metformin 2000 mg/d but his hemoglobin A1c remains slightly elevated at 7.2%. He heard on television that probiotics might help to keep him from needing to add another medication.

Most of the living organisms that comprise the human microbiome—all of the microbes that live on or in humans—are found in the gastrointestinal (GI) tract. The gut flora contribute 99% of the genetic material in the human body. The composition of the gut flora is remarkably diverse across the population; each individual has a unique microbial footprint. Within this microbial diversity, there appears to be a stable number of genes that are responsible for the major functions of the gut flora.[1] These microbes:

- supply essential nutrients by breaking down complex carbohydrates;
- generate secondary bile acids that assist in digesting fats;[2]
- synthesize vitamins such as K, B12, folate, and biotin;[3]
- contribute to the defensive barrier in the colon by keeping pathogenic bacteria from crossing the colonic mucosa; and
- interact with our systemic immune system in a way that maintains a level of homeostasis, allowing for appropriate activation in the face of pathogens without developing autoimmunity.[4]

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Meta-analyses have found that combination probiotics benefit patients with ulcerative colitis, but not those with Crohn's disease.

The gut flora also play a role in the communication between the central nervous system and the enteric nervous system by modulating the hormonal and neural pathways that have been labeled the "gut-brain axis." The gut-brain axis has been associated with numerous disease states, including irritable bowel syndrome and certain psychiatric disorders.[5]

Researchers are investigating interventions that target the microbiome to increase microbial diversity and the presence of certain species to prevent or treat various diseases. The use of probiotics and dietary changes to increase intake of soluble fiber have been the most studied of these interventions. The thought is that these interventions can correct an imbalance, or dysbiosis, of the gut flora.[6] Studies have shown that decreased microbial diversity is associated with elevations of certain disease markers (eg, adiposity, insulin, triglycerides, C–reactive protein)[7] and that increases in soluble fiber lead to the greatest long-term improvement in microbial diversity.[8] Fecal transplant—the transfer of a processed mixture of stool that contains "healthy" bacteria from a donor into the intestines of a patient—is being explored as a method of replacing colonic gut flora, but evidence is limited.

The following review takes a closer look at these options and identifies those that are most likely to benefit patients in the treatment—and prevention—of several diseases (**TABLE 1**).[9-16]

Evidence is best for using probiotics for digestive diseases

Dietary interventions for digestive diseases have long been studied, but are getting renewed attention for their potential impact on the microbiome.[17] Beyond dietary modification, other similar treatment options include probiotics (live microorganisms thought to confer a beneficial effect on the host), prebiotics (non-digestible food ingredients, including oligosaccharides and inulin, thought to promote the growth of "helpful" gut flora), and synbiotics (combinations of the 2).[18]

Irritable bowel syndrome (IBS) is a heterogeneous disorder characterized by altered intestinal transit, low-grade colonic inflammation, and/or alterations in the gut-brain axis. Research has increasingly focused on recently discovered increases in intestinal immune activation, intestinal permeability, and alterations in the colonic microbiome (decreased diversity and increased pathogenic bacteria) associated with IBS.[19]

A meta-analysis of 43 randomized control trials (RCTs) found probiotics ranging from *Lactobacillus* to *Saccharomyces* can significantly decrease global IBS symptoms, abdominal pain, bloating, and flatulence.[9] For a patient such as Ms. S, the evidence suggests a probiotic that contains a mixture of *Lactobacillus* and *Bifidobacterium* might help relieve her symptoms.[9] In terms of dietary modifications, soluble fiber, which is already known to help treat IBS,[20] has profound effects on improving microbiota diversity and in shifting the composition toward less pathogenic strains.[21] The Institute of Medicine's daily recommended intake of soluble fiber is about 15 g/d.[22]

Inflammatory bowel disease (IBD) is caused by inflammation of the GI lining due to an overactive immune response. Evidence shows that patients with IBD have an altered microbial composition—specifically, an increase in bacteria that produce pro-inflammatory molecules and a decrease in bacteria that have a dampening effect on immune activation.[23]

Most studies evaluating probiotics as a treatment for IBD have been small and have used a wide variety of bacterial mixtures, which makes comparisons difficult. Recent meta-analyses found combination probiotics can both induce and maintain remission in patients with ulcerative colitis, but have no beneficial effects in Crohn's disease.[10] In a review of 9 case series of patients with IBD, fecal transplant reduced IBD symptoms, and patients were able to decrease medication use.[24]

Diarrheal illness. The human intestine is protected from diarrheal illness by healthy bacteria that block the actions of pathogenic bacteria. This mechanism is called colonization resistance. Moderate levels of evidence support the use of probiotics to prevent or treat several types of diarrheal illness.[14]

TABLE 1

Probiotics and prebiotics: Which of your patients might benefit?

The following table summarizes the evidence for using probiotics for specific diseases. Almost all probiotic preparations contain one of a handful of genera but any number of species. Many products contain multiple strains, and they more consistently show efficacy. Some manufacturers have created their own strains unique to their products. The more common strains used in studies and found in commercial products are included in this table. The list that appears in the footnote is a representative sample of products and is not meant to be exhaustive.

Condition	The evidence	Recommended treatment	Level of evidence
Irritable bowel syndrome	Probiotics significantly decrease global IBS symptoms, abdominal pain, bloating, and flatulence[9]	A mixture of *Lactobacillus* and *Bifidobacterium* species* approximately 20-40 billion CFU/d for 4-6 weeks	A
Inflammatory bowel disease	Probiotics induce and maintain remission in ulcerative colitis; no beneficial effects for Crohn's disease[10]	A mixture of *Lactobacillus* and *Bifidobacterium* species 225 billion CFU/d for 8-12 weeks to induce remission, or longer to maintain remission	A
Antibiotic-associated diarrhea	Probiotics reduce risk of developing AAD[11,12]	*Lactobacillus* alone† or in combination with *Bifidobacterium* species 10-20 billion CFU/d for 7 days **OR** *Saccharomyces boulardii*‡ 250-500 mg (5-10 billion CFU) twice a day for 2 weeks	A
Acute infectious diarrhea	Probiotics shorten duration and reduce severity of illness[13]	*L casei rhamnosus* GG 10-20 billion CFU/d for 5-7 days **OR** *Saccharomyces boulardii* 500 mg/d for 5-7 days	A
Traveler's diarrhea	Probiotics prevent up to 85% of cases of traveler's diarrhea[14]	*Saccharomyces boulardii* 500 mg/d for 3 weeks **OR** *Lactobacillus* alone or in combination with *Bifidobacterium* 20 billion CFU/d for 3 weeks	B
Eczema	Prebiotics may prevent eczema in the first 2 years of life[15]	Galacto- and fructo-oligosaccharide (9:1 ratio) (6.8 g/L) and acidic oligosacccharide (1.2 g/L) in infants **OR** Galacto- and fructo-oligosaccharide (GOS/FOS 9:1 ratio) (8 g/L) in infants	B
Diabetes	Probiotics result in significant reduction in at least one of 6 parameters of glycemic control[16]	*Lactobacillus* alone or in combination with *Bifidobacterium* 10-40 billion CFU/d for 6-8 weeks	C

AAD, antibiotic-associated diarrhea; CFU, colony-forming units; IBS, irritable bowel syndrome.

* The following products contain a mixture of various amounts of *Lactobacillus* and *Bifidobacterium* species: Jarro-Dophilus, PB8, and Ortho Biotic.

† Culterelle contains *Lactobacillus GG* alone.

‡ The following products contain various amounts of *Saccharomyces boulardii:* Ortho Biotic and Florastar.

Antibiotic-associated diarrhea (AAD) is caused when antibiotic use alters the microbial balance. Recent meta-analyses have shown probiotics can prevent AAD and *Clostridium difficile*-associated diarrhea.[11,12] Several case series and one RCT have found that fecal transplants are safe and efficacious for treating recurrent *Clostridium difficile* infection.[25] Using probiotics to treat symptoms of AAD has been less studied.

Acute infectious diarrhea and traveler's diarrhea (TD). A Cochrane review found that probiotics decreased the duration of diarrheal episodes by 25 hours, decreased the

risk of an episode lasting more than 4 days by 59%, and led to one less diarrheal stool per day by the second day of the intervention.[13] In a separate meta-analysis of 12 studies, probiotics significantly prevented 85% of cases of TD.[14]

Encouraging early evidence for several other illnesses

Metabolic disorders. Both animal and human studies support the theory that gut flora contribute to energy homeostasis, and in some genetically predisposed people dysbiosis may lead to obesity and diabetes. The traditional western diet[4] and possibly decreased physical activity[26] are major contributors to gut flora dysbiosis. Healthy bacteria in the gut break down soluble fiber into short chain fatty acids (SCFAs). SCFAs are associated with increased satiety, decreased food intake, lower levels of inflammation, and improvement in insulin signaling in adipose tissue. In addition to decreased SFCA production, dysbiosis also leads to increased lipid deposition through higher levels of lipoprotein lipase.[27]

Obesity. The bacteria in our gut affect energy metabolism. In patients with obesity, increased amounts of bacteria in the taxa *Firmicutes* and a corresponding decrease in *Bacteroidetes* is associated with an increased energy harvest and decreased SCFA production, which leads to a pro-inflammatory state.[28] Probiotics that contain *Bifidobacterium* and *Lactobacillus* are thought to help correct this dysbiosis by increasing production of SCFAs.[28]

A recent meta-analysis of 4 RCTs found no significant difference between supplementation with probiotics and placebo on weight reduction.[29] However, lower-quality studies with more subjects and longer duration have shown a statistically significant improvement in weight reduction with probiotic use compared to placebo.[29]

Diabetes. Although dietary interventions to improve glycemic control have long been an important cornerstone of treatment, probiotic supplementation to further alter gut flora composition is also being evaluated. Studies have found probiotics have largely beneficial effects on glycemic control, especially in animals. The largest systematic review to date looked at 33 studies, including 5 human trials. The human studies each found a significant reduction in at least one of 6 parameters of glycemic control (levels of fasting plasma glucose, postprandial blood glucose, glycated hemoglobin, insulin, insulin resistance, and onset of diabetes).[16] It is unclear which probiotic strains confer benefit, and if those benefits are sustainable without dietary modification and increased physical activity.

Psychiatric illnesses. The gut-brain axis is thought to impact mental health by several mechanisms, including modulating the hypothalamic-pituitary-adrenal axis, activating the immune system, producing active metabolites, and affecting the vagus nerve. It is unclear which of these pathways may be clinically relevant.[5,30] The few human studies that have looked for a potential link between gut flora and psychiatric illness have focused on depression and autism spectrum disorders (ASD).

Depression. Small studies comparing the microbiome composition of depressed patients vs healthy controls have found differences in patterns of both over- and underrepresented microbiota species in depressed patients, although the patterns across studies have been inconsistent.[31,32] One small functional magnetic resonance imaging study of healthy women showed that a fermented milk product that contained probiotics affected activity in areas of the brain that control emotion and sensation.[33] A few small studies have shown that patients who used probiotics had improved depression scores.[34] Further studies are needed.

ASD. Children with ASD have GI disturbances—most commonly diarrhea, constipation, and/or bloating—more often than healthy controls.[35,36] This association has led to speculation of a connection between the gut and brain. The microbial composition and diversity appears to be different in individuals with ASD; several studies have found an increase in *Clostridia* species.[37]

Research on probiotics for treating ASD has been primarily in preclinical models. Human studies of probiotics for ASD are lacking.[38] Small studies on dietary modifications such as gluten-free and casein-free diets have

The evidence suggests that fecal transplants are safe and efficacious for treating recurrent *Clostridium difficile* infection.

had varying results; to what extent these dietary changes exert their influence via the intestinal microbiome is unknown.[38]

Eczema. Several studies have looked at the role of prebiotics and probiotics in reducing the risk for allergic disease. A 2013 Cochrane review found strong evidence that certain prebiotics can prevent eczema in children under age 2.[15] There is limited evidence that probiotics may also play a role in preventing eczema.[39,40] However, probiotics do not appear to be effective for treating eczema.[41]

Rheumatoid arthritis (RA). Patients with RA have a change in the balance of function of different T helper cells subsets, and several studies have shown that changes in the gut microbiome can affect this balance.[42] A recent small study of patients with RA found that 75% of those with new onset RA had *Prevotella copri* bacteria as the predominant species, and patients with chronic RA had a decrease in *Bacteroides* species compared to healthy counterparts.[42-44] The exact influence of gut flora dysbiosis on RA is unknown.[45] Small studies suggest dietary changes may improve RA symptoms, while data on the use of probiotics to alleviate symptoms is mixed.[46]

What to tell patients about gut flora and health

There is increasing evidence that the gut microbiome and the genes contained therein have an impact on an individual's health. (See **TABLE 2** for additional resources.) The best preventive advice for patients and their families is to eat a diet rich in fruits and vegetables. This measure has well proven benefits beyond its potential effects on gut flora.

Correcting dysbiosis with diet or probiotics may play a role in treating chronic conditions; however, in many cases, further research is required to elucidate specific recommendations. In the meantime, given the safety profile of probiotics and dietary fiber, it is reasonable to consider using these interventions, particularly probiotics for treating IBS, ulcerative colitis, and acute infectious diarrhea; probiotics for preventing antibiotic-associated diarrhea and traveler's diarrhea; and prebiotics for preventing eczema in high-risk infants. JFP

TABLE 2

To learn more about the human microbiome…

The Human Microbiome Project http://commonfund.nih.gov/hmp/index
Metagenomics of the Human Intestinal Tract http://www.metahit.eu/
International Human Microbiome Consortium http://www.human-microbiome.org/
American Microbiome Institute http://www.microbiomeinstitute.org/
AGA Center for Gut Microbiome Research and Education http://www.gastro.org/about/initiatives/aga-center-for-gut-microbiome-research-education
Earth Microbiome Project http://press.igsb.anl.gov/earthmicrobiome/

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Several studies have found a link between the use of probiotics and significant reductions in at least one of 6 parameters of glycemic control.

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