Many people likely think of bacteria negatively, as sources of infections and illnesses and as something to generally avoid. Yet bacteria are everywhere, including in the human body, and not all are a threat to human health. In fact, the gastrointestinal (GI) system is home to trillions of bacteria, many of which aid digestion and nutrient absorption, strengthen the immune system, protect against infections, and otherwise enhance human health.

These friendly bacteria are known as probiotics, a word that derives from Latin and Greek terms that mean “for life.” In recent decades, public interest in probiotics’ health benefits has grown considerably. As a result, demand has increased for probiotic products that contain strains of live bacterial microorganisms cultured for human consumption. From cultured yogurt and other foods to over-the-counter supplement products, the desire to introduce probiotics into the diet has become a popular health choice for many people.

Probiotic products are also big business. The global probiotics market was worth around $48 billion in 2018 and growing.1 While the over-the-counter sale of probiotic products raises issues about their safe and effective use by consumers, the popularity of probiotics is more than a passing health fad. In fact, emerging medical research suggests probiotics may have a preventive and treatment role for a wide variety of GI illnesses and other health conditions.

Although the U.S. Food and Drug Administration (FDA) does not currently approve probiotics for preventive health or treatment purposes, the field
A word on GERD

One person who has found probiotics beneficial is Candice Milam, MED, CMA (AAMA), an educator in the medical assisting program at Danville Area Community College in Danville, Illinois. Diagnosed with gastroesophageal reflux disease (GERD), along with a mix of other digestive symptoms, Milam says her primary care provider suggested she try a probiotic to see whether it would help with her symptoms.

It did, she reports. “I admit I was leery at first of the idea of introducing bacteria into my system. When people say the word bacteria, most of the time you think of something harmful. But after reading and researching the issue, I decided to give it a try. I take a probiotic daily now, and it has really helped. I don’t get sick or get that nauseated feeling I used to get. I don’t feel bloated as much either.”

Milam has been using a probiotic for about five years now. Initially, about four weeks passed before she started to notice an improvement in her symptoms.

“As a patient, I think it’s a good idea to always investigate any medicine or supplement you’re taking. I would encourage anyone thinking of using probiotics to do the same: do your research, but also give it time to work.”

The modern interest in the potential benefits of probiotics intersects with the growing scientific understanding of the human microbiome’s role in maintaining health. The human microbiome represents a complex community of trillions of bacteria, viruses, and fungi that live in the body. Largely present in the GI system, the microbiome plays an essential role in health by providing extensive functions:

- Development of immunity
- Defense against pathogens
- Promotion of nutrition, including the production of short-chain fatty acids important in energy metabolism
- Synthesis of vitamins and fat storage
- Influence on human behavior

Of course, the impact of probiotics on the gut microbiome is complex and not fully understood. Generally, the live microorganisms identified as probiotics may help prevent harmful bacteria from attaching to the gut lining where they can proliferate in the GI system. These microorganisms can signal cells to build up mucus in the gut that can act as a barrier against infection. Additionally, probiotics may prevent the release of certain bacterial toxins in the GI system and promote the growth of more health-supportive bacteria.

Gut checks

Overall, probiotics research might be best described as promising but limited. Indeed, much remains to be learned about the use of probiotics for GI diseases and other health conditions.

“Gastroenterologists and clinicians have minimal guidance regarding the appropriateness of probiotics in the context of GI diseases, or for that matter, other diseases,” says Geoffrey A. Preidis, MD, PhD, a scientific advisory board member for the American Gastroenterological Association (AGA) Center for Gut Microbiome Research and Education.

The AGA scientific advisory board graded recommendations as either strong or conditional, explains Dr. Preidis. “A strong recommendation essentially means that most patients should receive the recommended course of action and that we as clinicians should strive to adhere to the recommendation as a reasonable measure of high-quality care. A conditional recommendation simply means that we as clinicians should be prepared to help our patients make a decision that is consistent with their own values. So, either the evidence is not quite as strong or there’s a lot of evidence out there but it’s a little unclear as to whether the benefits really outweigh the risks.” Notably, the AGA scientific advisory board’s 2019 recommendations were all conditional recommendations, says Dr. Preidis.

“One of the most promising areas from my team’s review of the medical literature is for the use of probiotics among preterm, low-birth-weight infants in the NICU [neonatal intensive care unit],” notes Dr. Preidis, who is also a pediatric gastroenterologist at Texas Children’s Hospital in Houston.
and assistant professor at Baylor College of Medicine. “The evidence base here was moderate to high quality in support of using probiotics in this population. We made a conditional recommendation that probiotics should be used to prevent several major problems among [the NICU] population:

• Necrotizing enterocolitis (a serious bacterial infection that largely affects the intestines of premature infants)
• Sepsis (bacteria in the bloodstream)
• All-cause mortality

Another area “where probiotics showed some promise was for the prevention of Clostridium difficile infection in adults and children,” says Dr. Preidis. Clostridium difficile (or C. difficile) is a frequent cause of infectious diarrhea in hospital settings that mostly affects patients receiving antibiotics.

An additional promising application of probiotics was “for antibiotic-associated diarrhea in adults and children receiving antibiotics for some condition such as pneumonia or urinary tract infection,” says Dr. Preidis. “Here we found low-quality evidence, upon which we arrived at a conditional recommendation.”

Additionally, the AGA scientific advisory board investigated the use of probiotics for pouchitis, a complication of surgery for patients with inflammatory bowel disease. “For patients with pouchitis, the AGA once again made a conditional recommendation,” says Dr. Preidis. “This was based on very low quality of evidence that probiotics could be beneficial in this population.”

The technical review also yielded some recommendations against probiotics use. “We made a conditional recommendation, based on moderate quality of evidence, that probiotics should not be used for children with acute infectious gastroenteritis,” reports Dr. Preidis. He notes that many pediatricians and providers at children’s hospitals prescribe or recommend probiotics in emergency room or outpatient settings to children with viral diarrhea instead.

“Finally, we reviewed four other conditions extensively, but we were not able to make a recommendation, based on a knowledge gap,” says Dr. Preidis. “There just wasn’t enough evidence out there to say yes or no. One of these conditions involves the treatment of C. difficile infection. Now, this is distinct from our recommendation on probiotics for the prevention of C. difficile.”

The advisory panel noted a few other conditions for which they could not recommend probiotics to adults or children:

• Crohn disease
• Ulcerative colitis
• Irritable bowel syndrome (IBS)

Friend or foe?
As knowledge of probiotics continues to evolve, what practical advice should health care providers offer patients who ask about using probiotics? It depends. For the most part, the risk-benefit ratio of using probiotics is low. Many people report anecdotal health benefits from eating probiotic-rich foods rich in probiotics, such as yogurt, or over-the-counter supplements for GI symptoms. Thus, clinicians will sometimes suggest probiotics as a safe adjunct therapy to patients’ other care despite the lack of a strong evidence base for many probiotics.

For example, although the AGA scientific advisory board was unable to come up with a yes or no recommendation on probiotics for IBS, some reports suggest that several probiotic strains might help with particular IBS symptoms, such as bloating. Of course, IBS is a complicated condition, and its causes and symptoms are usually multifactorial. Most experts agree that it is not clearly defined how exactly probiotics might be used therapeutically for IBS, which reportedly affects between 25 and 45 million people in the U.S.

“The evidence remains mixed, and there continues to be disagreement about which group of probiotics is deemed to be the most beneficial [for IBS],” says Alicia A. Romano, MS, RD, LDN, CNSC, a national media spokesperson for the Academy of Nutrition and Dietetics. “There are not definitive therapeutic roles for probiotics at this time, and further research and investigation is needed.”

Thus, probiotics are not suggested as first-line therapy for IBS patients, explains Romano. She prefers proven therapies that are available for many GI diseases, such as IBS. As a registered dietitian and nutritionist at Tufts Medical Center in Boston, Massachusetts, Romano works with many patients who are referred by gastroenterologists, oncologists, and other providers. She says many of these referred patients with IBS will require low-FODMAP diet therapy

The dynamic duo
Probiotics have a similar sounding but distinct counterpart: prebiotics. Prebiotics are “natural, nondigestible food components that are linked to promoting the growth of helpful bacteria in the gut.” This boost of good bacteria in the human microbiome may result in improved gastrointestinal health and enhanced calcium absorption.

Prebiotics can be worked into a diet by eating more fruits, vegetables, and whole grains:

• Bananas
• Onions
• Garlic
• Leeks
• Asparagus
• Artichokes
• Soybeans
• Whole-wheat foods

Ultimately, probiotics (i.e., bacteria) and prebiotics (i.e., bacteria promoters) complement each other by introducing and maintaining beneficial bacteria. When the two are used together, the resulting combination is referred to as a synbiotic.
(FODMAP is an acronym for fermentable, oligosaccharides, disaccharides, monosaccharides, and polyols). This is a specialized dietary management approach designed to help control IBS symptoms and to stimulate the growth of beneficial gut bacteria.

As naturally occurring short-chain carbohydrates, FODMAPs are found in many foods. These carbohydrates tend to be poorly absorbed in the intestine. As a result, they can draw extra water into the intestine and quickly ferment in the gut. Though high-FODMAP foods are generally healthy foods, they can cause uncomfortable symptoms in IBS patients, such as bloating, gassiness, diarrhea, and abdominal pain. The therapeutic low-FODMAP diet is a temporary, highly individualized medical diet plan designed to help relieve such symptoms. And the diet is typically executed under close medical supervision, usually by a registered dietitian.

“I recommend probiotics very sparingly in my practice, and only if conventional diet therapy in conjunction with current medication regimens are not fully providing the patient with the appropriate digestive relief. A great example would be a patient with IBS-D [irritable bowel syndrome with diarrhea] who has been rigorously following a low-FODMAP diet and has achieved about 75% of symptom relief. This patient has been able to reintroduce a small number of high-FODMAP food groups; however, [the patient] continues [experiencing] occasional diarrhea.”

In such instances, Romano says she might consider an empirical trial of the probiotic preparation VSL#3 as an adjuvant therapy to the patient’s low-FODMAP diet. The goal would be to see if the probiotic improves the patient’s symptom relief, allowing them to reintroduce a larger number of FODMAPs and broaden their diet.

Finally, Romano cautions more generally that the variability in probiotic products can complicate any recommendations that might be made for specific conditions. “There are significant differences in composition, doses, and biologic activity among various commercial probiotic preparations; and therefore, it is challenging to apply recommendations to all preparations,” she explains.

Variability can also be a factor in how individuals respond to the same probiotics, notes Crane Holmes, ND, an adjunct professor at the National University of Natural Medicine in Portland, Oregon. “Probiotics, in general, are not a one-size-fits-all approach,” he says. “Just because person A takes this probiotic and notices a huge difference doesn’t mean person B will also. They may notice no difference or maybe even feel worse.”

Probiotics and possibilities

Undoubtedly, the popularity of probiotic supplements is influenced to some degree by their appeal as a so-called natural health product. But natural does not necessarily mean “without risk.” While probiotic supplements can be purchased over the counter, individuals should consult a health care provider on the best approach to introducing probiotics to their diets, suggests Holmes.

“I’ve known people to do things like buy probiotic ‘gut shots’ and drink those two or three times a day,” he says. “I’ve found some people can actually feel worse doing too much. You can overdo it. Even in cultures where people use kombucha [a traditional fermented tea that contains probiotics] as part of their normal diet, they’re usually taking just a few tablespoons, a small shot, or something along those lines once or so a day. They’re not drinking 12-ounce or 24-ounce bottles.”

At the same time, fermented foods and drinks, like kombucha, kimchi, kefir, and sauerkraut, can play a beneficial role in the gut microbiome when used appropriately, says Holmes. “I’m actually a big proponent of fermented foods as a source of probiotics,” he says. “There’s some evidence that people who eat fermented foods consistently do the best. If people are looking generally to improve their health by increasing their biodiversity and their microbiome health, I think fermented foods tend to be one of the best ways to do it.”

Another integrative practitioner who reports benefits from probiotics is Peter Lio, MD, a clinical assistant professor of dermatology and pediatrics at Northwestern University Feinberg School of Medicine in Chicago. Both oral and topical probiotics may be helpful for some inflammatory skin diseases, including atopic dermatitis, and for promoting wound healing.

How does Dr. Lio use probiotics for his patients with atopic dermatitis? “Right now, I keep it simple,” he says. “There seems to be the most evidence around simply using Lactobacillus rhamnosus GG. This is commonly available and inexpensive. They make an adult capsule, a packet for kids, and … even a great combination of [vitamins and] probiotic drops for infants, which I really like. I ask that all patients try taking it at least once per day or as directed by the manufacturer. I have
had a number of patients say things like, ‘We weren’t able to pick up any of the prescriptions you wrote over the weekend, but we did start the probiotic and already things are better!’ With any anecdotes, it’s impossible to determine causality, but given the evidence available, I do think there are individuals who respond very well to probiotics.”

“As for topical probiotics, my experience is more limited,” says Dr. Lio. “There is a topical spray that I have used and do like; the issue is that it is relatively expensive, needs refrigeration, and must be used with special topical [because] many preservatives will kill the probiotic. All of these make it much more difficult to use.”

**Hard to stomach, sometimes**

For most people who are generally healthy, probiotics are often safe. If adverse effects do occur, they usually involve mild digestive symptoms. However, probiotics could cause more serious side effects in vulnerable patients, says experts.

Patients with serious health problems (e.g., weakened immune systems) have been reported to develop serious complications, such as infections, says Romano. “Probiotics should be used with caution and under the guidance of a physician in these populations. Patients who have a health condition or are pregnant or breastfeeding should always consult with a physician before starting a probiotic. In healthy individuals, probiotics generally have minor side effects, if any. However, use should still be monitored. Using probiotics, as well as other complementary health products, should also not be a reason for postponing a health care provider.”

Notably, the AGA scientific advisory board found the reporting of safety data to be, in Dr. Preidis’s estimation, “woefully lacking.” A similar lack of harms reporting in probiotics research has also been recently noted by researchers in Annals of Internal Medicine.

“This field is not being held to the rigorous standards of pharmaceutical trials,” says Dr. Preidis. “I think this presents a large problem. So, how do we move forward? As clinicians, we have to balance potential benefits with the possibility of risks. You can certainly find case reports in which patients receiving a probiotic have been found to have bacteria in their bloodstream or in other organs in their body. There have also been reports of probiotic products being contaminated by other pathogens that were not related to the live beneficial microbe.”

Consequently, Dr. Preidis gives some advice on being heedful: “Typically, we will consider probiotics to be safe for most people, but caution should always be exercised when you have extremely fragile patients, such as immune-compromised patients, anybody with an immune system defect, or anybody taking chemotherapy. Here I think we have to be judicious. Again, there are no solid studies saying, ‘Do not use these products in these patients.’ But just based on the case reports and case series we have been following over decades and us knowing that those with compromised immune systems may get into trouble if the bacteria do leave their intestinal tract, we typically recommend against using probiotics in severely immune-compromised patients.”

Yet, interpreting data from probiotics studies can be challenging and requires careful assessment and interpretation. “[With this in mind] I think the data from low-birth-weight, preterm infants in the NICU is quite compelling,” says Dr. Preidis. “Certainly, these are fragile patients, and their immune systems are not fully developed. One of the main theoretical concerns about [giving] a live microbe would be the possibility of that live microbe making its way to the bloodstream, causing sepsis. In the more than 60 studies we reviewed, [which were] randomized controlled trials based on low-birth-weight infants in the NICU, we actually found reductions in sepsis and in bacteria making it into the bloodstream [as well as] reduced frequencies in those infants who received probiotics versus those who did not.”

**Getting on the right tract**

The nuances, limitations, and inconsistencies involved in interpreting current probiotic research and the heterogeneity in how clinical trials are designed and conducted highlight just how much remains to be learned about the way probiotics work in the human body.

“As far as looking to the future, we have to think about mechanism,” explains Dr. Preidis. To do this, he stresses the need to answer certain questions:

- How are these live microbes inducing the beneficial effects that we hope to find?
- Is there cross talk (i.e., interference, overlap, or interaction) with the human immune system?
- Are probiotics interacting with other microbes in the intestine?
- Are they interacting with the diet to create metabolites (a product of metabolism) that the body takes up?
- Do they change intestinal motility (i.e., movement capabilities)?
- Do they interact with other parts of the human body via secretion of small molecules that can influence faraway sites via the bloodstream?

Dr. Preidis does not anticipate the day when a single off-the-shelf probiotic formulation will work for every person with a given condition. Instead, he sees involving probiotic therapy moving toward a more individualized treatment approach.

“I think we will need to use our currently lacking knowledge of mechanism to design a more personalized approach to probiotics,” he concludes. “What microbes or microbial functions is [an] individual currently lacking? And how can we replace those missing functions in a sustainable way? We need to make sure that our [prescribed] therapy actually survives and hangs around in the patient’s intestinal tract. My guess is that these clinical conditions and the various patient populations are quite heterogeneous, and we will [eventually] be able to identify
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subsets of microbiome disturbances that can be addressed in more individualized ways.”

Despite whatever challenges the field of probiotics poses for researchers and clinicians, the study of probiotics will continue to be dynamic in the years to come. As clinical knowledge of probiotics grows, the promise of more refined, effective, and customized treatment applications may offer even more promising new possibilities for using probiotics in improved clinical care.

References