With interest growing in natural therapies, the popularity of probiotics is on the rise. In 2012, almost 4 million US adults reported using probiotics or prebiotics—4 times more than in 2007. Probiotics were used in more than 50,000 hospitalizations in 139 US hospitals in 2012. And last year alone, US consumers spent an estimated $2.4 billion on the supplements.

Two recent studies by researchers in Israel, however, are raising questions about the widespread use of probiotics to impart general wellness and restore intestinal flora after the use of antibiotics, 2 common indications.

In 1 study, the bacteria in a probiotic supplement failed to colonize the guts of a proportion of participants, suggesting that the bugs may pass through some people with no effect. In the other study, the same bacteria took up residence in the intestines after a course of antibiotics but appeared to delay the return of the native microbiota. Both studies, which involved healthy participants, were published in the journal Cell last October.

Probiotics are defined as “[l]ive microorganisms which when administered in adequate amounts confer a health benefit on the host.” But some experts say that any evidence of benefit, which is limited to a small number of indications, is conflicting and often low quality. A 2018 Cochrane analysis concluded that in 10 of 14 systematic reviews of clinical trials, the data were insufficient to determine if probiotics improved specific gastrointestinal conditions.

The best case could be made for diarrhea-related conditions, according to the analysis. However, many trials suggest that the supplements can prevent or treat antibiotic-associated diarrhea and Clostridium difficile infection, others involving both children and adults haven’t shown a benefit in these conditions. Most recently, 2 trials published late last year in the New England Journal of Medicine failed to show a benefit of Lactobacillus rhamnosus probiotics in children with gastroenteritis, or stomach flu.

For scientists and clinicians interested in bacterial therapy, the confusion has "created a very big mess," said Eran Elinav, MD, PhD, of the Weizmann Institute of Science in Rehovot, Israel, a senior author of the new studies in Cell.

Tracking Colonization
In 2015, Elinav and colleague Eran Segal, PhD, a computational biologist, demonstrated that the same meal can have a variable effect on blood glucose in different nondiabetic individuals depending, in part, on the makeup of their gut microbiota.

The pair developed a way to predict individuals’ postmeal blood glucose spikes largely based on a combination of clinical, laboratory, and stool microbiome features. The predicted blood glucose responses were used to create personalized dietary interventions that lowered postmeal glucose, an approach that’s since been licensed by a nutrition start-up.

Elinav and Segal’s more recent work suggests that the most effective gut microbiome interventions might also be personalized ones. In the new studies, they and Zamir Halpern, MD, a senior physician at the Tel Aviv Sourasky Medical Center’s Gastroenterology Institute in Israel, revisited basic questions that they thought hadn’t been adequately addressed in prior work: To what extent do probiotics colonize the human gut, and what effects do they have there?

In their first study, 19 healthy volunteers received either a commercially available 11-strain probiotic supplement or a placebo twice daily for 4 weeks. The supplement included the 4 major bacterial genera used in the majority of probiotics around the world, Elinav said.

Rather than relying solely on study participants’ stool—a routine practice in gut microbiome studies—the researchers also studied sites along the entire gastrointestinal tract both before and during the intervention. Using colonoscopy and deep upper endoscopic techniques, they collected samples of bowel contents and intestinal lining and took biopsies of intestinal tissue. The samples then underwent sophisticated genetic sequencing to determine microbiome content and function and host gut gene expression.

Intestinal lining samples taken 3 weeks into the intervention showed that the participants given probiotics fell into 2 camps: “permissive” or “resistant.” The permissive
volunteers had a significant increase in probiotic strains in their intestinal lining, whereas the resistant volunteers’ guts weren’t significantly colonized. Permissive individuals also had changes in their indigenous microbiome and gene expression profile along the gut that were not observed in resistant individuals or those receiving placebo.

According to Colleen Kelly, MD, a gastroenterologist and a professor at the Warren Alpert Medical School at Brown University, who was not involved with the research, the study is 1 of the first to show that some people’s guts resist probiotic colonization at the level of the intestinal lining, “where all the action is.”

The volunteers’ preexisting microorganisms largely determined whether they were permissive or resistant to probiotics. Interestingly, the fecal samples didn’t uncover these differences; both permissive and resistant participants shed comparable amounts of probiotic bugs, and more than the placebo group, in their stool.

To Elinav, the findings suggest that “our currently applied one-size-fits-all probiotic approach is probably incorrect.” Such interindividual variability means that some people may benefit from probiotics, while others may not.

This should come as no surprise, said Rob Knight, PhD, who directs the Center for Microbiome Innovation at the University of California, San Diego, and was not involved with the work. He pointed out that different people respond differently to the same foods, medications, and pathogens. “This is extending that to beneficial organisms,” he said of the study, adding that previous work has turned up the same variability.

There’s a general belief among some physicians and the public that consuming “good” bacteria in the form of a pill can edge out “bad” bugs and promote gut health even in healthy people. Yet in most clinical trials that involved healthy people, probiotics didn’t significantly change gut flora. With the Weizmann Institute study, the claim may be more dubious than ever, Kelly said: “The idea that people could just take probiotics for general health—you might be wasting your money.”

After Antibiotics

In their second study, the researchers looked at what happens in the gut when a person follows up antibiotics with probiotics. Twenty-one healthy volunteers were given broad-spectrum antimicrobial therapy with oral ciprofloxacin and metronidazole for a week, after which they either received a 4-week, twice-daily course of the same supplement used in the first study; an autologous fecal microbiome transplant, in which they got back a sample of their own preantibiotic microbiota via upper endoscopy; or watchful waiting.

This time, none of the individuals who received probiotics were resistant to their colonization. The antibiotics had killed off much of the indigenous microbiome, allowing the exogenous strains to thrive. But there was a price: the native gut bacteria took far longer to return in the probiotics group compared with the watchful waiting group. The resetting of the host gut gene expression profile was also inhibited in the probiotics group through a 6-month follow-up period.

Alexander Khoruts, MD, a gastroenterologist and medical director of the University of Minnesota Microbiota Therapeutics Program, who was not involved with the study, said he was surprised that the pills had any demonstrable effect at all. “I didn’t expect that these microbes were actually potent enough to interfere with microbiome recovery,” he said.

Khoruts primarily treats patients with refractory C difficile infections, and virtually all his patients tell him that they’re taking probiotics. Although he doesn’t argue with them, simply steering them toward fermented foods instead, he said the evidence supporting the use of probiotics is weaker than many people assume. “In my review of the literature—and others may disagree—there is really no convincing evidence, at least for C difficile infection, that there is any benefit from probiotics,” he said.

One major failing is a glaring lack of randomized trials that sufficiently report safety data for probiotics, a topic that was the subject of a recent systematic review in Annals of Internal Medicine.

Despite the Weizmann Institute study, it’s unknown if taking probiotics during or after antibiotics is sure to delay the return of the native microbiome, or if that perturbation could cause problems. All probiotic formulations are different, and according to Knight, the researchers administered a particularly high dose. Plus, the study was not designed to look at clinical outcomes. However, prolonged postantibiotic disturbances in the indigenous microbiome are associated with a range of health issues, including infections, obesity, allergies, and chronic inflammatory disorders, according to Elinav. In his view, the persistent disturbances caused by the probiotics his team studied “potentially could lead to long-term adverse effects in those consuming them.”

Knight cautioned that the research involved a healthy population administered antibiotics for a scientific study. In real life, people take antibiotics because they’re sick. Will probiotics slow the return of the native gut flora in those situations?

“The study doesn’t actually address that question at all,” Knight said. “It’s talking about antibiotics administered to healthy subjects, where the situation may be totally different from a clinical population.”

Khoruts said he suspects that any harms from most probiotics products would likely be minimal. But for him, “It’s certainly enough to pause and reflect on what one believes. I think the primary care physician should have a healthy degree of skepticism about the claims made by these products.”

Harnessing the Findings

Like Khoruts, Kelly treats a substantial number of patients with recurrent C difficile infections. In the past, she’s encouraged them to take probiotics if they’re prescribed antibiotics. She’s now second-guessing this: “Am I doing the right thing? By telling them to take probiotics, am I delaying normal recovery of the bacteria?” Concurring with Knight, she said studies in clinical populations will be needed to bear this out. For now, the American Gastroenterological Association has advised that “in general, probiotics should not be used indiscriminately.”

There was a bright side to the research, however. Individuals who got their own bugs back through autologous fecal transplants reverted to their preantibiotic microbiota and gut gene expression profile within days, “demonstrating the power of personalizing microbiome interventions,” Elinav said.

However, scaling up autologous fecal microbiome transplants would be challenging—it necessitates sample collection when a person is healthy, followed by storage for an indefinite amount of time. But it might be possible to develop personalized consortia of probiotic bacteria tailored to individuals.

Elinav believes that in the not-so-distant future, machine learning algorithms
could be used to tailor specific probiotic strains to individuals based on their baseline gut microbiome and gene expression profile, thereby increasing the probiotic’s chances of inducing meaningful clinical effects. Because there appears to be universal probiotic colonization after antibiotic therapy, this approach would only apply to those not taking antibiotics.

Elinav also sees a silver lining in the finding that antibiotics stall the native microbiome from returning after antibiotics. Why not use the combination of antibiotics and probiotics to reset the gut ecosystem and, ideally, reverse microbiome-associated diseases like inflammatory bowel disease or even obesity? “I think it’s a very exciting and interesting prospect that needs to be investigated,” he said.

Note: Source references are available online through embedded hyperlinks in the article text.