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Probiotics in GI Practice: Evidence, Guidelines, and Emerging Innovations

Dr. Buch:
This is *GI Insights* on ReachMD. I'm Dr. Peter Buch, and today I'm joined by Dr. Alexa Weingarden to discuss practical probiotic usage. Dr. Weingarden is an Assistant Professor of Gastroenterology, Hepatology, and Nutrition who's passionate about studying gut immunology at the University of Minnesota Medical School.

Dr. Weingarden, welcome to the program.

Dr. Weingarden:
Thank you, Dr. Buch. Thanks for having me on.

Dr. Buch:
It's a true pleasure. To start us off, Dr. Weingarden, would you provide some background on probiotics and how they differ from prebiotics, synbiotics, and postbiotics?

Dr. Weingarden:
So there's some formal definitions that have been outlined for all of these categories of, fundamentally, supplements. One important aspect that's true for all four of these categories is that they are all substances that are supposed to provide some kind of health benefit to the person who's taking them, but within that, you have, first, probiotics. And probiotics are defined as live organisms, so you're taking a live organism in order to have some kind of health benefit for you.

A prebiotic is like microbial food, so rather than being a live organism, it's a substrate that organisms—either a probiotic species or usually native species in the gut—can metabolize in order to increase the abundance of beneficial bacteria or increase metabolic activity of an important metabolic pathway that's going to provide some benefit to the person taking them.

And a synbiotic is just simply a mixture of these two things. So you're taking a probiotic—the live organism—and you're taking the prebiotic—the microbe food—at the same time.

Now, a postbiotic is really a microbial leftover or an end metabolite, so it's specifically a preparation of inanimate or usually killed microbes and their metabolic bits, so to speak. So it might be the dead organisms themselves that might be having a benefit; it might be the metabolites that they've generated that are still present in the package that you're consuming, but they're no longer alive, unlike probiotics or synbiotics.

Dr. Buch:
Thank you very much. And this leads to another question that I'm sure you've had asked of you many times. Patients come up and ask, "Which of these products should I be using?"

Dr. Weingarden:
Oh gosh. That's a very loaded question. It's also a very complicated one because, to start off with, although we think these products are generally safe, they're not usually regulated by the FDA. And that means that the companies that make them don't have any necessity to determine that they've got the right organism, that the organisms are alive, and that they're doing the thing that we think they're doing. And so that makes it very hard to say one product is really good and the other products are not very good, at least with the testing we currently have.

But there is one particular product formulation called the De Simone formulation. It's a set of eight probiotic organisms combined together, and the company that makes that states that they're very good about making sure they're including the right organism and

enough live colony-forming units, or CFUs, of each of those organisms. So you could make the argument maybe that one's a little bit better, but overall, it's hard to say that one product is truly better than another.

Dr. Buch:
So that's a wonderful segue to go into some details. What do current guidelines recommend when it comes to using probiotics to prevent Clostridium difficile?

Dr. Weingarden:
So, interestingly, the most recent guidelines in the past five years or so—there's one from the ACG, the American College of Gastroenterology, and then the AGA, the American Gastroenterological Association—that actually had slightly different takes on whether probiotics were a good idea to use to prevent C. difficile infection.

So the ACG guideline actually recommends against using probiotics both to prevent an initial episode of C. difficile infection, and they don't think they're a useful, good idea to prevent a recurrence of the infection once you've had an infection the first time. The AGA was a little bit more ambivalent. They had a conditional recommendation for certain strains that might be useful. Predominantly, what they state is to prevent recurrence, so questionable if they were really coming out and saying this is useful for preventing an initial episode of C. difficile infection. But maybe there's some benefit for recurrence.

A lot of this is based on the PLACIDE trial that looked at whether if you had hospitalized adults who were at higher risk of getting an initial C. difficile infection and you gave them probiotics, there was any benefit, and it was pretty mixed. So I think that's why especially the ACG ruled against using them. And even though the AGA technically has this conditional recommendation, I think the majority of GI providers, especially those that are more closely hooked into the AGA and ACG guiding bodies, would probably say these are probably not a great idea for C. difficile infection.

Dr. Buch:
Thank you for that. And what is the latest evidence about probiotic use in pouchitis?

Dr. Weingarden:
Yeah, that's a really interesting situation. I have to say this is probably the area that there is the best data that there's some benefit to using a probiotic. And again, if you look at the most recent AGA recommendations, they actually do give probiotics a conditional recommendation specifically to prevent a reoccurrence of pouchitis.

Of course, this comes with a lot of caveats. First of all, they're predominantly recommending that De Simone eight strain combination of organisms. That's really where the best data are—not so much in other probiotic preparations. If you look at some of the larger meta-analyses with, again, this particular preparation, there does seem to be some evidence that there's maybe some efficacy in preventing an initial episode of pouchitis, but really where the data is strongest is, again, the secondary prevention—so preventing a reoccurrence of pouchitis in someone who had an episode already and then responded to an antibiotic at that time.

Dr. Buch:
Thank you.

For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Alexa Weingarden about how we should be using probiotics.

Shifting gears, Dr. Weingarden, what should we know about microbiome testing and how it informs probiotic use?

Dr. Weingarden:
I'm sure many of us have encountered patients who have gotten one of these commercial microbiome analyses tests, and then they come in and say, "Look, it says my microbiome is altered." Unfortunately, I think that probably winds up just causing more anxiety for patients than giving them or us as clinicians any beneficial information that we can really use to help them.

We know that there are alterations in gut microbial composition or function in different conditions that might either predispose to those conditions or, in some cases, could be a signal that something has gone awry that's led to the disrupted gut microbial community. Again, by and large, the clearest signal for this is in recurrent C. difficile infection, but if someone has recurrent C. difficile infection, they probably don't need a commercial gut microbial analysis test to tell them or us that something's gone awry with their gut microbiome.

And outside of that condition, I would say even though we do see trends towards community composition, and in some cases, even particular species as being either beneficial or harmful in different conditions, I think we're a long ways away from saying you should therefore run out and get a gut microbial analysis test to determine if you're at risk for one of these things. Again, other than C. difficile infection, I don't think we have any clear data that on a population-wide level that's a test that we could really rely on to determine

someone's risk for a particular disease.

Dr. Buch:
So basically, not ready for primetime?

Dr. Weingarden:
I don't think so, no.

Dr. Buch:
Thank you. And looking ahead, what role do you see microbiome engineering playing in patient care?

Dr. Weingarden:
Yeah, this is a really exciting field. In particular, one issue with probiotics is whether or not these organisms are even capable of colonizing the GI tract in different individuals. And the beauty or the hope of these engineered gut microbial communities is that we're starting with organisms that are already well adapted and well suited to living in the human gut, and so this engineered community has a better chance of taking root. It's a mixture of organisms that might have interconnected metabolic functions that can support each other's growth as well as ideally the production of metabolites or other molecules that are beneficial to the host.

This is an area that's still in its infancy, but I think long term, it's probably going to be more likely to have an impact than individual or even combination probiotics by themselves. The most obvious area that I think people are looking into right now to use these engineered gut microbial communities is in recurrent C. difficile infection because that's the place where we already know there's really the strongest signal for reconstitution of the normal gut microbial community as being truly the way that we need to treat this disease.

So I think that's the initial bar to hit for these engineered communities—can they be beneficial for recurrent C. difficile infection? And if so, can you start to look at some of the more subtle changes that we see in different diseases, and can we alter the microbial community? Can we give someone an artificial or synthetic microbial community that will have a benefit in those conditions as well?

Dr. Buch:
Thank you. Do you see any future for microbiome engineering in inflammatory bowel disease?

Dr. Weingarden:
Oh yeah, that's another really hot area. I hope so. I think that unlike in C. difficile infection, it's a lot less cut and dry how exactly the gut microbiome is disrupted from patient to patient and from subtype to subtype of IBD, and therefore, of course, if we don't understand really well how these things are disrupted, then it becomes harder to design something that can treat them.

And I think a lot of this is going to come down to being more and more headed towards a personalized medicine direction. So at the end of the day, the most likely beneficial path forward is probably going to be by understanding, if not person to person, then at least within different subtypes of IBD, what's been altered in the gut microbial communities. And therefore, can we have a set of products ready to go that are going to be tailored directly towards those individuals or those subtypes?

So again, I think the disruptions are just more subtle than they are in recurrent C. difficile infection, and that just means that we're going to need to be more flexible in terms of the individualized, potentially synthetic microbial communities that we can give to individual patients.

Dr. Buch:
Thank you. And before we wrap up, Dr. Weingarden, do you have any additional thoughts you'd like to share with our audience today?

Dr. Weingarden:
When you think about probiotics, prebiotics, and these over-the-counter therapies that are widely available, a lot of the issues come down to inconsistency in terms of regulation of the products as well as even which species or which strains have been used across different studies. And I think until we get to that point where we're able to really standardize those things, it's going to be hard for most conditions to say that we could move forward with these probiotics as a recommended therapy. And that's probably why this increased interest in synthetic microbial communities is probably going to take over because almost by definition, they have to be really well regulated. They have to be really well defined. And that's already a much better starting point than most of these over-the-counter probiotics.

Dr. Buch:
I want to thank my guest, Dr. Alexa Weingarden, for an excellent update on probiotics.

Dr. Weingarden, it was a pleasure speaking with you today.

Dr. Weingarden:
Thank you, Dr. Buch. Thanks for having me on.

Dr. Buch:
It was our pleasure. For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit *GI Insights* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening, and looking forward to learning with you again very soon.