Beyond R_x: OTC Corner

Probiotics in clinical practice

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Probiotics may be beneficial for antibioticassociated diarrhea, digestive symptoms, necrotizing enterocolitis, respiratory tract infections, and other health conditions.



Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host."1 This definition necessitates that probiotics must be alive when administered (dead microbes cannot be called probiotic), must be the subject of research documenting health benefits (usually in humans, but probiotics are also used in companion and agriculture animals), and must be microbiologically defined. Mixed cultures (as found in fermented foods) or undefined mixtures (as comprising fecal microbial transplants) are not microbiologically defined to the strain level and do not meet the definition of a probiotic. Some publications have suggested that dead bacteria can have positive physiologic effects, but such products are not probiotics.

GENUS, SPECIES, AND STRAIN IDENTITY

The microbes most often used as probiotics include species of the genera *Lactobacillus* and *Bifidobacterium*. Other probiotics include the lactic culture, *Streptococcus thermophilus*, the yeast, *Saccharomyces cerevisiae* (biovariant *boulardii*), and the bacterial sporeformer, *Bacillus coagulans*. Each probiotic should be identified using current methods to the species or, if applicable, subspecies level. Furthermore, a strain designation for each strain should be provided. For example, the probiotic "*Lactobacillus acidophilus* NCFM" (genus, species, and strain, respectively) refers to a specific strain of *L acidophilus*. Some probiotic benefits are likely a general property of a species, so all strains of that species are expected

This article is part of an ongoing series entitled, **Beyond** R_x : **OTC Corner**, which will include topics such as OTC medications, dietary supplements, and other health care approaches that will help nurse practitioners and physician assistants provide patients with tools to manage their health.

Robert D. Sheeler, MD, is guest editor of the series. He is an associate professor of family medicine, Mayo Clinic, in Rochester, Minn. He is board certified in family medicine, integrative medicine, and holistic medicine. to impart the benefit. For example, yogurt cultures (*L bulgaricus* and *S thermophilus*)—regardless of the strain—seem to aid lactose digestion in situ; however, for most specific, clinical benefits, the strain identity is important because different strains can use different mechanisms of action and ultimately have different physiologic effects. Research should always identify the probiotic to the strain level, and commercial probiotics should disclose the strain designation so that consumers and health care providers can link studies to specific probiotic strains.

REGULATORY CATEGORIES OF PROBIOTIC PRODUCTS

Probiotics encompass a broad range of product types, including foods, supplements, medical foods, drugs, infant formula, animal foods, nonoral applications, and even devices (such as tampons with probiotics). Although foods and dietary supplements are the most common product types, probiotic drugs are sure to be developed from targeted probiotic research dovetailed with human microbiota findings. Probiotic supplements are typically capsules or powders that often deliver 1 billion bacteria or more per dose. Probiotic drugs (and some devices) require premarket approval of safety and efficacy by the FDA. The remaining categories of products previously listed do not. Claims and safety standards differ depending on the regulatory category. Whereas a drug is intended to cure, treat, prevent, or mitigate disease, and is targeted for a healthy or diseased person, a food or dietary supplement cannot make a drug claim, and is intended for the generally healthy population.

PROBIOTIC PRODUCT LABELS

The following information optimally should be provided on a probiotic product label or accompanying website. Many products on the market do not fully provide this information; missing information makes it difficult for health care providers to best match probiotic products with client needs.

- Identification of the genus, species, and strain of each probiotic present in the product
- The level of each probiotic strain in the product through the end of shelf life; products labeled with a live count "at time of manufacture" are suspect, because it is unclear if an efficacious level will be in the product at time of consumption
- Indication of the health benefit(s) associated with the product; note that there are regulatory restrictions on

what types of information can be communicated for different categories of products

- Product information website
- Proper storage conditions
- Recommended dose based on the level shown to be effective in the published studies

DOSE

It is not possible to state one dose for all probiotics. The dose must be specific to the product based on the benefits shown to be delivered at that dose in clinical trials.

WHAT HAPPENS ONCE YOU CONSUME A PROBIOTIC?

The probiotic definition does not dictate a method of administration. Probiotics are being studied as a topical application for skin and an intravaginal application for urogenital infections. Most probiotics are taken orally, as foods or dietary supplements. Probiotic strains-even those isolated from human sources-generally do not last in a consumer's intestinal tract for more than 2 weeks. This is because the normal microbes colonizing the digestive tract effectively prevent transient microbes from colonizing. Therefore, regular consumption of probiotics is necessary for continued benefits. The benefits that probiotics impart are incurred during their transit through the alimentary canal, including the mouth, stomach, small intestine, and large intestine, into a woman's vaginal tract, and onto a newborn's body. Mucosal interfaces along this path provide a means for probiotics to intimately interact with the host immune system, and the relatively slow transit through the colon provides enough time for dynamic metabolic activity that can affect colonizing microbes or host cells, and interaction with the CNS through the vagus nerve. Bron and colleagues² provide an excellent review of probiotic mechanisms of action.

SAFETY OF PROBIOTICS

Probiotics have been studied and used safely for decades. Many probiotics were isolated either from the native microbiota of healthy humans or from fermented foods. Thus, traditional probiotics comprise genera and species with a history of safe use. They are included on the European Qualified Presumption of Safety list for live microbes used in foods. Many probiotic strains have also undergone testing and review and have fulfilled the FDA status of "Generally Recognized as Safe" for use in foods. Although more complete reporting of safety end points in published studies would be useful, most experts in the field recognize that use of common probiotic *Lactobacillus* and *Bifidobacterium* species and *S cerevisiae* (biovariant *boulardii*) in the generally healthy population carries little risk. Newly proposed probiotic species that do not have a history of safe use, such as those identified through the human microbiome project, will require safety assessments. In addition, use of probiotics in vulnerable populations may require more stringent quality standards than those for use in the general population.

BENEFITS OF PROBIOTICS

Studies have provided evidence for efficacy of some probiotics for different health and clinical conditions, including antibiotic-associated diarrhea, digestive symptoms (including those associated with irritable bowel syndrome), necrotizing enterocolitis, respiratory tract infections, acute pediatric diarrhea, and pediatric eczema. Health care providers in the United States and elsewhere use probiotics in their practices, even though the quality of evidence varies and additional, well-controlled human trials would enable stronger conclusions on best probiotic use. Hospital formularies often carry one or more probiotics, but the ones carried are not necessarily probiotics with best evidence. Clinical use of probiotics for vulnerable patients (such as premature infants or critical care patients) must be done with care. Probiotics for such uses should have demonstrated safety for the target patient population and should meet high quality standards. In cases in which patient vulnerability is not a concern, probiotics may be a low-risk option for conditions lacking suitable, safe interventions.

Research on new applications for probiotics includes use for different mental health conditions, such as depression, anxiety, and autism, and some metabolic syndrome applications, such as weight management, cholesterol lowering, and insulin sensitivity.

See *Table 1* for a list of end points with positive outcomes for probiotics.

Resources

- usprobiotics.org
- isapp.net/Probiotics-and-Prebiotics/Resources

CHOOSING A PROBIOTIC PRODUCT

Not all probiotics are the same. Different strains of even the same species may function differently, and different commercial probiotics have been studied for different effects. Furthermore, each person has unique colonizing microbes, host genetics, and diet and medication usage; therefore, each person has the potential to respond to probiotics differently. Those interested should choose a probiotic made by a reputable company and tested for the desired outcomes. Pragmatism may rule the day; if after 2 to 3 weeks a probiotic does not seem to be working, it should be exchanged for another one.

FREQUENTLY ASKED QUESTIONS

Do we naturally harbor probiotics in our bodies?

We naturally harbor many potentially beneficial bacteria. Probiotic bacteria are frequently derived from these normal colonizing bacteria. Commensal microbes may be beneficial; however, until they are isolated, characterized, and shown in human studies to impart a health benefit, they cannot be accurately called "probiotic."

Are the best probiotics isolated from a human?

Some hypothesize that a probiotic isolated from a human has properties that make it better able to function in a human. However, bacteria that are native to one person are foreign to another. Furthermore, several probiotic strains not isolated from humans have been shown to have health benefits (such as strains of *Bifidobacterium animalis* subsp *lactis*). It is important to know whether human studies have shown the probiotic in question to be effective and safe.

Are refrigerated probiotics best?

In general, microbes survive better at lower temperatures. However, technologies for keeping probiotics alive at room temperature have been developed by product manufacturers. It is not necessarily the case that refrigerated products will be superior to those that are not refrigerated.

Many probiotic yogurts and other food products contain added sugar. Does this negate any health benefits from probiotics?

There is no evidence that the sugar added to sweetened yogurt negates the health benefits associated with the probiotics contained in the yogurt. Sugar is digested and absorbed in the small intestine and would not be expected

TABLE I. Potential clinical uses of probiotics

Condition/Benefit	Strain(s)	Product
Treatment of acute diarrhea, adult		
Treatment of acute diarrhea, pediatric	Lactobacillus rhamnosus GGL reuteri DSM 17938	CulturelleBioGaia dropsBioGaia chewable tablets
Treatment of mild to moderate irritable bowel syndrome symptoms or other functional bowel symptoms	 Bifidobacterium infantis 35624 L plantarum 299v B animalis subsp lactis (DN-173 010) starter cultures L paracasei Shirota 	• Align • TuZen, GoodBelly • Activia • Yakult
Treatment of vaginitis	L rhamnosus GR-1, L fermentum RC-14	RepHresh Pro-B Fem-Dophilus
Prevention of antibiotic-associated diarrhea: • Adult	• L acidophilus CL1285, L casei LBC80R	• BioK+
• Adult and pediatric	• L rhamnosus GG	• Culturelle
• Adult and pediatric	• Saccharomyces cerevisiae var boulardii	• Florastor
Prevention of <i>Clostridium difficile</i> in hospitalized patients on antibiotics	 <i>L acidophilus</i> CL1285, <i>L casei</i> LBC80R <i>S cerevisiae</i> var boulardii 	• BioK+ • Florastor
Treatment of eczema, infant	L rhamnosus GG	Culturelle
Treatment of necrotizing enterocolitis*	Various Lactobacillus and Bifidobacterium strains tested	
Treatment of colic	L reuteri DSM 17938	BioGaia drops, BioGaia chewable tablets
Cholesterol lowering	Lactobacillus reuteri NCIMB 30242	Cardioviva
Treatment of mildly active ulcerative colitis or pouchitis and maintenance of remission	Multiple strain blend of <i>Lactobacillus</i> , <i>Bifidobacterium</i> and <i>Streptococcus thermophilus</i> ; strain designations not disclosed	VSL#3
Reduced incidence and duration of common infectious diseases: • Adult	• Lactobacillus plantarum HEAL9, Lactobacillus paracasei 8700:2	• UltraFlora Cold Support
• Pediatric	• Lactobacillus reuteri DSM 17938	• BioGaia drops, BioGaia chewable tablets
• Pediatric	• Lactobacillus acidophilus NCFM, Bifidobacterium animalis subsp lactis Bi-07	• UltraFlora Children's
• Pediatric	• Lactobacillus paracasei CNCM I-1518	• DanActive

Probiotics for particular conditions that have been studied in at least one properly designed randomized trial. In the United States, foods and dietary supplements are not intended to cure, treat, prevent, or mitigate disease; therefore, the uses noted may represent off-label uses. Clinicians must evaluate their patients' conditions, review any applicable manufacturers' product information, and compare with recommendations of recognized authorities. This information is provided to medical professionals for information purposes only.

*Hospital protocol required; prophylactic probiotics administered to premature infants significantly reduced the incidence of severe stage II to III necrotizing enterocolitis and all-cause mortality.⁶ Data from Skokovic-Sunjic D³; Guarner F et al.⁴; Floch MH et al.⁵

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to interfere with microbial effects farther down the intestinal tract. However, studies comparing identical probiotic products with and without added sugar have not been conducted. When choosing probiotic foods, these foods should be part of a balanced diet.

Are probiotics still alive if they are dried?

If bacteria are dried and stabilized properly, they remain alive (although dormant) and start to grow again after they reach the moist environment inside your body.

How do probiotic foods differ from fermented foods?

Probiotics must be researched and shown to have health benefits. Unless the cultures in a fermented food have been defined and the food shown to have health benefits due to the live microbes in it, fermented foods do not reach the standard of a probiotic. This is contrary to many popular press communications touting the so-called probiotic benefits of fermented foods such as kim chi, sauerkraut, aged cheeses, kefir, and kombucha tea. Emerging research suggests that our microbiota is deficient and that adding live microbes (including those from fermented foods) may be beneficial to health. However, those assertions are untested hypotheses, not the subject of controlled research. Although fermented foods are tasty, nutritious, and beneficial to health, their study falls short of the scientific rigor needed to elevate them to the status of probiotic. Some probiotic yogurts that are researched are fermented foods that are also probiotic foods.

Can products containing live bacteria that have not been tested in human studies still be effective?

Some companies know very little about the specific health effects of the bacteria they are selling. Scientific studies are expensive to conduct, and not all companies sponsor them. If studies have not been conducted on a strain, it is not known if the strain can survive and function as a probiotic in the human body. A strain that has not been studied for human health effects *might* be effective. But such a product, in general, cannot be strongly recommended. It is best to purchase a product made by a trustworthy company that can provide documentation of its health effects.

Which are better: foods or supplements?

Probiotics from either foods or pills can be effective. The important consideration is that you are getting high enough numbers of a strain or combination of strains that have been tested for efficacy and work for you. Food sources of probiotics have the advantage in that they can offer good nutrition along with the probiotic bacteria. Supplements can be more convenient for some people and may provide higher levels of probiotic, depending on the specific products.

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"And will you be taking part in our toxicology study tonight?"