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answering frequently asked questions about probiotics

introduction

With the growing appreciation for the role of the human microbiota in health, a diverse range of health benefits have been increasingly recognized.¹ The intestinal flora, in particular, may impact human health through various protective, structural, and metabolic functions.² Although these mechanisms have not been fully characterized, probiotic bacteria are believed to confer health benefits by bolstering these effects.³ Research regarding probiotics has exploded over the past decade, with the volume of medical literature involving these agents increasing more than 10-fold in the past decade, compared to the previous decade.⁴ Probiotics are a growing trend in the marketplace, attributable to increasing consumer education and awareness as well as new product introductions. In recent years, hundreds of probiotic foods, beverages and supplements have become available in the U.S. market,⁵ with claims of offering various health benefits. The retail sales of probiotic supplements in the U.S. continues to grow each year, exceeding 800 million in 2012.⁶ This growth is consistent with current initiatives emphasizing the patient-centered medical home model of care, a partnership between primary care practitioners, patients and their families that encourages patients to have the education and support they need to make decisions and participate in their own care.⁷ Despite the interest and extensive research in probiotics, many questions about these products remain, among both healthcare providers and patients.

This publication features the insights of Leonard Fromer, MD. Dr. Fromer is the Executive Medical Director of the Group Practice Forum in Los Angeles, California and Assistant Clinical Professor in the Department of Family Medicine at the University of California at Los Angeles. He has been in private practice in Santa Monica, California, with Prairie Medical Group for 28 years. He lectures extensively on the topics of health system reform, the patient-centered medical home and the accountable care organization.

common questions about probiotics

What is a probiotic?

Probiotics are defined by the Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) as live microorganisms, which when administered in adequate amounts, confer a health benefit on the host.⁸ Probiotics can be typically naturally occurring microbes, such as those used in foods or isolated from humans or animals, or microbes that have been genetically altered for a specific effect.⁹ Although many probiotics are considered to be live cultures, the terms are not synonymous. Live cultures—but not all probiotics—are associated with foods as food fermentation agents.¹⁰ However, live cultures have not necessarily been tested for health benefits. Similarly, the term probiotic is not synonymous with native commensal bacteria, although they may be isolated from the same source.^{3,10} In order to be considered a probiotic, the native commensal bacteria must be shown to have a health benefit when administered to humans.

Is a probiotic the same as a prebiotic?

Prebiotics are non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and activity of one species or a limited number of species of bacteria in the colon.^{11,12} Unlike probiotics, prebiotics are not alive, are usually carbohydrates, act on microbiota and focus on the colon as opposed to probiotics, which are live microorganisms that can act on numerous sites around the body.^{10,13}

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What is the difference between probiotic supplements and yogurts?

While it is true that yogurts contain live bacteria as starter cultures, not all of the live active cultures in yogurt have been shown to provide a health benefit.¹⁰ Further, the delivery of probiotics in either yogurt or fermented milk is limited by the need for cold storage and an associated shorter shelf life. However, as Dr. Fromer pointed out, this may be due to “spoilage of the dairy component of the yogurt, not the cultures themselves.” If looking for a yogurt with probiotic benefits, it is important to differentiate between starter cultures and added probiotic bacteria. Further, up to three daily servings may be required to achieve all of the claimed health benefits of some probiotic yogurts.¹⁴

How are probiotics regulated in the United States?

Most probiotics in the U.S. are available and regulated as foods or dietary supplements; there are currently no approved probiotic drugs in the U.S. The U.S. government regulates dietary supplements on the basis of the Dietary Supplement Health and Education Act (DSHEA) of 1994, which was enacted to provide the legal framework specifically for dietary supplements.¹⁵

Why do the packaging/materials on probiotic products in the U.S. state that they “have not been evaluated by the Food and Drug Administration (FDA)?”

Under DSHEA, claims are not approved by the FDA and products may not claim to diagnose, mitigate, treat, cure or prevent a disease.¹⁵ Rather, DSHEA allows for structure/function claims and claims of general well-being. Thus, dietary supplements that make claims to benefit structures or functions of the human body (such as digestive health) are required by the FDA to carry the following DSHEA disclaimer: “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.”¹⁵

Are all probiotics the same?

Probiotic products contain microbes that can differ by genus, species and even different strains of the same species.³ Because the health benefits of probiotics are strain-specific, probiotics within the same genus, or even species, do not necessarily provide the same benefits. The effect(s) of a probiotic can only be attributed to the strain or strains tested, and not to the group of probiotics as a whole.¹¹

The concept of strain specificity can be clearly illustrated by an *E. coli* example. One strain of *E. coli* (*E. coli* Nissle 1917) has been shown to have a positive gastrointestinal (GI) health benefit, where as a different strain of *E. coli* (*E. coli* O157:H7) has not demonstrated a health benefit, and in fact can cause serious food poisoning.^{16,17} These differences may be related to the genetic make-up of bacteria which diverges and becomes more specific at the strain level. There are many examples of probiotic products marketed as different strains of the same species (e.g., *Lactobacillus acidophilus* NCFM and La-1; *L. rhamnosus* GR-1 and GG; *Bifidobacterium infantis* 35624 and *Bifidobacterium infantis* SD-5845; *Bifidobacterium lactis* HN019 and BB-12).³ Clinical support to substantiate health benefit claims must be shown for each probiotic strain. Data from studies conducted on specific strains cannot be used as evidence to support health effects of untested strains.¹¹

How are probiotics dosed?

The amount of a probiotic is usually expressed as the number of colony-forming units (CFUs), which is a way of expressing the number of viable microbes per serving.¹⁸ The optimum amount of a probiotic is the amount that has been shown to have a health benefit in human studies. The required amount of probiotics may vary greatly for

different strains and the specific health effect under investigation, with efficacious amount ranging from 50 million to more than one trillion CFUs/day.³ Different probiotics are recommended for use at different amounts (**Table 1**).

Table 1. Labeled directions for various probiotic products

Product Name	Strain(s)	Recommended CFUs*
Align®	<i>Bifidobacterium infantis</i> 35624	1 billion once daily ¹⁹
Culturelle® Digestive Health	<i>Lactobacillus rhamnosus</i> GG	10 billion once or twice daily ²⁰
Florastor®	<i>Saccharomyces boulardii</i> lyo	5 billion twice daily ²¹
Phillips® Colon Health®	<i>Lactobacillus gasseri</i> KS-13, <i>Bifidobacterium bifidum</i> G9-1, <i>Bifidobacterium longum</i> MM-2	1.5 billion once daily ²²
Digestive Advantage® Daily Probiotic	<i>Bacillus coagulans</i> GBI-30, 6086	2 billion once daily ²³

*CFUs, colony-forming units

Package directions for use:

Align®: Directions: Take one capsule per day. Store at room temperature.

For best results store in the original blister package.

Culturelle® Digestive Health: Suggested use for adults: As a dietary supplement, take one (1) capsule per day to support digestive and immune health.

Continued daily use is suggested. If experiencing digestive upset, two (2) capsules daily are recommended until discomfort subsides. When traveling, take two (2) capsules daily throughout the trip. Best results if started two to three days prior to travel. For children over 1 year of age: Take one (1) capsule daily.

Capsule may be opened and mixed into cool drink or food. Do not add to warm or hot foods or beverages. Consult your medical professional for more information.

Florastor®: Suggested Use: One (1) capsule in the morning, one (1) capsule in the evening.

Phillips® Colon Health®: Directions: Adults and children 3 years of age and older: Take one (1) capsule daily with a meal. Children under 3: Consult a doctor.

Digestive Advantage® Daily Probiotic: Directions: Adults 18 and over take one (1) capsule daily with water.

All trademarks are the properties of their respective owners.

Are higher amounts of probiotics better than lower amounts?

A recent consumer publication rated marketed probiotic products and yogurts on the basis of how many CFUs they deliver per unit cost, suggesting that products containing higher amounts of probiotics are more effective.²⁴ Despite this common misconception, however, the amount of a probiotic should be based on human studies showing a health benefit. It is not possible to make general recommendations about the minimum amount of probiotics that is needed for an effect.^{3,10,11} There is no minimum or maximum number of bacteria that must be ingested to obtain a beneficial effect. Dr. Fromer stated “more is not necessarily better” specifically as it relates to amount or, as will be discussed below, number of strains.

Are more strains better?

A probiotic with multiple strains is not necessarily better than a probiotic with a single strain. Although using multiple strains may be thought to more closely replicate the normal GI environment, which contains hundreds of diverse bacterial species,^{2,25} few studies have assessed the health effects of single-strain probiotics versus those of multispecies or multistrain products. There is no minimum or maximum number of strains of bacteria that must be ingested to obtain a beneficial effect. To the contrary, the American College of Gastroenterology (ACG) has stated that there is no evidence to support the claim that either preparations with multiple species/strains or higher concentrations of bacteria is associated with better health benefits.²⁶ Further, it is important to evaluate the compatibility of the strains in a multiple-strain probiotic product to ensure that the combination of strains has a synergistic rather than antagonistic effect.²⁷

How can I evaluate the credibility of a probiotic product?

Given the growing number probiotic products on the market and the misconceptions regarding these products, various scientific organizations have developed criteria to help healthcare professionals and patients evaluate and guide appropriate selection of these products (**Table 2**). Not all products on the market claiming to be probiotics meet these key minimum criteria.^{10,11} Strain specificity is recognized by national^{28,29} and international^{11,18,30} organizations as a key factor in determining the credibility of a probiotic product.

Recognizing that different strains of even the same species can be different, probiotics should be identified to the strain level.^{10,12,18,28,30} The labeled strain should have been shown in human studies to benefit human health.^{10,18} In addition to containing the specific strain(s) of bacteria that was used in the published research, the product should contain the same levels that was used to demonstrate a health benefit.¹⁸ Despite these criteria, some products labeled as “probiotics” do not contain adequate levels of clinically validated strains.^{10,31,32} Commenting on these observations, Dr. Fromer noted the importance of quality control in determining the credibility of a product. “You want to get something from a manufacturer that you have confidence in, and you want to know that what the label says actually reflects the content of the product.”

Table 2. Organizations With Published Statements Regarding Probiotic Products^{11,19,26,28-30,33}

- American Academy of Microbiology (AAM)
- American College of Gastroenterology (ACG)
- American Gastroenterological Association (AGA)
- International Scientific Association for Probiotics and Prebiotics (ISAPP)
- National Center for Complementary and Alternative Medicine (NCCAM)
- World Gastroenterology Organisation (WGO)
- Food and Agriculture Organization/World Health Organization (WHO)

What information should the label of a probiotic product contain?

Given the recognized importance of strain specificity and amount, the labels of probiotic products should indicate the following information, at a minimum, to help guide product selection (**Table 3**).^{10,18,28}

Table 3. Key Information for Probiotic Labeling^{18,30}

Information	Comments
Genus, Species, and Strain	A listing of only the bacterial group and species is not sufficient to support strain-specific health claims.
Amount in CFUs, Suggested Serving Size, and Expiration Date	Packaging should ensure an effective level of live bacteria through the “best by” or expiration date.
Health Benefits	Claims of health benefits should be based on human studies conducted on the product or specific strains in the product.
Storage Instructions	As living organisms, probiotic products can lose viability if not stored properly. Some products require refrigeration, while others do not.
Corporate Contact Information	The product manufacturer should be able to provide information regarding the content of the product, storage instructions, and health benefits. The use of products manufactured by well-established and trusted companies is encouraged. ²⁸

Are probiotics safe?

Although probiotics are considered safe for the generally healthy population, there have been reports associating specific strains with severe illness in certain medical settings (e.g., intensive care settings, catheter line contamination).^{26,34,35} Complications from probiotics are rare, but appear to occur more frequently in immunocompromised patients and/or in those with underlying medical conditions.^{9,26} It has been suggested that caution be used when considering probiotic use in certain populations, including newborns, immunocompromised patients, patients with severe underlying illness or short bowel patients.³ As with other dietary changes, patients should be properly evaluated to determine if probiotics are right for them.

What are some resources that are available to help patients understand probiotics?

Several organizations such as the AGA, the ACG, the ISAPP and the NCCAM/NIH provide educational resources on their Web sites for helping patients/patients better understand and choose probiotic products appropriately (**Table 4**).^{18,26,28,29}

Probiotic Resources For Your Patients^{18,26,28,29}

- American Gastroenterological Association (AGA)
<http://www.gastro.org/patient-center/diet-medications/probiotics>
- American College of Gastroenterology (ACG)
<http://patients.gi.org/topics/probiotics-for-the-treatment-of-adult-gastrointestinal-disorders/>
- International Scientific Association for Probiotics and Prebiotics (ISAPP)
http://www.isapp.net/docs/Consumer_Guidelines_final.pdf
- National Center for Complementary and Alternative Medicine (NCCAM)
National Institutes of Health (NIH)
<http://nccam.nih.gov/health/probiotics/introduction.htm>

conclusions

Despite growing interest and recognition of health benefits associated with probiotics, there are many questions regarding these products. Probiotics are live microorganisms that confer a health benefit on the host,⁸ but live cultures or yogurts are not necessarily probiotics.¹⁰ Although many patients and healthcare providers may question if all probiotics are the same, the efficacy of a probiotic depends on the demonstration of health effects of the particular strain or combination of strains (not only genus or species) in clinical studies. Thus, strain specificity is a key criteria in determining the credibility and health benefits of a probiotic product.^{11,18,28-30} Similarly, despite a popular belief that “more is better,” the amount of various probiotics demonstrated to have health effects varies widely, and there is no minimum or maximum amount of bacteria that must be ingested to achieve a beneficial effect.^{3,10,11} A probiotic with a higher amount of

microbes is not necessarily more effective than a lower amount, nor is a product containing multiple strains necessarily better than a single-strain product. Although choosing among various probiotics can be complicated by misinformation and the growing number of these products, patients and healthcare providers can evaluate products by ensuring that the health claim(s) are substantiated with well-controlled strain-specific studies and have been adequately characterized for strain, amount and stability.

DSHEA allows for structure/function claims and claims of general well-being and should promote, support, maintain a healthy body system. Under this provision, certain probiotics can be important for maintaining and supporting digestive health. As our health system rapidly moves to a model of patient-centered and patient-activated care processes, healthcare providers must direct more time and effort in maintaining wellness for our patients.

What is Align? Align is a daily probiotic supplement that helps promote a healthy digestive system.* With continued daily use, Align fortifies the digestive system with healthy bacteria to help build and support a healthy digestive system and help maintain digestive balance.*

What is Bifantis? Bifantis is the trademarked name for a unique, patented strain of probiotic bacteria, *Bifidobacterium infantis* 35624. Bifantis is the natural probiotic ingredient found only in Align. For more information about the unique strain of probiotic bacteria found in Align, visit www.bifantis.com

How many bacteria are in each capsule of Align? Each Align capsule contains at least 1×10^9 (one billion) colony-forming units (CFU) of live Bifantis bacteria at the time of manufacture and 1×10^7 live Bifantis bacteria at expiry date. Align contains an effective level of probiotic bacteria throughout the shelf life of the product.

How does Align compare to other probiotics available in the US? The benefits of probiotics are strain specific. Only Align contains the patented probiotic strain, *Bifidobacterium infantis* 35624 (Bifantis®). No well-controlled clinical trials comparing the efficacy and safety of the various probiotics available in the U.S. have been performed.

What forms does Align come in? How often do I need to take Align? Align comes in a capsule that you take once a day, each day. Align can be taken at any time of the day, with or without food.

Does Align need to be refrigerated? No, it is not necessary to refrigerate Align.

Are there any known interactions with medications with Align? Align has no known clinically meaningful interactions with medications. However, some antibiotics may make Align less effective. For example, Bifantis, the probiotic in Align, is susceptible to antibiotics with gram-positive coverage, including ampicillin, ciprofloxacin, erythromycin, gentamycin, penicillin and vancomycin.

What are the side effects of Align? In clinical studies, there was no significant difference in side effects between Align and placebo. Side effects, if they occur, tend to be mild and digestive in nature. As with other probiotics, in the first few days of taking Align, some patients have reported experiencing some gas and bloating. This may be temporary while their systems are adjusting to Align.

Is there anybody who should not use Align? Individuals who have allergies to milk and/or milk protein should not use Align, as Align contains small amounts of milk and milk protein. Milk is used in the culturing of the bacteria and sodium caseinate (milk protein) is added during the freeze drying process. Patients with serious or chronic gastrointestinal (GI) conditions should be properly evaluated to determine if Align is right for them.

Can Align be used in patients who are pregnant/breastfeeding/trying to become pregnant? Align has not been studied in pregnant or breastfeeding women, or in women trying to become pregnant. A review of available probiotic data provides no evidence to suggest a cause for concern with the use of supplements containing *Bifidobacterium*. As with other dietary changes, these patients should be evaluated to determine if Align is right for them.

Can Align be used in patients who are severely ill or immunocompromised? Align has not been studied in people who are severely ill or immunocompromised. A review of available probiotic data provides no evidence to suggest a cause for concern with the use of supplements containing *Bifidobacterium*. As with other dietary changes, these patients should be evaluated to determine if Align is right for them.

***THESE STATEMENTS HAVE NOT BEEN EVALUATED BY THE FOOD AND DRUG ADMINISTRATION. THIS PRODUCT IS NOT INTENDED TO DIAGNOSE, TREAT, CURE OR PREVENT ANY DISEASE.**

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