COURSE #98060 — 2.5 CONTACT HOURS/CREDITS RELEASE DATE: 11/01/22 EXPIRATION DATE: 10/31/25

Microbiome Medley: Pre-, Pro-, and Postbiotics

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

Chelsey McIntyre, PharmD, is a clinical pharmacist who specializes in drug information, literature analysis, and medical writing. She earned her Bachelor of Science degree in Genetics from the University of California, Davis. She then went on to complete her PharmD at Creighton University, followed by a clinical residency at the Children's Hospital of Philadelphia (CHOP). Dr. McIntyre held the position of Drug Information and Policy Development Pharmacist at CHOP until her move to Washington state in 2017, after which she spent the next six years as a clinical editor for Natural Medicines, a clinical reference database focused on natural products and alternative therapies. She continues to create rigorous professional analysis and patient education materials for various publications while also practicing as a hospital pharmacist. Her professional interests include provider and patient education, as well as the application of evidence-based research to patient care.

Faculty Disclosure

Contributing faculty, Chelsey McIntyre, PharmD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planners/Director Disclosure

The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for healthcare professionals whose patients are taking or are interested in taking microbiome-based products.

Accreditations & Approvals

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A complete Works Cited list begins on page 14.

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Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency, and California Assembly Bill 241, Implicit Bias.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective

The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of microbiome-based products, including prebiotics, probiotics, and postbiotics.

Learning Objectives

Upon completion of this course, you should be able to:

1. Explain the definitions for prebiotics, probiotics, synbiotics, and postbiotics.
2. Describe the contents and clinical use of prebiotic products.
3. Compare and contrast available probiotic supplements and their various uses.
4. Outline the evidence for the use of postbiotic products.
5. Discuss combination biotics, including biotics in the diet.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

UNDERSTANDING "BIOTICS"

The human microbiome has sparked significant interest from researchers, clinicians, and patients for many years. The human body is estimated to be host to 10–100 trillion microbial cells, with the exact composition of micro-organisms differing from person to person. These micro-organisms have been shown to influence health in a variety of ways, and a disruption of the regular composition of micro-organisms, also known as the normal flora, can have downstream health consequences.

Much of the terminology used in this field, as well as on product labels, commonly causes confusion. For example, microbiome and microbiota, while similar, do not have the same meaning:

- Human microbiota: The specific micro-organisms harbored in the human body
- Human microbiome: The collective genomes of the micro-organisms that are harbored in the human body

The growing number of microbiome-based therapies available to consumers also use terminology that commonly causes confusion. Many of these products make claims about potential health benefits, and use terms such as prebiotics, probiotics, and postbiotics. Although the root of these words is the same, they represent very different ingredients, with different intended effects.

While there is no regulatory body governing the use of these terms, there are definitions that are generally accepted by the scientific community. The International Scientific Association for Probiotics and Prebiotics (ISAPP) is a nonprofit organization comprised of academic scientists dedicated to promoting research in the field of prebiotics, probiotics, and all associated topics. Over the past decade, this organization has published consensus statements that have helped to define different classes of ingredients and provide guidance for future research [1; 2].

Although the ISAPP is a valuable source of guidance on these topics, it should be noted that not all experts agree with the ISAPP consensus statements, and some organizations have published definitions that differ in certain ways. For the purposes of this course, the ISAPP definitions will be used to guide the discussion on each type of ingredient and, when relevant, any differing expert opinions.

ISAPP DEFINITIONS

Prebiotics: Substances that act as food for beneficial microbes [3].

Formal definition: A substrate that is selectively utilized by host micro-organisms that, in turn, confer a health benefit.

Probiotics: Live microbes that have demonstrated health benefits [1].

Formal definition: Live micro-organisms that, when administered in adequate amounts, confer a health benefit on the host.

Postbiotics: Non-viable microbes and/or cell components, with or without cell metabolites [2].

Formal definition: Preparation of inanimate micro-organisms and/or their components that confers a health benefit on the host.

It is important to recognize that products labeled with these terms may not meet the definitions set forth by ISAPP or any other organizations—there is no governing body that reviews or approves the use of this terminology on product labels or in manufacturer claims.

PREBIOTICS

As our knowledge of the human microbiota has expanded, so has the definition of prebiotics. Although prebiotics were originally thought to only be beneficial in the gastrointestinal (GI) tract, we now know that prebiotic effects can occur in any part of the body that hosts microbial species. Over

the years, the definition of prebiotic has been rewritten to incorporate this knowledge and to separate prebiotics from other substances that can affect micro-organisms, such as fats, proteins, probiotics, vitamins, and antibiotics [1].

Traditionally, prebiotics have been selected for inclusion in commercially available products due to their utilization by bacteria in the lactobacilli and bifidobacteria genera. In fact, for the most part, prebiotics have been included in commercial products and scientific studies specifically to induce the growth of bifidobacteria (bifidogenesis).

It is now recognized that prebiotic effects likely extend beyond these genera; however, it is still important that any prebiotics have a focused effect. Otherwise, it would be possible for prebiotics to encourage the growth of pathogenic or detrimental organisms, such as *Escherichia* or *Clostridioides*. This is why the definition of prebiotic acknowledges that it must have a net health benefit to the host [1].

The most commonly used prebiotics are a small group of carbohydrates that are not digested in the intestines or absorbed by the body. Rather, these molecules are fermented by the bacteria in the colon.

Some dietary fibers can be prebiotics in other animals, but not in humans. For instance, cellulose is considered a prebiotic for ruminant animals, such as cows, which host a bacterium that readily breaks down cellulose. But cellulose is not considered a prebiotic in humans due to its poor utilization by the human gut microbiota [1].

GI PREBIOTICS

Inulin

Inulin is a polysaccharide (long-chain carbohydrate) comprised of up to 60 chains of glucose and fructose molecules. It is isolated from various plant roots and tubers and is commonly used as a food additive to increase bulk and palatability. It is also a natural component of the diet, with the most common food sources being wheat, onions, bananas, leeks, artichokes, and asparagus [4].

Inulin seems to be a preferred food source for lactobacilli and bifidobacteria, leading to its use as a prebiotic. Some research has shown that taking oral inulin increases gut and fecal microbiota diversity and increases concentrations of bifidobacteria. However, not all research to date has confirmed this finding [4].

Inulin is most often derived from chicory (*Cichorium intybus*). On product labels, it may be referred to as chicory inulin. Another ingredient sometimes found on product labels is chicory fructans. These products typically contain inulin in combination with other fructans such as fructo-oligosaccharides [4].

Fructo-oligosaccharides (FOS) and Galacto-oligosaccharides (GOS)

Oligosaccharides are short-chain carbohydrates. They are comprised of three to ten monosaccharides (simple sugars). Fructo-oligosaccharides (FOS) are oligosaccharides comprised of one sucrose molecule bonded to two to four fructose molecules. FOS occur naturally in a wide variety of fruits, vegetables, and cereals, but they can also be produced via enzymatic conversion of sucrose or partial hydrolysis of inulin [5].

Galacto-oligosaccharides (GOS) are also oligosaccharides, but these molecules are primarily comprised of galactose and lesser amounts of glucose and lactose. They are found naturally in dairy products, legumes, and certain root vegetables [6].

FOS and GOS are preferred by bifidobacteria. The linkage bonds found in these molecules are easily broken down by an enzyme prevalent in bifidobacteria. Thus, this genus can rapidly utilize FOS and GOS as energy sources. In human research, these oligosaccharides have been shown to increase the fecal content of beneficial bacteria in the gut, including bifidobacteria [5; 6].

Numerous studies have also shown that prebiotics, including FOS and GOS, promote the establishment of beneficial bacteria that mimics the GI flora of infants consuming human milk. This is thought to have a long-term impact on the function of the infant's immune system [5; 6].

Human Milk Oligosaccharides (HMOs)

HMOs are naturally present in human milk and are important for the development of an infant's intestinal microbiota and immune function. Consuming human milk containing HMOs increases the proportion of *Bifidobacterium* and *Bacteroides* in the gut [5; 6].

Clinical Uses

Although clinical research on the use of FOS is limited, inulin and GOS have been extensively studied. There is interest in using prebiotics for a wide range of purposes; only the indications with the strongest available evidence are discussed briefly here.

GI Health

Most research suggests that oral inulin improves stool frequency in adults with constipation, and may improve stool softness in children with constipation, when compared with placebo. Doses used in clinical research include 12 – 40 grams daily (divided into three doses) in adults, and 2 grams twice daily in children 2 to 5 years of age. However, it does not seem to reduce discomfort related to constipation [4].

Small clinical studies suggest that taking oral GOS 5.5 – 11 grams daily for two to three weeks does not improve symptoms of constipation in adults. Similarly, small studies in patients with irritable bowel syndrome (IBS) or ulcerative colitis suggest that taking oral GOS does not improve symptoms [6].

Clinical research in adults with symptoms of lactose intolerance despite avoidance of lactose suggests that titrating up to an oral dose of GOS 7.5 – 10 grams twice daily for 30 days might help to reduce overall symptoms. This effect seems to persist even after the discontinuation of GOS, suggesting that GOS might increase the prevalence of lactose-fermenting bacteria [6].

Glycemic Control

Most research in adults with diabetes shows that taking oral inulin 8.4 – 10 grams daily for 6 to 12 weeks reduces glycated hemoglobin (HbA1c) by 0.65% and fasting plasma glucose levels by an average of 16 mg/dL when compared with a control group. However, early research suggests that these benefits may not occur in adults with prediabetes [4].

Atopy

In infants who are at risk for allergies, providing an oral syrup or formula containing GOS with either a probiotic or another prebiotic appears to reduce the risk of atopic dermatitis (eczema). However, providing oral GOS and probiotics does not seem to reduce the risk of developing allergic rhinitis or food allergies [6].

Safety

Inulin, FOS, and GOS are well tolerated when used appropriately in recommended doses, short-term [4; 5; 6]. The most common adverse effects are GI upset, such as bloating, cramping, flatulence, constipation, and increased stool frequency. The studied doses are [4; 5; 6]:

- Inulin: Up to 18 grams daily for up to 24 weeks; long-term safety is unclear.
- FOS: Up to 30 grams daily for up to four weeks; long-term safety is unclear.
- GOS: Up to 20 grams daily for up to four weeks. The European Food Safety Authority (EFSA) has set a safe intake level for GOS at 16.2 grams daily, although long-term safety has not been specifically evaluated.

NON-GI PREBIOTICS

Prebiotics can theoretically also promote the growth of beneficial bacteria in any other part of the body that hosts microbes, including the skin, mouth, and vagina. Due to the differences in environment and microbiota composition, most prebiotics would be expected to exert beneficial effects in only one part of the body. One example is xylitol, which is considered a prebiotic in the oral cavity but has not demonstrated prebiotic activity elsewhere in the human body.

Xylitol is a five-carbon polyhydric alcohol that is not viable as a source of energy for the bacteria commonly found in the mouth. Thus, xylitol-containing products do not promote the growth of oral bacteria and may even inhibit some bacterial enzymes, interfering with bacterial metabolism of typical energy sources [7]. Clinical research shows that the use of products such as foods, chewing gum, candies, and toothpaste that provide 1–20 grams of xylitol per day can reduce the incidence of cavity formation in adults and children [7].

PREBIOTIC EFFECTS THROUGHOUT THE BODY

For many years, it was thought that prebiotics were only beneficial in the GI tract. However, it is now understood that they can provide benefits in various parts of the body.

Mouth

As a host to many caries-inducing micro-organisms, the mouth may benefit from prebiotic effects that discourage the growth of unwanted bacteria. Clinical research has shown that xylitol may be beneficial for this purpose [7].

Skin

The skin is home to a large number of micro-organisms. Some scientists hypothesize that certain prebiotics may promote the growth of normal, beneficial bacteria and discourage the growth of micro-organisms that may contribute to various health issues, including acne, psoriasis, dermatitis, and eczema [4; 5; 6].

Intestines

The GI tract is home to a diverse mix of micro-organisms and has been the subject of extensive research. There is strong evidence suggesting that certain prebiotics, including FOS and GOS, can encourage the growth of beneficial bacteria, which may lead to downstream health benefits [5; 6].

Vagina

The vagina hosts many micro-organisms and is also at risk for pathogenic colonization. There is interest in developing prebiotics that encourage the growth of beneficial vaginal bacteria and discourage the growth of pathogens [4; 5; 6].

PROBIOTICS

"Probiotics" is the most well-recognized microbiome-based term in use today, and the definition from ISAPP was actually adopted from the original definition created by the World Health Organization (WHO). Probiotics represent the majority of microbiome-based products currently found on the market. Not surprisingly, most of the available research in this area has focused on probiotics as well. However, despite a rapidly expanding body of research, our knowledge on the benefits of probiotics remains limited. The available research strongly indicates that any health benefits obtained from probiotics are not only likely to be species-specific, but possibly also subspecies-specific and even strain-specific [1].

In order to read a probiotic product label, it is important to understand probiotic nomenclature. Most probiotics appear as a scientific name, such as *Lacticaseibacillus rhamnosus*. In this example, *Lacticaseibacillus* is the genus, and *rhamnosus* is the species.

Some, but not all, species are also divided into individual subspecies. For example, one of the most extensively studied probiotics, *Bifidobacterium animalis* subsp. *lactis*, is a subspecies. In this case, subsp. indicates that this organism is a subspecies, and the following name, *lactis*, defines the subspecies. Some manufacturers may abbreviate these organism names on the label (e.g., *Bifidobacterium lactis*). Do not be misled by this abbreviation—these are the same organism [1].

Many probiotic ingredients are further classified into strains. These organisms will be listed on the label with the strain name provided last. For example, with *L. rhamnosus* GG, GG is the strain.

EXAMPLES OF RECLASSIFIED LACTOBACILLUS ORGANISMS	
New Name	**Previous Name**
Lacticaseibacillus paracasei	*Lactobacillus paracasei*
Lacticaseibacillus rhamnosus	*Lactobacillus rhamnosus*
Lactiplantibacillus plantarum	*Lactobacillus plantarum*
Ligilactobacillus salivarius	*Lactobacillus salivarius*
Limosilactobacillus reuteri	*Lactobacillus reuteri*
Lacticaseibacillus paracasei	*Lactobacillus paracasei*
Source: [1]	*Table 1*

Similarly, with *B. animalis* subsp. *lactis BB-12*, *BB-12* is the strain. Most probiotic strains available on the market are proprietary, and much of the research conducted on these strains has been funded by the manufacturer [1].

Another factor limiting our understanding of probiotic efficacy is the fact that most of the available research has utilized combination products. In some cases, benefits are seen with specific combinations, but not others, and it is unclear which component(s) of those combinations, if any, are responsible for the gain or loss of benefit seen in research. Due to the prevalent use of combination products in research, it is often unclear whether any specific probiotic species, subspecies, or strain is beneficial when used alone, or if the identified benefits can only be obtained when specific strains are combined [1].

LACTOBACILLI

Some of the most recognizable probiotic ingredients found on store shelves are known as *Lactobacillus*. But in 2020, the *Lactobacillus* genus was reclassified into 25 different genera, meaning that many of the most recognizable probiotic ingredients on the market now have a slightly different name (***Table 1***) [1].

In general, all bacteria previously known as *Lactobacillus* are lactic acid-producing, gram-positive, rod-shaped, anaerobic bacteria. Many of the species that are commonly used in probiotic products are part of the normal flora in various parts of the human body, including the oral cavity, GI tract, and vagina [1].

There are also some relatively well-known lactobacilli that were not reclassified, such as *Lactobacillus acidophilus* and *Lactobacillus helveticus*. These species have retained their classification and name.

Additionally, some bacteria that were originally considered to be distinct species have been re-classified as subspecies. For example, *Lactobacillus bulgaricus* is now known to be *Lactobacillus delbrueckii* subsp. *bulgaricus*.

Many manufacturers have not yet updated their labeling to include the new genus names, and some manufacturers have chosen to abbreviate the genus in an effort to avoid confusion (e.g., listing *Lacticaseibacillus casei* as *L. casei*). Product labels may continue to refer to these ingredients in various ways for some time [1].

Biological Effects

Lactobacilli are believed to play an important role for maintaining and restoring the normal GI flora. When taken orally, some lactobacilli pass through the gut and attach to the intestinal mucosa. When lactobacilli latch on to and colonize the intestinal mucosa, this seems to prevent epithelial attachment by pathogenic bacteria. Lactobacilli also inhibit bacterial pathogens by producing lactic acid [1].

Other effects of lactobacilli may be more species-specific. For example, some lactobacilli produce hydrogen peroxide, which can also inhibit bacterial pathogens. There is also some evidence that certain species and strains attach to intestinal epithelial cells better than others. These differing effects have led to a hypothesis that multi-species products may offer more benefit than single-species products; however, this has not yet been validated in research [1].

Lactobacilli are also thought to have immunomodulating effects. Lactobacilli seem to modulate non-specific cellular and humoral immunity, possibly by stimulating lymphocyte and macrophage activity and modulating cytokine production. Lactobacilli also seem to decrease markers of hypersensitivity and intestinal inflammation, such as tumor necrosis factor (TNF) [1].

There is also some evidence that certain species can increase resistance to certain pathogens. For example, *Lacticaseibacillus casei Shirota* has been shown to reduce cytomegalovirus and Epstein-Barr virus antibody titers in endurance athletes [14]. *Limosilactobacillus reuteri* secretes reuterin, an organic compound that has demonstrated in vitro activity against *Salmonella*, *Listeria*, *Clostridium*, and *Escherichia* species [15].

As a component of the normal flora in the vagina, some lactobacilli also appear to promote vaginal health. These organisms attach to the urogenital mucosa, and the lactic acid they produce lowers the vaginal pH, which can reduce pathogen growth. Similarly, those species that produce hydrogen peroxide are bactericidal to the vaginal pathogen *Gardnerella vaginalis*, which may help to reduce the rate of bacterial vaginosis [1].

Clinical Use

It is difficult to summarize the evidence for the clinical use of lactobacilli, as each species has demonstrated very different effects in human research. A large body of evidence suggests that certain species and strains may be beneficial for various GI conditions, including abdominal pain, constipation, and diarrhea, as well as for the prevention of atopic disease. However, many species and strains have also failed to show benefit for these uses, so it is important to identify a product containing a species and/or strain that has been evaluated in clinical research [1; 16].

BIFIDOBACTERIA

Bifidobacteria are anaerobic, rod-shaped, gram-positive, lactic acid- and acetic acid-producing bacteria that normally colonize in the human colon. Various species of bifidobacteria are found in probiotic products, the most common of which are [1]:

- *Bifidobacterium animalis* susbp. *lactis* (often referred to as *B. lactis* on product labels)
- *Bifidobacterium bifidum*
- *Bifidobacterium breve*
- *Bifidobacterium longum*

Biologic Effects

Bifidobacteria appear to be the most important organisms in the intestine for providing a microbial barrier to infection. When used orally, some species of bifidobacteria pass through the gut and bind to the intestinal mucosa, preventing attachment of pathogenic coliform bacteria. Similarly to lactobacilli, some species of bifidobacteria might attach to intestinal epithelial cells better than others [1].

Some species of bifidobacteria produce antimicrobial substances that have activity against many gram-positive and gram-negative organisms. It is thought that these antimicrobial effects might contribute to the protection that human milk provides against GI infections in infants. Additionally, GI colonization by bifidobacteria in infants appears to be essential for the development of oral tolerance to dietary antigens [1]. Bifidobacteria are also thought to have similar immunomodulating effects to those seen with lactobacilli.

Clinical Use

As with lactobacilli, it is difficult to summarize the evidence for the clinical use of bifidobacteria. The evidence is variable depending on the species and strain used in clinical research. The currently available evidence suggest that certain species and strains may be beneficial for constipation and IBS, as well as for colic and the prevention of respiratory tract infections. However, other species and strains have either not been evaluated or have failed to show benefit for these uses, so it is important to identify a product containing a species and/or strain that has been evaluated in clinical research [1].

BACILLUS

Bacillus is a large genus of spore-forming, gram-positive bacilli, some of which are considered probiotics and others which are considered pathogenic. The two species most often found in probiotic products are *B. coagulans* and *B. subtilis* [8].

Biological Effects

Similarly to lactobacilli and bifidobacteria, *B. coagulans* produce chemicals that exert antibacterial activity, including coagulin, lactic acid, and lactosporin. These chemicals might reduce pathogenic bacteria growth in the GI tract. Additionally, some animal research suggests that *B. coagulans* spores may stimulate the immune system [8].

Clinical Use

The best evidence for the use of *B. coagulans* is for constipation and IBS. Research on the use of *B. coagulans* or *B. subtilis* for other indications is lacking [8].

SACCHAROMYCES BOULARDII

Saccharomyces boulardii is a nonpathogenic yeast that is actually now considered to be a strain of *Saccharomyces cerevisiae*. However, because it was previously thought to be a unique species, it is often listed on product labels and discussed in clinical research as *S. boulardii*. *S. boulardii* is used in some food processes that require fermentation. It is also commonly used in single-ingredient probiotic supplements [9].

Biological Effects

Laboratory research suggests that *S. boulardii* competes for intestinal epithelial attachment sites and blocks the adherence of *Clostridioides difficile* (previously known as *Clostridium difficile*). *S. boulardii* also produces proteases that might decrease the toxicity of *C. difficile* toxins A and B [9].

Clinical Use

Clinical research shows that taking *S. boulardii* in conjunction with antibiotics can help to prevent a recurrent *C. difficile* infection. However, the evidence for its use in the prevention of an initial *C. difficile* infection is conflicting. *S. boulardii* also seems to offer some benefit for the reduction of acute diarrhea in children, including rotaviral diarrhea and antibiotic-associated diarrhea [9].

In adults and children on antibiotic treatment, the American Gastroenterological Association suggests the use of *S. boulardii*; or the 2-strain combination of *L. acidophilus* CL1285 and *L. casei* LBC80R; or the 3-strain combination of *L. acidophilus*, *L. delbrueckii* subsp *bulgaricus*, and *B. bifidum*; or the 4-strain combination of *L. acidophilus*, *L. delbrueckii* subsp *bulgaricus*, *B. bifidum*, and *S. salivarius* subsp *thermophilus* over no or other probiotics for prevention of *C. difficile* infection.

(https://www.gastrojournal.org/article/S0016-5085(20)34729-6/fulltext. Last accessed October 27, 2022.)

Strength of Recommendation/Level of Evidence: Conditional/Low

Probiotic preparation strength is usually provided as the number of living organisms, or colony-forming units (CFUs), found in each dose. The number of living organisms in a dose can range from 1 million CFUs to 30 billion CFUs, depending on the species and product [9].

S. boulardii, unlike most probiotic species, may be dosed in either CFUs or mg. For *S. boulardii*, specifically, 250 mg is equivalent to about 5 billion CFUs.

SAFETY

Most research suggests that probiotics are generally safe when used in studied doses for three to nine months, depending on the specific species and strain. In general, the long-term safety of regular probiotic use is unknown. In some clinical studies, probiotics have been reported to cause mild GI side effects, such as abdominal discomfort, dyspepsia, flatulence, bloating, and burping; however, these reports are uncommon [1; 8; 9].

Immunocompromised or critically ill patients may have an increased risk of systemic infection from probiotics. Several case reports and case series have described bacteremia or fungemia in this population, especially those with intravenous lines and those receiving enteral feeding [1]. Most cases of fungemia that have been associated with the use of *S. boulardii* products occurred when powder packets were used or when capsules were opened at the bedside [9]. The FDA has also issued a warning letter regarding the use of probiotics in preterm infants after a preterm infant (birthweight <1,000 g) died after developing sepsis caused by *Bifidobacterium longum* related to administration of a probiotic as part of in-hospital care [17].

Probiotic-associated bacteremia has also occurred in patients with various conditions leading to compromised gut integrity, including short bowel syndrome and inflammatory bowel disease [1].

Patients with valvular heart disease may be at increased risk for pathogenic colonization with probiotic use. Rare cases of lactobacilli endocarditis have been reported in patients with valvular heart disease who used probiotics before dental surgery, upper endoscopy, or colonoscopy [1].

Caution at-risk patients against the use of probiotics, and to ensure that they are not exposed to aerosolized probiotics that are being used by another member of the household.

In 2023, the International Scientific Association for Probiotics and Prebiotics convened a meeting with the intent of generating evidence-based recommendations to ensure the safe use of probiotics [18]. They concluded that established practices are generally addressing factors important to the safety of traditional probiotics used by the general population. However, they do recommend that probiotics targeted for specific patient populations should undergo stringent testing to meet quality standards appropriate for that population, preferably verified by an independent third party [18].

PRODUCT POTENCY

The quantity of bacteria listed on a probiotic product label represents the minimum number of living organisms (or CFUs) found in that product prior to expiration. For example, if a product states that it contains 30 billion CFUs, this indicates that, on the date of expiration, the product should contain 30 billion CFUs. Since the micro-organisms found in these products die off over time, they are released to market with a much higher quantity of living organisms than is listed on the label. To ensure the viability of probiotic products, it is important to store them at the temperature stated on the box and to keep them in their original packaging [1].

Although research has not evaluated the potential for differing benefits and risks with the use of probiotics in relation to expiration date, be aware that the dosage listed on a probiotic label does not represent the actual contents of a product in the same way that is expected for conventional medicines.

POSTBIOTICS

"Postbiotics" is the newest microbiome-based product term. Although researchers have been interested in these ingredients for many years, only recently has this topic become a common source of interest for healthcare professionals and consumers [2].

There is still some controversy around the appropriate definition for this emerging topic. Some experts have proposed conflicting definitions of postbiotics, and the ISAPP definition is not universally accepted. Under the ISAPP definition, in order for a product to be considered a postbiotic, the micro-organisms, their matrix, and the method used to inactivate the organisms must be known, and beneficial health effects must be confirmed [10].

The inactive micro-organism can, but is not required to, be present in the final product. Although the micro-organism itself does not need to be present, at least some part of the original bacterial cell (e.g., pili, cell wall, cell component, etc.) must be present in the final product.

Other experts have developed postbiotic definitions that exclude inactive micro-organisms. Instead, this term is reserved for molecules and soluble factors secreted by live micro-organisms or released after the cell dies, as well as cell metabolites that exert biological effects on the host [2]. Thus, some definitions allow a postbiotic product to contain the original inanimate micro-organism in the product, whereas others disallow this ingredient.

Despite the controversy, experts tend to agree on the use of the word "inanimate" to define the current state of the original microbe. This terminology helps to clarify that although these micro-organisms are no longer alive, they are not necessarily biologically inactive. The factors that these organisms release after death can still exert activity on the host [2].

Due to its recent surge in popularity, there are still many names for postbiotics that appear in the literature and online. Some of these terms include "paraprobiotics," "ghost probiotics," and "zombie probiotics." In research, terminology may include "tyndallized probiotics," "bacterial lysates," and "heat-killed bacteria" [2].

There are a number of reasons for the growing interest that postbiotics are receiving. From the manufacturing perspective, these products are theorized to have superior stability when compared with living organisms. And many scientists theorize that these products may have an improved safety profile when compared with their living counterparts.

It is also important to recognize that many probiotic products found on the market are likely to contain a relatively large quantity of inactive (dead) or injured micro-organisms. This is also the case for many fermented foods that are pasteurized or baked. Thus, even for traditional probiotic or fermented products, there is much to be gained from having a better understanding for the effects these cells and byproducts can have on human health [2].

CLINICAL USES

Many of the postbiotics currently being studied are derived from the same live microbial species that are commonly used as probiotics. So far, research has primarily focused on the use of heat-killed versions of the following species [2]:

- *Bacillus coagulans*
- *Bifidobacterium bifidum*
- *Lactobacillus acidophilus*
- *Lacticaseibacillus paracasei*
- *Lacticaseibacillus rhamnosus*
- *Lactiplantibacillus plantarum*
- *Saccharomyces cerevisiae*

Brewer's yeast (a group of specific strains of *S. cerevisiae*) has been available as a food additive and dietary supplement for some time. In foods, it is used as a source of chromium, B-complex vitamins, and selenium. Brewer's yeast products may contain either live *S. cerevisiae* or dried, inactive *S. cerevisiae*. If a specific brewer's yeast product providing non-living, dried strains of yeast were to demonstrate a health benefit to the host, it would qualify as a postbiotic [11].

Despite its longer history of use, there is still only a limited amount of research on the clinical effects of brewer's yeast. Most of the available research on non-living, dried brewer's yeast has evaluated the use of a specific product, Epicor. Although this research suggests that this product is safe when used in doses of up to 500 mg daily for up to three months, there is not enough evidence to determine whether it is beneficial for any clinical indication [11].

For the most part, the research to date on any heat-killed micro-organisms is limited, and the safety and effectiveness of these products remain unclear [2].

As postbiotics, by definition, do not contain living organisms, the dosing units for these products are different than those seen for probiotics. Instead of colony-forming units (CFUs), many postbiotic products will list the dose in cells or mg. If cell count is used, this indicates the number of inanimate micro-organisms contained in the product. If mg is used, this indicates the total quantity of postbiotic material found in the product.

BRINGING IT ALL TOGETHER

SYNBIOTICS

According to the ISAPP definition, synbiotics are a mixture comprising live micro-organisms and substrate(s) selectively utilized by host micro-organisms that confers a health benefit on the host [12]. In simple terms, a synbiotic is a mixture of prebiotic and probiotic.

As the definition suggests, synbiotics are products that combine prebiotics and probiotics together with the goal of providing a synergistic beneficial effect (e.g. to confer a health benefit on the host). Some individual products may be specifically marketed as synbiotics. However, there are also many products marketed as probiotics that have also been formulated to contain prebiotic ingredients.

Probiotics and prebiotics can be provided in different combinations with different intended effects, but most synbiotic products tend to fit into two general categories: complementary and synergistic.

Complementary Synbiotics

These contain probiotic and prebiotic ingredients that are intended to work independently toward the same goal. In this case, the prebiotic ingredient included in a product may not be a source of energy for the probiotic ingredients found in the same product. But the ultimate intended health effect of every ingredient in the product is the same.

Synergistic Symbiotics

These contain prebiotic ingredients that are specifically utilized by the probiotic ingredients as a source of energy. The prebiotic in this product might also be used as a source of energy by other microbes found in the GI tract, but its primary purpose as a component of the product is to serve as a food source for the probiotic ingredient(s).

BIOTICS IN THE DIET

Products that claim to contain prebiotics, probiotics, or postbiotics are most often found in the supplement aisle. However, these claims can also be found on many foods and drinks. There is nothing prohibiting a manufacturer from adding any of the ingredients discussed in this course to a food or drink product.

Probiotics and postbiotics are naturally found in fermented foods and drinks, and these are the products most likely to contain these ingredients. Not every fermented food product on the market claims to provide health benefits, but for the many that do, the ISAPP has developed a definition for these as well.

Fermented foods are defined as "foods made through desired microbial growth and enzymatic conversions of food components" [13]. This definition encompasses products with and without living micro-organisms that are present at the time of consumption. For example, many yogurts contain living micro-organisms, whereas most beers and wines undergo a process that filters living micro-organisms out of the final product.

Some common examples of fermented foods and drinks include:

- Beer
- Cider
- Kefir
- Kimchi
- Kombucha
- Miso
- Sauerkraut
- Wine
- Yogurt

Fermented foods are proposed to exert benefit via various mechanisms, many of which have not yet been validated in clinical research. Some of these proposed benefits include reduced glycemic index, improved digestibility and tolerability, increased bioavailability of bioactive compounds, and the biosynthesis of vitamins, amino acid derivatives, and organic acids.

Many fermented foods contain high concentrations of alcohol, salt, and/or tyramine. These byproducts may be of concern when used in certain patient populations, such as those with hypertension or those taking certain medications (monoamine oxidase inhibitors [MAOIs], etc.), and should be kept in mind when discussing the use of these products.

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

For patients who are not proficient in English, it is important that information regarding the benefits and risks associated with the use of dietary supplements be provided in their native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter.

CONCLUSION

Microbiome-based therapies continue to become more prevalent and widely used. Although many of these products utilize the catchy terminology discussed in this course, there is no regulatory agency confirming that these terms are used appropriately or that these products have been evaluated for safety and efficacy.

Although many of these ingredients appear to be safe for most adults when used short-term, long-term safety remains unclear. Additionally, the available evidence suggests that any beneficial effects differ greatly depending on the single ingredient or combination of ingredients being used. It is important for clinicians to understand the terminology and claims found with these products so that they can provide practical, evidence-based guidance to their patients.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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Evidence-Based Recommendations Citation

Su GL, Ko CW, Bercik P, et al. AGA Clinical practice guidelines on the role of probiotics in the management of gastrointestinal disorders. *Gastroenterology.* 2020;159(2):697-705. Available at https://www.gastrojournal.org/article/S0016-5085(20)34729-6/fulltext. Last accessed October 27, 2022.