CHAPTER 116

Probiotics

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INTRODUCTION

The term probiotic is derived from the Greek and literally means "for life." It was first coined in 1965 by Lilley and Stillwell to describe substances secreted by one microorganism that stimulate the growth of another.[1] In 1974, Parker modified this definition to "... organisms and substances which contribute to intestinal microbial balance."[2] The current World Health Organization definition of probiotics is "live microorganisms which when administered in adequate amounts confer a health benefit to the host."[3] This definition includes fermented foods such as yogurt, sauerkraut, and kefir, as well as specific supplements containing freeze-dried bacteria. The microorganisms found in these products are usually lactobacilli and bifidobacteria.[4]

Humans have been consuming probiotics for many thousands of years and fermented foods have been, and still are, of great importance to the diets of most of the world's people. Microbial cultures have been used to produce beer, wine, yogurt, tempeh, sauerkraut, olives, cheese, and many other fermented foods.[5] Thus, the symbiotic relationship between humans and probiotic microorganisms has a long history of important nutritional and therapeutic benefits for humans.

Currently, there is renewed interest in the field of fermented foods and probiotics. This interest has been stimulated by the recent explosion of research in this area. This chapter focuses on the health benefits and therapeutic uses of probiotic-containing foods and supplements.

DESCRIPTION

At the turn of the century, Metchnikoff[6] asserted that yogurt was the elixir of life. He theorized that putrefactive bacteria in the large intestine produce toxins that invite disease and shorten life. He believed that eating yogurt would cause lactobacilli to become dominant in the colon and displace the putrefactive bacteria. For years, these claims of healthful effects from fermented foods were considered unscientific folklore. However, a substantial and growing body of scientific evidence has now demonstrated that lactobacilli, bifidobacteria, and fermented foods play a significant role in human health.

The genus *Lactobacillus* is characterized by considerable heterogeneity. Bacteria are classified as lactobacilli if they are gram-positive, nonsporing, and rod-shaped bacteria that produce lactic acid as the major end product of carbohydrate fermentation. Lactobacilli appear to be fairly unique, in that they have been isolated from a number of diverse environments, such as fermented vegetables and dairy foods, as well as the human gastrointestinal tract (GIT) and vagina.[7]

In contrast, bifidobacteria are not found in natural fermentative processes, but are native to the GIT.[8] Bifidobacteria are also gram-positive, nonsporing bacteria; however, they are Y-shaped instead of rod-shaped and their major fermentative end product is acetic acid.[9]

Intestinal colonization by lactobacilli and bifidobacteria begins during the birthing process. Before birth, the GIT of the neonate is completely sterile. During delivery, the newborn is inoculated with microorganisms from the birth canal and the mother's fecal flora, as well as from organisms in the environment. In the first week, the organisms that are best suited to the intestinal environment become established. Initially, there is often a predominance of *Escherichia coli*, enterococci, and streptococci. A diet of breast milk creates a colonic environment that favors the

growth of a simple flora of bifidobacteria and a few other anaerobes. Breast-milk contains many bifidogenic oligosaccharides,[10] as well as living bacteria. Amazingly, breast milk from healthy women can contain up to 10^9 bacteria/L, including various strains of lactobacilli and bifidobacteria.[11-13] In formula-fed infants, the microbiota is more complex (resembling the adult flora), containing far fewer bifidobacteria and more *Bacteroides* spp., clostridia, and anaerobic streptococci. The introduction of solid food to the breast-fed infant causes major changes to the microflora. A rapid rise in the numbers of enterococci and enterobacteria is followed by increases in *Bacteroides* spp., anaerobic streptococci, and clostridia. As the amount of solid food increases in the diet, the bacterial flora of formula-fed and breast-fed infants approaches that of adults.[14-16] Common species of lactobacilli and bifidobacteria found in the infant and adult human GIT are listed in Box 116-1.[11,17-23]

PROPOSED MECHANISMS OF ACTION

The exact mechanisms by which probiotics accomplish their beneficial actions have not been well documented. However, there are several postulated mechanisms that explain many of their favorable effects. One such mechanism is competition for adhesion sites.

Many pathogenic organisms must associate with the GIT epithelium to colonize effectively. However, some strains of bifidobacteria and lactobacilli can adhere to the epithelium and act as "colonization barriers" by preventing pathogens from adhering to the mucosa.[24] This effect was demonstrated with the *Lactobacillus rhamnosus* strain GG and *L. plantarum* 299v. Both of these organisms showed the ability to inhibit attachment of *E. coli* to human colon cells.[25]

Another possible mechanism of action is the modification of the microbial flora through the synthesis of antimicrobial compounds. Many types of lactobacilli and bifidobacteria produce bacteriocins or other antimicrobial compounds. Bacteriocins are defined as "compounds produced by bacteria that have a biologically active protein moiety and a bactericidal action."[26] Other biologically active compounds produced by lactic acid bacteria include hydrogen peroxide, diacetyl, and short-chain fatty acids. The release of these compounds by probiotic organisms results in a beneficial modification of the microflora.[27] However, not all strains of lactobacilli or bifidobacteria produce antimicrobial compounds, and some produce compounds that are fairly nonspecific in their activity, so that beneficial bacteria, as well as pathogenic organisms, may be negatively affected.

It has also been observed that probiotics can stimulate the immune response. This immune response may take the form of increased secretion of immunoglobulin-A (IgA),[28] elevated numbers of natural killer cells, or enhanced phagocytic activity of macrophages.[29] Increased secretion of IgA may decrease numbers of pathogenic organisms in the gut, thus improving the composition of the microflora.[24,30]

Probiotics may also compete for nutrients that would otherwise be utilized by pathogens.[31] This situation occurs with *Clostridium difficile*, a potentially pathogenic organism that is dependent upon monosaccharides for its growth. Probiotic organisms in sufficient numbers can utilize most of the available monosaccharides, which results in the inhibition of *C. difficile*.[32]

BOX 116-1 Common Colonizers of the Human Gastrointestinal Tract Among Lactobacilli and Bifidobacteria

***Lactobacillus* spp.**	***Bifidobacterium* spp.**
reuteri	*adolescentis*
crispatus	*infantis*
acidophilus	*longum*
jensenii	*bifidum*
gasseri	*breve*
plantarum	*catenulatum*
casei	*pseudocatenulatum*
rhamnosus	*angulatum*
paracasei	*ruminantium*
ruminis	*dentium*
salivarius	

Data from references 11, 19-23.

PROBIOTIC CHARACTERISTICS

Probiotic organisms require certain characteristics to enable them to exert maximum therapeutic effects. These qualities are summarized in Table 116-1.

Of these characteristics, there are some that are considered almost essential for a probiotic to have therapeutic effects. These are: (1) gastric acid and bile salt stability; (2) an ability to adhere to the intestinal mucosa; and (3) an ability to colonize the intestinal tract.[34] Unfortunately, many commercially available probiotic supplements and yogurts contain strains that do not

TABLE 116-1 **The Desirable Characteristics of Effective Probiotic Strains**

CHARACTERISTICS	FUNCTIONAL BENEFIT
Human origin	Human origin should translate to ability to survive conditions in the human GIT, as well as the possibility of species-specific health effects.
Gastric acid and bile salt stability	Survival through stomach and small intestine
Adherence to intestinal mucosa	Believed to be essential for immune cell modulation and competitive inhibition of pathogens.
Colonization of intestinal tract	Multiplication in the intestines suggests that daily ingestion may not be needed; immune cell modulation
Safety in food and documented clinical safety	Adverse effects absent or minimal; accurate identification (genus, species, strain)
Production of antimicrobial compounds	Normalization of GIT flora; suppressed growth of pathogens
Antagonism against pathogenic organisms	Prevention of adhesion and toxin production by pathogens
Clinically documented and validated health effects	Clinicians can be confident of therapeutic effects; dose–response data for minimum effective dosage in different formulations is known.

GIT, gastrointestinal tract.
Modified from Mattila-Sandholm T, Salminen S. Up-to-date on probiotics in Europe. Gastroenterol Int. 1998;11(suppl 1):8-16.[33]

exhibit these vital characteristics. If a probiotic strain does not exhibit these characteristics, then it will be nowhere near as effective as those that do.

Probiotics in Use

There are many different microorganisms currently used as probiotics. Table 116-2 lists commonly used probiotic species.

To better understand how bacteria are named and classified, the following discussion may be helpful. Genus is the first name of a bacterium (e.g., *Lactobacillus*). It is somewhat general and refers to a grouping of organisms based on similarity of qualities, such as physical characteristics, metabolic needs, and metabolic end products. Species is a bacterium's second name (e.g., *acidophilus*). It is a much more narrow classification based on shared common characteristics that distinguish them from other species. Strain is an even more specific classification that divides members of the same species into subgroups based on several properties that these bacteria have in common that are distinct from other members of the species (e.g., strain LA5).[37]

Issues in Probiotic Nomenclature

There are some changes in nomenclature, some recent and some fairly antiquated, that should be noted to make better sense of probiotic literature.

- The species *Lactobacillus bulgaricus* is now referred to as *Lactobacillus delbrueckii* ssp. *bulgaricus*.[38]
- *Lactobacillus bifidus* (also known as "bifidus") was renamed *Bifidobacterium bifidum* over 30 years ago, yet the improper nomenclature continues to be widely used.[38]
- Many strains of bacteria that were once classified as *Lactobacillus casei* have been reclassified as strains of *Lactobacillus rhamnosus* (e.g., *L. rhamnosus* GG) or *Lactobacillus paracasei* (e.g., *L. paracasei* Shirota strain).[39]
- Strains of *Lactobacillus sporogenes* have been renamed *Bacillus coagulans* (they are not true lactobacilli because they form spores).[40]
- Bacterial strains that were once classified as *Lactobacillus acidophilus* (often referred to as "acidophilus") have now been divided into six species: *L. acidophilus, L. gasseri, L. amylovorus, L. gallinarum, L. johnsonii* and *L. crispatus*.[39]
- Strains of *Saccharomyces boulardii* are now definitively regarded as a distinct group within the species *Saccharomyces cerevisiae*.[41,42]

Importance of Strain

Strains of bacteria can be likened to different breeds of dogs. All dogs belong to the genus *Canis* and the species *familiaris*. Within this one species there is great diversity in size, shape, strength, and other physical characteristics—ranging from the Irish wolfhound to the chihuahua. A similar division occurs within species of bacteria.

Within each species of bacteria there is a multitude of strains. Some probiotic strains are resilient and strong, able to survive passage through the upper GIT and inhibit pathogenic bacteria, whereas others are weak and cannot survive the upper GIT or kill pathogenic bacteria. It is also important to note that just because one strain of bacteria in a given species has a proven action does not mean that another strain will too, even if they are closely related. Furthermore, actions found in one strain of *L. rhamnosus* cannot be extrapolated to a strain of *L. acidophilus* or *L. plantarum*. Actions and qualities are fundamentally strain specific.[43] Therefore, strains of bacteria within the same species can have significantly different actions, properties, and characteristics.

Unfortunately, this strain specificity is not well known, leading to inaccurate extrapolations from the literature. For example, some supplement manufacturers will quote a study that utilized *L. rhamnosus* strain GG and then say that their probiotic supplement containing a strain of *L. acidophilus* or another strain of *L. rhamnosus* will do the same. This is quite incorrect. Unless proven, one cannot assume that a given strain of *L. acidophilus*, *B. bifidum*, or any other species of lactic acid bacteria will survive transit through the upper GIT, let alone colonize the intestines or have specific therapeutic actions. They might, but unless proven, it is impossible to know. Two recent studies demonstrated this strain specificity.

Two strains of *L. rhamnosus* were utilized in a trial assessing their efficacy in the treatment of viral gastroenteritis. One strain was *L. rhamnosus* strain GG (LGG); the other was a strain found in a supplemental product (Lactophilus). LGG accelerated recovery from diarrhea, whereas the closely related strain did not.[44]

Additional in vitro research using two closely related strains of *B. bifidum* (CIDCA 537 and 5310) found that one strain (CIDCA 5310) inhibited enterocyte invasion by *Salmonella arizonae*, whereas the other had no effect.[45] The results of both these studies demonstrate the principle of strain specificity, that is, different bacterial strains within the same species can have significantly different actions and therapeutic effects.

TABLE 116-2 **Common Probiotic Microorganisms**

Lactobacillus Spp.	*Bifidobacterium* Spp.	*Bacillus* Spp.	*Streptococcus* Spp.	*Enterococcus* Spp.	*Saccharomyces* Spp.
acidophilus	*breve*	*coagulans*	*thermophilus*	*faecium*	*cerevisiae*
plantarum	*infantis*				
rhamnosus	*longum*				
paracasei	*bifidum*				
fermentum	*thermophilum*				
reuteri	*adolescentis*				
johnsonii	*animalis*				
brevis	*lactis*				
casei					
lactis					
delbrueckii gasseri					

Organisms that are currently used as probiotics (listed by genus and species).[33,35,36]

Thus, clinicians are urged to utilize well-researched probiotic strains whenever possible. By choosing well-researched strains, one can be assured of getting probiotics that have documented gastric acid and bile tolerance, can adhere to the intestinal mucosa, and can temporarily colonize the intestinal tract, as well as having proven therapeutic actions. This will increase the probability of achieving good clinical outcomes.

COMMERCIAL FORMS

There are two main forms in which probiotic organisms can be ingested—fermented foods and supplements. Fermented foods can be of both dairy and vegetable origin, with the most commonly known of each being yogurt and sauerkraut, respectively. Probiotic supplements consist of freeze-dried (lyophilized) bacteria in powder, capsule, or tablet form. Regardless of the form in which the microorganisms are consumed, for clinical efficacy, products containing probiotic organisms must provide live organisms in sufficient numbers to exert therapeutic effects. Both types of fermented foods and supplements are able to do this. Common probiotic delivery systems are compared in Table 116-3.

Fermented Dairy—Yogurt

The origin of fermented dairy products is somewhat obscure, but their consumption is believed to date back to at least 5000 BC.[46] Sour milks have always been popular throughout Europe, Asia, and Africa as nutritious, long-lasting foodstuffs. Fermented milks were also considered medicine, with ancient physicians like Hippocrates, Galen, and Avicenna advocating their use for the treatment of gastrointestinal ills.[47]

TABLE 116-3 **The Pros and Cons of Different Probiotic Delivery Systems**

DELIVERY SYSTEM	PROS	CONS
Fermented dairy	Affordability and easy availability Ease of incorporation into daily patterns Additional nutritional benefits Enhanced bacterial survival through upper GIT (100× less bacteria can be given per dose)[63] Effective in the upper GIT	Contains dairy proteins and lactose Taste can be issue Not suitable when travelling Not suitable for vegans
Capsules	Ease of administration Contain no binders	Not therapeutic in upper GIT (unless opened or chewed) May contain allergenic excipients Higher cost
Tablets	Ease of administration Effective in the upper GIT	May contain allergenic or otherwise problematic binders and excipients (e.g., gluten) Higher cost
Powders	Effective in the upper GIT Dosages can be easily adjusted Can be incorporated into foods or drinks Contain no binders	

GIT, gastrointestinal tract.

Early in the twentieth century, Nobel prize laureate Elie Metchnikoff popularized the idea that fermented milk products could beneficially alter the microflora of the GIT. He attributed the long life of Bulgarian peasants to their consumption of soured milk, which he believed to arrest the abnormal putrefaction of proteins within the bowel.[6] Metchnikoff later researched the bacteria found in this Bulgarian milk, *Bacillus bulgaricus* (now known as *L. delbrueckii* subspecies *bulgaricus*) and a type of cocci (now known as *Streptococcus thermophilus*).[47] He utilized these cultures in the manufacture of a type of sour milk he launched in Paris at the beginning of the twentieth century.[46]

These same species of bacteria are still used today in the manufacture of commercial yogurts. These two bacterial species (*L. delbrueckii* ssp. *bulgaricus* and *S. thermophilus)* are responsible for the taste, consistency, and smell that we associate with yogurt.[48,49] It is now known, however, that these species lack the ability to survive in the human GIT. Hence, yogurt manufacturers now routinely add additional probiotic species of bacteria to yogurt in an attempt to enhance its therapeutic effects (e.g., *L. acidophilus* and *B. bifidum*).[46]

The therapeutic efficacy of a specific yogurt depends substantially upon the characteristics of the strains of bacteria that it contains, as well as the number of viable bacteria present at the point of consumption. A therapeutic yogurt will contain bacterial strains with the desired characteristics as outlined in Table 116-1, and these strains should be in sufficient numbers to exert therapeutic effects once consumed (i.e., $>10^6$ bacteria/mL of each bacterial strain).[50] Recent market-basket surveys showed that some yogurts do achieve and maintain this level of bacterial viability throughout their shelf-life, and furthermore, these same brands of yogurt often utilize bacterial strains with the desired probiotic characteristics.[51]

A number of studies have attested to the therapeutic efficacy and ability of yogurt and fermented milks to successfully deliver probiotic bacteria to the human GIT.[52-62] Yogurt appears to act as an ideal transport medium for probiotic bacteria, as it has been shown to enhance the survival of bacteria through the upper GIT.[50] One study found that 10^8 bacteria given in a milk-base demonstrated greater fecal recovery after oral administration than 10^{10} organisms given as a freeze-dried powder. Thus, significantly smaller numbers of probiotic bacteria can be given in yogurt than in supplements to achieve similar numbers of viable organisms in the lower GIT.[63]

Fermented Vegetables—Sauerkraut and Kimchi

Fermented plant foods have always been an important component of the human diet, and are still common food items throughout the world, from sauerkraut in Eastern Europe to kimchi in Southeast Asia. Traditionally prepared, both these foods contain large amounts of probiotic bacteria. Strains of *L. plantarum* are involved in the final stages of fermentation in both kimchi and sauerkraut, and they typically reach populations of more than 10^8 bacteria/mL by the end stages of fermentation,[64-67] and thus are present in sufficient quantities to have therapeutic effects when consumed. Additionally, research found that many of the *L. plantarum* strains isolated from fermented foods can survive exposure to gastric acid and bile salts, thereby indicating an ability to survive transit through the upper GIT. These same strains were also able to

adhere to intestinal epithelial cells, thus fulfilling three of the main criteria needed by desirable probiotic organisms.[68] Kimchi and sauerkraut can be used as therapeutic tools in a similar manner to probiotic supplements and yogurts. However, the characteristics of the bacterial strains found in these fermented foods are not known, so therapeutic effects will not be as certain.

Some strains of *L. plantarum* isolated from fermented foods also utilize a mannose-specific mechanism to adhere to human intestinal cells. Many pathogenic bacteria and parasites (e.g., enterotoxigenic *E. coli*, *Shigella* spp., *Vibrio cholerae*, *Salmonella* spp., and *Giardia lamblia*) also utilize a mannose-specific binding mechanism.[69,70] Hence, strains of *L. plantarum* compete directly with these microorganisms for a limited number of binding sites along the human GIT. The consumption of traditionally prepared kimchi and sauerkraut may thus play a role in the prevention and treatment of gastroenteritis caused by these pathogens.

Supplements

The quality of probiotic supplements depends upon two main factors: (1) the characteristics of the strains contained in the supplement; and (2) adequate viability, so that sufficient numbers of bacteria are viable at the point of consumption. Bacterial strains used in probiotic supplements should ideally demonstrate all the characteristics outlined in Table 116-1. Viability at consumption depends upon a number of factors, such as proper manufacturing and the "hardiness" of the strain, as well as packaging and storing the product in the right amount of moisture and at the correct temperature. Many strains of lactobacilli and bifidobacteria do not respond well to freeze-drying (lyophilization), spray drying, or conventional frozen storage, and excessive temperature during packaging or storage can dramatically reduce viability. Typically, unless the product has been shown to be stable, refrigeration is necessary during storage and ideally during transport. Some products may not have to be refrigerated until after the bottle has been opened, however.

Some manufacturers utilize enteric coatings on their tablets and capsules to improve survival through the acidic medium of the stomach. Research suggests that this practice does enhance survival through the upper GIT,[71] although enteric coatings are not necessary if the strain has demonstrated satisfactory tolerance to gastric acid.

Although there are a number of excellent companies providing high-quality probiotic products, it is difficult to sort through all of the manufacturer's claims of superiority. Additionally, market-basket surveys found that some supplements contain potentially pathogenic contaminants,[72] whereas the majority fail to contain the species and quantity of bacteria listed on the label.[73]

Clearly, the clinician needs documentation of strain characteristics, product quality/viability, and microbiological content before prescribing to his or her patients.

CLINICAL APPLICATIONS

The intestinal flora plays a major role in the health of the host.[15,74] The beneficial effects of the intestinal flora include the stimulation of the immune system, synthesis of vitamins (B group and K), enhanced GIT motility and function, improved digestion and nutrient absorption, improvement of gas-induced abdominal distension, inhibition of pathogens (colonization resistance), metabolism of important plant compounds/drugs, and the production of short-chain fatty acids and polyamines.[15,75,76] Due to the important role of lactobacilli and bifidobacteria within the human GIT microflora, and therefore impact on human health, probiotic supplements can be used to promote overall good health. There are, however, several more specific uses for probiotics. These indications and the most appropriate probiotic strains for these conditions are detailed in Table 116-4.

USING THE RIGHT STRAIN

To achieve successful and reproducible clinical outcomes, it is imperative to use the exact probiotic strain that has been proven to have the specific therapeutic action that is desired. For example, *L. rhamnosus* GG was found to prevent viral gastroenteritis[77] and maintain ulcerative colitis in remission.[78] Other strains of *L. rhamnosus* cannot be assumed to act in a similar manner. The clinician who chooses to use the exact strain that had the effects in clinical trials can be confident of similar results. Using another closely related strain may or may not have any effect. Whenever possible, use the exact strain used in research, as other strains, even closely related ones, may not have the same effects. Table 116-4 outlines the most appropriate probiotic strains available for some common health conditions. If it is not possible to prescribe the specific strains delineated in Table 116-4, the best option is to use an alternative bacterial strain that possesses the characteristics outlined in Table 116-2.

DOSAGE

The dosage of probiotic foods and supplements is based solely upon the number of live organisms present in the product. Successful results have been attained in clinical trials using between 10^7 and 10^{11} viable bacteria per day.[129,178,180] Interestingly, it appears that 100 times fewer viable bacteria need to be given in a dairy medium than in a freeze-dried supplement to achieve similar numbers of live bacteria in the lower bowel.[63] Dairy appears to work as an ideal transport medium for the bacteria, enhancing their survival through the upper GIT.[50]

Supplements

Supplements are best consumed with meals to take advantage of the increased alkalinity of the gastric environment (which equates to greater bacterial survival).[181] A dosage of 10^8 bacteria per sitting is often mentioned in the probiotic literature as the minimum quantity of bacteria needed to produce therapeutic effects.[50,181] Additionally, there have been a handful of studies that demonstrated therapeutic effects utilizing 10^7 to 10^8 viable bacteria per dose.[129,178,182] However, most of the successful probiotic research utilized greater than or equal to 10^9 bacteria per dose.

The minimum concentration of probiotic bacteria needed to achieve therapeutic effects appears to be somewhat strain dependent, in that for some strains (e.g., *L. reuteri* MM53) 10^7 bacteria is a sufficient quantity to produce beneficial effects,[178] whereas for other strains, 10^9 viable bacteria is needed (e.g., *L. rhamnosus* GG—if given as lyophilized bacteria).[63] This situation, unfortunately, makes it hard to give firm dosage recommendations, as the minimum effective dosage appears to differ by strain. Thus, it is best practice to ensure that supplements contain bacteria in concentrations greater than or equal to 10^9 bacteria per dose, unless research has demonstrated that the specific strain contained in the supplement is effective in smaller amounts.

Therefore, the dosage of viable bacteria given in supplemental forms should generally be 10^9 to 10^{11} bacteria per dose. If a formulation contains multiple strains, each strain must be present in

TABLE 116-4 **Choosing the Right Strain for Specific Therapeutic Applications**

CONDITION	METHODOLOGY	MOST APPROPRIATE PROBIOTIC STRAIN(S)	RESULTS
Allergic rhinitis	R, DB, PC	*Lactobacillus acidophilus* NCFM and *Bifidobacterium lactis* BI-04	Tendency for fewer subjects to report runny nose in the probiotic group (76% vs 95%; $P = 0.078$) and to report nasal blocking (11% vs 33%; $P = 0.101$); fewer subjects had infiltration of eosinophils into the nasal mucosa (57% vs 95%; $P = 0.013$)[79]
	R, DB, PC	*L. rhamnosus* GG and *L. gasseri* TMC0356	Significant reduction in nasal blockage scores ($P < 0.05$) and reduction in symptom medication scores for nasal blockage ($P < 0.05$)[80]
Antibiotic use	Meta-analysis	*L. rhamnosus* GG	70% reduced risk of developing AAD in children ($P = 0.00003$)[81]
	R, DB, PC	*L. plantarum* 299v	31% reduced risk of developing loose or watery stools ($P = 0.012$); 49% reduced risk of experiencing nausea ($P = 0.0097$)[82]
	R, DB, PC	*L. reuteri* MM53	Reduced incidence of a number of GI symptoms relative to placebo in triple therapy-treated children: epigastric pain (15% vs 45%; $P < 0.04$), abdominal distension (0% vs 25%; $P < 0.04$), disorders of defecation (15% vs 45%; $P < 0.04$), and halitosis (5% vs 35%; $P < 0.04$)[83]
	R, DB, PC	*L. rhamnosus* GG, *L. acidophilus* LA5, and *B. lactis* Bb12	79% reduced risk of developing AAD ($P = 0.035$)[84]
	R, DB, PC	*Saccharomyces cerevisiae* Hansen CBS 5926	71% reduced risk of developing AAD ($P = 0.02$)[85]
Atopic eczema (AE)	Prevention		
	R, DB, PC	*L. paracasei* F-19	Cumulative incidence of eczema was significantly reduced at 13 mo (11% vs 22%; $P < 0.05$)[86]
	R, DB, PC	*L. reuteri* MM53	Incidence of eczema was similar in both groups at 2 y of age; infants in the MM53 group did have less IgE-associated eczema (8% vs 20%; $P = 0.02$) and less skin-prick test reactivity for those infants with allergic mothers (14% vs 31%; $P = 0.02$)[87]
	R, DB, PC	*L. rhamnosus* GG	49% reduced risk of eczema development at 2 y of age ($P = 0.008$); 43% reduced risk of eczema at 4 y of age ($P < 0.05$); 36% reduced risk at 7 y of age[88-90]
	R, DB, PC	*L. rhamnosus* HN001	49% reduced risk of eczema development at 2 y of age ($P = 0.01$)[91]
	Treatment		
	R, DB, PC	*B. lactis* Bb12	Addition of Bb12 to EHWF decreased SCORAD score to 0 vs 13.4 in EHWF only controls ($P = 0.002$) in infants with AE[92]
	R, DB, PC	*L. fermentum* VRI-003	Significantly more probiotic-receiving children had an improvement in SCORAD index compared with placebo controls (92% vs 63%; $P = 0.01$); more children in the probiotic group had mild AE at the end of the study compared with controls (54% vs 30%; $P = 0.066$)[93]
Bacterial gastroenteritis	*Clostridium difficile*		
	R, DB, PC	*L. plantarum* 299v	In antibiotic-treated, critically ill patients, 299v ingestion prevented colonization by *C. difficile* (none vs 19%; $P < 0.05$)[94]
	R, DB, PC	*S. cerevisiae* Hansen CBS 5926	In combination with high-dose vancomycin, supplementation reduced *C. difficile* recurrence (17% vs 50%; $P = 0.05$).[95]
	OL	*L. rhamnosus* GG	27/32 subjects with relapsing *C. difficile* diarrhea were cleared after a single oral administration; the remaining 5 subjects relapsed; 3 of these were re-treated and cured; the other 2 were lost to follow-up[96]
	Vancomycin-resistant enterococci (VRE)		
	R, DB, PC	*L. rhamnosus* GG	All subjects who received LGG were cleared of VRE compared with 8% of controls ($P < 0.001$)[59]
Bacterial vaginosis (BV)	R, DB, PC	*L. rhamnosus* GR-1 and *L. reuteri* RC-14	After a single dose of tinidazole and 4 wks oral treatment, subjects in the probiotic group had a higher rate of BV cure (88% vs 50%; $P = 0.001$); vaginal flora normalized in 75% of probiotic-treated subjects compared with 34% of controls ($P = 0.011$)[97]
	R, OL	*L. rhamnosus* GR-1 and *L. reuteri* RC-14	Intravaginal application of probiotics nightly for 5 d resulted in 90% cure rate by day 30; follow-up at days 6, 15, and 30 showed cure of BV in significantly more probiotic-treated subjects (16, 17, and 18/20, respectively) compared with metronidazole gel (9, 9, and 11/20, respectively; $P = 0.016$ at day 6, $P = 0.002$ at day 15, and $P = 0.056$ at day 30)[98]

TABLE 116-4 **Choosing the Right Strain for Specific Therapeutic Applications—cont'd**

CONDITION	METHODOLOGY	MOST APPROPRIATE PROBIOTIC STRAIN(S)	RESULTS
Bladder cancer	R, DB, PC	*L. paracasei* Shirota	Decreased tumor recurrence in patients with superficial bladder cancer ($P = 0.01$) except in subjects with recurrent multiple tumors [99]
	Animal	*L. rhamnosus* GG	Significantly increased the number of cured mice ($P = 0.006$) in a murine model of bladder cancer[100]
Chemotherapy-induced diarrhea	R, OL	*L. rhamnosus* GG	41% reduced frequency of severe diarrhea in subjects undergoing 5-fluorouracil-based chemotherapy for colorectal cancer ($P = 0.027$); 83% reduction in abdominal discomfort scores ($P = 0.025$); 55% decreased frequency in bowel toxicity-induced dose reductions ($P = 0.0008$)[101]
Chronic fatigue syndrome	R, DB, PC	*L. paracasei* Shirota	Significant decrease in anxiety symptoms compared with controls ($P = 0.01$)[102]
	OL	*L. paracasei* F19, *B. lactis* Bb12, and *L. acidophilus* NCFB 1748	Significant improvement in neurocognitive functioning compared with baseline ($P = 0.04$)[103]
Collagenous colitis	R, DB, PC	*L. acidophilus* LA5 and *B. lactis* Bb12	Compared with baseline, there was a median reduction in weekly bowel frequency (32-23; $P < 0.005$) and a reduction in number of days with liquid stools/wk (from 6-1; $P < 0.005$)[104]
	OL	*Escherichia coli* Nissle 1917	Decrease in stool frequency from 7.6-3.7/day ($P = 0.034$)[105]
Colon cancer—prevention	R, PC	*L. paracasei* Shirota	Decrease in fecal β-glucuronidase activity ($P < 0.05$)[60]
	R, PC	*L. rhamnosus* GG	Decrease in fecal β-glucuronidase ($P < 0.01$), nitroreductase ($P < 0.01$), and glycocholic acid hydrolase ($P < 0.05$) activities compared with baseline; decreased urinary *p*-cresol levels ($P < 0.05$)[58]
	OL	*L. acidophilus* NCFM	Decrease in the activities of fecal bacterial enzymes compared with baseline: β-glucuronidase ($P < 0.001$), nitroreductase ($P < 0.002$), and azoreductase ($P < 0.02$)[106]
Constipation	R, DB, PC	*B. lactis* Bb12	In elderly nursing home residents, defecation frequency improved after Bb12 ingestion ($P = 0.038$), as did the number of days experiencing normal bowel movements ($P = 0.002$)[107]
	R, DB, PC	*E. coli* Nissle 1917	Increase in number of stools/wk (4.9 vs 2.6; $P < 0.001$) and a decrease in occurrence of hard stools (both $P < 0.05$)[108]
	R, DB, PC	*L. paracasei* Shirota	Significant decrease in occurrence of moderate and severe constipation ($P < 0.001$) and in occurrence of hard stools ($P < 0.001$); increase in defecation frequency ($P = 0.004$); improvement in stool consistency ($P < 0.001$)[109]
Crohn's disease	R, OL	*S. cerevisiae* Hansen CBS 5926	In combination with mesalamine, probiotic treatment reduced relapse rate compared with mesalamine alone (6% vs 38%; $P = 0.04$)[110]
Cystic fibrosis	R, SB, PC, CO	*L. rhamnosus* GG	37% decrease in incidence of pulmonary exacerbations in children ($P = 0.003$); 50% reduction in hospital admissions ($P = 0.001$)[111]
Diverticular disease	OL	*E. coli* Nissle 1917	Addition to standard treatment resulted in significant lengthening of remission (2.4 vs 14.1 mo; $P < 0.001$)[112]
Gastrointestinal candidiasis	R, DB, PC	*L. rhamnosus* GG	69% decreased risk of gastrointestinal *Candida* colonization in preterm infants ($P = 0.01$); significantly reduced enteric *Candida* population in infants who were colonized ($P = 0.005$)[113]
Giardia infection	Animal	*L. johnsonii* La1	Ingestion of La1 before *Giardia* inoculation decreased numbers of infected gerbils compared with placebo-treated animals (27% vs 83%; $P = 0.01$); after 14 d, 100% of La1-treated animals were *Giardia*-free vs 57% of controls ($P = 0.02$); prevented parasite-induced mucosal damage[114]
Helicobacter pylori infection	R, DB, C	*L. casei* DN-114	Addition of DN-114 to triple therapy resulted in eradication of *H. pylori* in 92% of subjects vs 85% in controls ($P = 0.0045$)[115]
	R, DB, PC	*L. johnsonii* La1	In asymptomatic children, daily La1 ingestion for 3 wks resulted in *H. pylori* eradication in 15% of subjects vs 1.5% in controls ($P < 0.01$)[116]
	R, DB, PC	*L. reuteri* MM53	Treatment with omeprazole + MM53 eradicated *H. pylori* in 60% of subjects after 30 days compared with none in the placebo + omeprazole group ($P < 0.0001$)[117]
	R, OL	*L. acidophilus* LA5 and *B. lactis* Bb12	4 wks pretreatment with probiotics improved *H. pylori* eradication rates from 71%-85% ($P < 0.05$) after quadruple therapy in subjects in which triple therapy failed[118]

Continued

TABLE 116-4 **Choosing the Right Strain for Specific Therapeutic Applications—cont'd**

CONDITION	METHODOLOGY	MOST APPROPRIATE PROBIOTIC STRAIN(S)	RESULTS
	R, OL	*L. paracasei* Shirota	Addition of Shirota to triple therapy resulted in eradication of *H. pylori* in 94% of subjects vs 76% in controls ($P < 0.05$)[119]
	OL	*L. acidophilus* LA5 and *B. lactis* Bb12	Daily ingestion for 6 wks resulted in decreased *H. pylori* density ($P = 0.006$) and gastritis ($P = 0.015$) on the antrum, as well as decreased urea breath test values compared with baseline ($P < 0.05$)[61]
	OL	*L. acidophilus* NAS	Daily ingestion over a 2-mo period resulted in eradication of *H. pylori* in 43% of subjects[120]
HIV/AIDS-associated diarrhea	DB, PC	*L. rhamnosus* GR-1 and *L. reuteri* RC-14	Increase in CD4 counts observed in probiotic-treated female HIV-infected subjects compared with a decrease in controls ($P < 0.02$); all probiotic-treated subjects were free of diarrhea after 15-d treatment vs 9% of controls[121]
Hypercholesterolemia	R, DB, PC	*L. plantarum* 299v	10% decrease in total cholesterol ($P < 0.05$) and 7% decrease in LDL ($P < 0.05$) compared with baseline after 6 wks[122]
	OL	*Bacillus coagulans ATCC#31284*	32% decrease in total cholesterol over a 3-mo period[123]
Immune enhancement: decreased rates of infection	R, DB, PC	*B. lactis* Bb12	Reduced fever episodes by 34% ($P < 0.001$), diarrhea episodes by 58% ($P < 0.001$), and duration of diarrhea by 37% ($P < 0.001$) in infants[124]
	R, DB, PC	*L. acidophilus* NCFM	Reduced fever incidence by 53% ($P = 0.0085$) and coughing incidence by 41% ($P = 0.027$) in children; use of antibiotics reduced by 68% ($P = 0.0002$); 32% reduction in days absent from childcare ($P = 0.002$)[125]
	R, DB, PC	*L. acidophilus* NCFM & *B. lactis* Bi07	Reduced fever incidence by 73% ($P = 0.0009$), coughing incidence by 62% ($P = 0.005$), and rhinorrhea incidence by 59% ($P = 0.03$) in children; use of antibiotics reduced by 84% ($P < 0.0001$); 28% reduction in days absent from childcare ($P < 0.001$)[125]
	R, DB, PC, CO	*L. fermentum* VRI-003	Over a 4-mo winter period, elite male distance runners taking the probiotic reported less than half the number of days of respiratory symptoms (30 vs 72; $P = 0.00006$) compared with placebo; illness severity was also decreased ($P = 0.06$)[126]
	R, DB, PC	*L. johnsonii* La1	Percentage of days with infections decreased from 15.4 at baseline to 5.7 during probiotic treatment in elderly hospital inpatients ($P = 0.018$); this was significantly greater than the reduction in controls ($P = 0.047$)[127]
	R, DB, PC	*L. reuteri* MM53	Reduced fever episodes by 73% ($P < 0.001$), diarrhea episodes by 94% ($P < 0.001$), duration of diarrhea by 75% ($P < 0.001$), and childcare absences by 67% ($P = 0.015$) in infants[124]
	R, DB, PC	*L. reuteri* MM53	58% reduction in number of subjects reporting sick days in the MM53 group compared with placebo ($P < 0.01$); among shift workers, 33% of those in the placebo group reported sick over the 80-day study period vs none in the MM53 group ($P < 0.005$)[128]
	R, DB, PC	*L. rhamnosus* GG	16% fewer days absent from daycare in children ($P = 0.03$); 19% reduction in antibiotic use for respiratory tract infections ($P = 0.03$)[129]
	R, DB, PC	*L. rhamnosus* GG	34% reduced risk of upper respiratory tract infections in toddlers; 43% reduced risk of respiratory tract infections lasting >3 days; significantly fewer number of days with respiratory tract symptoms (all $P < 0.001$); trend for reduced number of days with GI symptoms ($P = 0.06$)[130]
	R, DB, PC	*L. rhamnosus* GG and *B. lactis* Bb12	56% reduced risk of otitis media in toddlers ($P = 0.014$); 48% reduced risk of antibiotic prescription ($P = 0.015$); 49% reduced risk of recurrent respiratory tract infections ($P = 0.022$)[131]
Infantile colic	R, OL	*L. reuteri* MM53	Significant reduction in daily crying time by day 7 in the MM53 group compared with the simethicone group ($P = 0.005$); improvement continued until day 28, when median crying time was reduced to 51 min/d in the MM53 group vs 145 min/d in controls ($P < 0.001$)[132]
Intestinal dysbiosis	OL	*L. rhamnosus* GG	Significant increases in fecal concentrations of bifidobacteria and lactobacilli (both $P < 0.05$); decrease in lecithinase-negative clostridia concentrations[133]

TABLE 116-4 **Choosing the Right Strain for Specific Therapeutic Applications—cont'd**

CONDITION	METHODOLOGY	MOST APPROPRIATE PROBIOTIC STRAIN(S)	RESULTS
	R, DB, PC	*B. lactis* Bb12	Significant increases in fecal concentrations of bifidobacteria (P <0.001) in preterm infants compared with placebo; decrease in enterobacteria (P = 0.015) and clostridia (P = 0.014)[134]
	R, DB, PC	*B. lactis* HN019	Significant increases in fecal concentrations of bifidobacteria (P <0.0005), lactobacilli (P <0.005), and enterococci (P <0.005) compared with baseline; decrease in coliforms (P <0.005)[135]
	R, DB, PC	*L. johnsonii* La1	Significant increase in fecal bifidobacteria (P <0.01) and lactobacilli (P <0.001) compared with placebo period; decrease in lecithin-positive clostridia (P <0.05)[136]
	R, PC	*L. paracasei* Shirota	Significant increase in fecal bifidobacteria concentrations compared with controls (P <0.05)[60]
IBS	R, DB, PC	*L. acidophilus* strains CUL-60 and CUL-21, *B. lactis* CUL-34, and *B. bifidum* CUL-20	Significant reduction in composite IBS symptom score (P = 0.0217) and improvement in quality of life scores (P = 0.0068) compared with controls[137]
	R, DB, PC, CO	*L. fermentum* VRI-003	Significant reductions in abdominal pain (P = 0.041), constipation (P = 0.045), alternating bowel habit (P = 0.021), flatulence (P = 0.001), and bloating (P = 0.006) scores observed after probiotic treatment, but not after placebo treatment[138]
	R, DB, PC	*L. plantarum* 299v	All subjects in 299v group reported improvement in abdominal pain scores vs 58% of controls (P = 0.012); more 299v-treated subjects rated their overall IBS symptoms as improved (95% vs 15%; P <0.0001)[139]
	R, DB, PC	*L. rhamnosus* GG, *L. rhamnosus* Lc705, *Propionibacterium freudenreichii ssp. shermanii* JS and *B. breve* Bb99	42% reduction in composite IBS symptom score vs 6% in placebo group (P = 0.015); borborygmi reduced compared with controls (P = 0.008)[140]
	R, DB, PC	*L. rhamnosus* GG, *L. rhamnosus* Lc705, *P. freudenreichii ssp. shermanii* JS, and *B. lactis* Bb12	37% reduction in composite IBS symptom score vs 9% in placebo group (P = 0.0083); reduction in abdominal distension (P = 0.023) and pain (P = 0.052) scores compared with controls[141]
	R, DB, PC	VSL#3	Significant reduction in flatulence scores compared with placebo (P = 0.011)[142]
	R, DB, PC	VSL#3	Significant reduction in abdominal bloating scores from baseline in VSL#3 group but not in controls (P = 0.046)[143]
Lactose intolerance	R, SB, CO	*L. acidophilus* LA5	Significantly decreased breath hydrogen values after ingestion of La5-inoculated milk (P <0.05)[144]
	R, SB, CO	*L. acidophilus* NCFM	90% of subjects who were symptomatic after ingestion of uninoculated milk experienced a reduction in symptoms after ingestion of milk inoculated with NCFM; mean symptoms were significantly reduced (P <0.001)[145]
Liver cirrhosis	R, PC	*E. coli* Nissle 1917	Increased fecal concentrations of lactobacilli and bifidobacteria; decreased stool counts of potentially pathogenic bacteria (P <0.001 vs controls); decreased level of endotoxin (P = 0.07) and overall Child-Pugh score (P = 0.07)[146]
	OL	*L. paracasei* Shirota	Significantly improved neutrophil phagocytic capacity compared with baseline (P <0.05)[147]
Nosocomial diarrhea	R, DB, PC	*L. rhamnosus* GG	80% reduced risk of nosocomial diarrhea in infants (P = 0.002)[77]
NSAID use/erosive gastritis	OL	*L. rhamnosus* GG	LGG pretreatment significantly reduced gastric permeability caused by indometacin administration (P = 0.012)[148]
Postpartum obesity	R, DB, PC	*L. rhamnosus* GG and *B. lactis* Bb12	At 12 mo postpartum, central obesity occurred in 25% of probiotic-treated subjects vs 43% in the placebo group; proportion of body fat was also 3.5% lower (P = 0.018)[149]
Prevention of dental caries	R, DB, PC	*L. rhamnosus* GG	49% reduced risk of dental caries in children (P = 0.004)[150]
	R, DB, PC, CO	*B. lactis* Bb12	Significantly decreased salivary levels of *Streptococcus mutans* (P <0.05)[151]
	R, DB, PC	*L. reuteri* MM53	Ingestion of probiotic lozenge significantly decreased oral carriage of *S. mutans* (P <0.05)[152]

Continued

TABLE 116-4 **Choosing the Right Strain for Specific Therapeutic Applications—cont'd**

CONDITION	METHODOLOGY	MOST APPROPRIATE PROBIOTIC STRAIN(S)	RESULTS
Prevention of gestational diabetes	R, DB, PC	*L. rhamnosus* GG and *B. lactis* Bb12	Probiotic combination reduced frequency of gestational diabetes by 62% ($P = 0.003$)[153]
Prevention of traveler's diarrhea (TD)	R, PC	*L. acidophilus* LA5 and *B. lactis* Bb12	Significantly fewer tourists given probiotics developed TD (43% vs 71%; $P < 0.001$)[154]
	R, DB, PC	*L. rhamnosus* GG	Risk of developing TD reduced in LGG group compared with placebo group (3.9 vs 7.4%; $P = 0.05$); 47% reduced risk of developing TD[155]
	R, DB, PC	*S. cerevisiae* Hansen 5926	21% reduction in incidence in 250 mg/d group ($P < 0.007$) and 25% reduction with 500 mg/d ($P < 0.002$) compared with placebo[156]
Radiation-induced diarrhea	R, DB, PC	VSL#3	In subjects undergoing adjuvant postoperative radiation therapy for sigmoid, rectal, or cervical cancer, VSL#3 significantly reduced incidence of radiation-induced diarrhea (52% vs 32%; $P < 0.001$); daily bowel movements were reduced (14.7 vs 5.1; $P < 0.05$); incidence of severe diarrhea was reduced (55% vs 1%; $P < 0.001$)[157]
	R, OL	*L. acidophilus* NCFB-1748	In patients receiving external pelvic radiotherapy for cervical or uterine cancer, diarrhea incidence was significantly reduced (27% vs 90%; $P < 0.01$)[158]
Small intestinal bacterial overgrowth	OL	*L. paracasei* Shirota	64% of subjects had a reversal in their positive early first rise in breath hydrogen after lactulose test results; median time of first rise in breath hydrogen increased from 45 to 75 min ($P = 0.03$); 28% decrease in flatulence scores from baseline ($P = 0.04$)[159]
Ulcerative colitis (UC)	R, DB, C	*E. coli* Nissle 1917	In conjunction with standard IBD therapy (corticosteroids), remission rate ($P = 0.05$) and time to remission was equivalent to mesalazine ($P = 0.009$); duration of remission was also equivalent ($P = 0.017$)[160]
Inducing remission	R, DB, PC	VSL#3	At 6 wks, 33% of VSL#3-treated subjects achieved a >50% decrease in the UC disease activity index vs 10% of controls ($P = 0.001$); at week 12, 43% of subjects in the VSL#3 group were in remission vs 16% of controls ($P < 0.001$)[161]
	R, DB, PC	VSL#3	In conjunction with standard IBD therapy (steroid induction and mesalamine maintenance), remission was achieved in 93% of VSL#3-treated children vs 36% of controls ($P < 0.001$); 21% relapsed within 1 y vs 73% of controls ($P = 0.014$).[162]
Maintaining remission	R, DB, C	*E. coli* Nissle 1917	Equally effective as mesalazine in preventing relapse ($P = 0.003$)[163]
	R, OL	*L. rhamnosus* GG	Equally effective as mesalazine in maintaining clinical remission; significantly more effective than mesalazine in prolonging the relapse-free time ($P < 0.05$)[78]
	OL	*E. coli* Nissle 1917	At 12 mo, the relapse rate was 25% in probiotic-treated teens vs 30% in the mesalazine group[164]
	OL	VSL#3	After 12 mo, 15/20 participants remained in remission, which compares favorably with rates of remission observed during long-term mesalazine therapy.[165]
Preventing pouchitis	R, DB, PC	VSL#3	Remission was maintained at 1 y in 85% of VSL#3-treated patients vs 6% of controls ($P < 0.0001$)[166]
	OL	*L. rhamnosus* GG	Significantly delayed first onset of pouchitis compared with no-treatment controls (cumulative risk at 3 y: 7% vs 29%; $P = 0.011$)[167]
Treating pouchitis	OL	VSL#3	69% of subjects achieved remission after treatment; significant reductions in mean pouchitis disease activity index scores from baseline ($P < 0.01$)[168]
Urinary tract infection (UTI)	R, DB, C	*L. rhamnosus* GR-1 and *L. reuteri* B-54	In women with recurrent UTIs, weekly intravaginal application resulted in a 73% decrease in UTI incidence compared with the previous year (1.6 infections vs 6.0; $P = 0.001$)[169]
Vaginal candidiasis (VC)	R, DB, PC	*L. acidophilus* NAS	In HIV-infected women, weekly intravaginal application of NAS was associated with a 50% reduced risk of VC ($P = 0.09$)[170]
	R, DB, PC	*L. rhamnosus* GR-1 and *L. reuteri* RC-14	After a single dose of fluconazole and 4 wks oral treatment, subjects in the probiotic group had reduced *Candida* colonization (10% vs 39%; $P = 0.014$) and decreased vaginal discharge (10% vs 35%; $P = 0.03$)[171]
	R, PC, CO	*L. acidophilus* LA5	Mean number of infections per 6 mo decreased while taking the probiotic (0.38 vs 2.54; $P = 0.001$); incidence of *Candida* colonization decreased during probiotic treatment (0.84 vs 3.23 per 6 mo; $P = 0.001$)[57]

TABLE 116-4 **Choosing the Right Strain for Specific Therapeutic Applications—cont'd**

CONDITION	METHODOLOGY	MOST APPROPRIATE PROBIOTIC STRAIN(S)	RESULTS
	OL	*L. rhamnosus* GG	Twice daily intravaginal application of LGG resulted in decreased symptoms of VC, as well as less erythema and discharge; 4/5 women who were positive for *Candida* at baseline had negative cultures at the end of 7 d[172]
Vaginal dysbiosis	R, DB, PC	*L. rhamnosus* GR-1 and *L. reuteri* RC-14	60% of postmenopausal women had a reduction in Nugent score by at least 2 grades after oral ingestion of the probiotic vs 16% of controls ($P = 0.0001$); median Nugent score decreased by 3 grades in the probiotic group vs 0 in controls after 14-d treatment ($P = 0.0001$)[173]
	R, PC	*L. rhamnosus* GR-1 and *L. reuteri* RC-14	Ingestion of the probiotic resulted in a significant increase in vaginal lactobacilli ($P = 0.01$), as well as a decrease in vaginal yeasts ($P = 0.01$) and coliform bacteria ($P = 0.001$) populations compared with controls[174]
	OL	*L. rhamnosus* GR-1 and *L. reuteri* RC-14	In women diagnosed with either BV or vaginitis, after antibiotic therapy and 15-d oral probiotic therapy, 92% of subjects had complete lactobacilli vaginal recolonization[175]
Viral gastroenteritis prevention	R, DB, PC	*B. lactis* Bb12 and *Streptococcus thermophilus*	In infants admitted to a long-term medical hospital, probiotic supplementation reduced diarrhea incidence (7 vs 31%; $P = 0.035$) and rotavirus shedding (10 vs 39%; $P = 0.025$)[176]
	R, DB, PC	*L. rhamnosus* GG	In hospitalized children, relative risk of rotavirus gastroenteritis was reduced by 87% ($P = 0.02$)[77]
Treatment	Meta-analysis	*L. rhamnosus* GG	Significantly reduced duration of rotavirus diarrhea by 2.1 d in children ($P = 0.006$); risk of diarrhea lasting >7 d was reduced by 75% ($P = 0.01$)[177]
	R, DB, PC	*L. reuteri* MM53	Duration of diarrhea reduced from 2.5 d in the placebo group to 1.5 d in MM53-treated toddlers ($P = 0.01$)[178]
	R, DB, PC	VSL#3	On day 4 of treatment, 89% of VSL#3-treated children had recovered vs 40% of controls ($P < 0.001$)[179]

AAD = antibiotic-associated diarrhea; C, controlled; CO, crossover; DB, double-blind; EHWF, extensively hydrolyzed whey formula; GI, gastrointestinal: IBD, inflammatory bowel disease; IgE = immunoglobulin-E; IBS, irritable bowel syndrome; LDL, low-density lipoprotein; NSAID, nonsteroidal antiinflammatory drug; OL, open-label; PC, placebo-controlled; R = randomized; SB, single-blind; SCORAD = SCORing Atopic Dermatitis ; VSL#3 = proprietary probiotic mixture.

amounts greater than or equal to 10^9, because dosages of less than 10^9 living bacteria may not produce therapeutic effects.

Yogurts

The minimum dosage of viable bacteria needed in a dairy medium is 10^8 per dose. Therapeutic yogurts contain greater than or equal to 10^6 viable bacteria per milliliter, thus a 100 g serving (approximately 1/2 cup) will provide sufficient probiotic bacteria for therapeutic effects.[181] Unfortunately, many so-called "acidophilus" and/or "bifidus" yogurts do not contain this minimum level.[183] Only yogurt brands that are guaranteed to contain this level of viable bacteria or those that have done so in market-basket surveys should be utilized. A serving of yogurt containing less than 10^8 viable bacteria is unlikely to have any medicinal effects beyond its inherent nutritional content.

A 100 g serving of yogurt contains only 3.1 to 3.5 g of lactose,[184] which is well below the threshold level in individuals with lactose intolerance. Hence, lactose-intolerant individuals should be able to consume the minimum amount of yogurt without ill effects.[185]

Fermented Vegetables

Traditionally prepared fermented vegetables generally contain more than 10^8 living bacteria per gram, thus 10 g is the minimum dosage required.[64,65]

TOXICITY

Lactobacilli have been consumed in large numbers throughout recorded history. The fermentation of foodstuffs is one of the oldest known uses of biotechnology, and even today, fermented foods and beverages constitute 20% to 40% of the human food supply worldwide. Thus, lactobacilli have a long history of safe use.[5]

In 143 human clinical trials, no adverse effects or events were reported by any of the 7526 subjects who participated in these studies.[5] Despite increased use of probiotic supplements worldwide, epidemiologic evidence suggests there has been no corresponding increase in cases of bacteremia or fungemia as a consequence.[186]

There have been a number of cases of fungemia reported in the literature from the oral administration of *Saccharomyces cerevisiae* (also known as *S. boulardii*). These have occurred almost exclusively in immunocompromised or critically ill individuals. Thus, administration of strains of *S. cerevisiae* should be limited to immunocompetent individuals.[187,188]

DRUG INTERACTIONS

Lactobacilli and bifidobacteria are negatively affected by alcohol and antibiotics.[189,190] Although there is no evidence that the organism interferes with the activity of most antibiotics, the metabolism of sulfasalazine, chloramphenicol palmitate, and phthalylsulfathiazole may be affected by some strains of *L. acidophilus*.[191]

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