World Gastroenterology Organisation Global Guidelines: Probiotics and Prebiotics

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The concept of beneficial microbes was first suggested by Elie Metchnikoff who postulated that lactic acid bacteria offered health benefits capable of promoting longevity. Disorders of the intestinal tract were frequently treated with viable nonpathogenic bacteria to change or replace the intestinal microbiota. The German professor Alfred Nissle isolated a nonpathogenic strain of *Escherichia coli* from the feces of a First World War soldier who did not develop enterocolitis during a severe outbreak of shigellosis. In Japan, Dr. Minoru Shirota isolated *Lacticaseibacillus paracasei* strain Shirota to battle diarrheal outbreaks.

Today, a search of human clinical trials in PubMed shows that over 1500 trials have been published on probiotics. Although these studies are heterogeneous with regard to the strains and populations included, accumulated evidence supports the view that benefits are measurable across many different outcomes that have been assessed. This article is an update of a previous publication in the Journal of Clinical Gastroenterology,[1] and is based on the guideline recently posted on the WGO website.

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.[2] Our glossary of terms is based on the definitions proposed by the International Scientific Association of Probiotics and Prebiotics. Lactobacilli, along with species of *Bifidobacterium*, have historically been common probiotics. In 2020, the genus *Lactobacillus* underwent a major restructuring to better address the wide diversity of microbes assigned to the genus. Twenty-three new genera were defined, including some with well-studied probiotic species (Table 1).

GLOSSARY OF TERMS

Probiotics	Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host
Prebiotic	A selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health
Synbiotics	A mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host. There are 2 types of synbiotic: complementary (mixtures of probiotics and prebiotics) and synergistic (mixtures of live microbes selected to utilize a coadministered substrate for a health effect)
Postbiotic	A preparation of inanimate microorganisms and/or their components that confers a health benefit on the host

The yeast *Saccharomyces boulardii* and some *E. coli* and *Bacillus* species are also used. Newcomers to the probiotic ranks include *Clostridium butyricum*, recently approved as a novel food in the European Union. Lactic Acid Bacteria, which have been used for the preservation of food by fermentation for thousands of years, may also potentially impart health benefits. However, the term "probiotic" should be reserved for live microbes that have been shown in controlled human studies to impart a health benefit. Fermentation is globally applied in the preservation of a range of raw agricultural materials, such as cereals, roots, tubers, fruit and vegetables, milk, meat, and fish.

The prebiotic concept, first proposed by Gibson and Roberfroid in 1995,[3] is a more recent one than probiotics. The key aspects of a prebiotic are that it is nondigestible by the host and that it leads to health benefits for the consumer through a positive influence on the resident beneficial microbes. The administration or use of prebiotics or probiotics is intended to influence the gut environment, which is inhabited by trillions of microbes, for the benefit of

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TABLE 1. New Names for Some Prominent Former *Lactobacillus* Probiotic Species. Still Included in the *Lactobacillus* Genus are *Lactobacillus acidophilus, L. gasseri, L. crispatus, L. johnsonii, L. helveticus, and L. delbrueckii* subsp. *bulgaricus* (Sometimes Abbreviated as *L. bulgaricus*).

Former name	New name
Lactobacillus casei	*Lacticaseibacillus casei*
Lactobacillus paracasei	*Lacticaseibacillus paracasei*
Lactobacillus rhamnosus	*Lacticaseibacillus rhamnosus*
Lactobacillus plantarum	*Lactiplantibacillus plantarum*
Lactobacillus brevis	*Levilactobacillus brevis*
Lactobacillus salivarius	*Ligilactobacillus salivarius*
Lactobacillus fermentum	*Limosilactobacillus fermentum*
Lactobacillus reuteri	*Limosilactobacillus reuteri*

From the International Scientific Association for Probiotics and Prebiotics (ISAPP), "The big breakup of *Lactobacillus,*" available at https://www.nestlenutrition-institute.org/infographics/big-breakup-lactobacillus.

human health. Both probiotics and prebiotics have been shown to have beneficial effects that extend beyond the gut, but this guideline will focus on gut effects.

Prebiotics typically consist of nonstarch polysaccharides and oligosaccharides, although other substances are being studied as candidate prebiotics—such as resistant starch, conjugated linoleic acid, and polyphenols. Most prebiotics are used as food ingredients in foods such as biscuits, cereals, chocolate, spreads, and dairy products. Commonly known prebiotics are:

- Oligofructose (fructooligosaccharide, FOS)
- Inulin
- Galactooligosaccharides (GOSs)
- Lactulose
- Breast milk oligosaccharides (human milk oligosaccharides or HMOs)

Lactulose is a synthetic disaccharide used as a drug for the treatment of constipation and hepatic encephalopathy. The prebiotic oligofructose is found naturally in many foods, such as wheat, onions, bananas, honey, garlic, and leeks. Oligofructose can also be isolated from chicory root or synthesized enzymatically from sucrose.

Fermentation of oligofructose in the colon may result in several physiologic effects, including:

- Increasing the numbers of bifidobacteria in the colon
- Increasing calcium absorption
- Increasing fecal weight
- Shortening gastrointestinal transit time
- Lowering blood lipid levels

However, the extent to which these physiological effects may be experienced by a consumer varies due to a number of factors, including baseline gut microbiota and diet.

It has been hypothesized that the increase in colonic bifidobacteria benefits human health by producing compounds that inhibit potential pathogens, by reducing blood ammonia levels, and by producing vitamins and digestive enzymes.

Synbiotics were originally described as appropriate combinations of prebiotics and probiotics. More recently, the concept of synbiotics has evolved to include both complementary and synergistic synbiotics. A complementary synbiotic is defined simply as a mixture of probiotic(s) and prebiotic(s), where the 2 components meet the criteria defined for each, including proper characterization, and are used at a dose shown to provide a health benefit. However, a synergistic synbiotic has been described as a mixture of a live microbe selected to utilize a coadministered substrate, which together leads to a documented health benefit. The components of a synergistic synbiotic do not need to independently meet the criteria for a probiotic or prebiotic (Fig. 1).

Genera, Species, and Strains Used as Probiotics

A probiotic strain is identified by the genus, species, subspecies (if applicable), and an alphanumeric designation that identifies a specific strain (Table 2). In the scientific community, there is an agreed nomenclature for genus, species, and subspecies names. Strain designations, product names, and trade names are not controlled by the scientific community. According to the guidelines of the World Health Organization (WHO) and Food and Agriculture

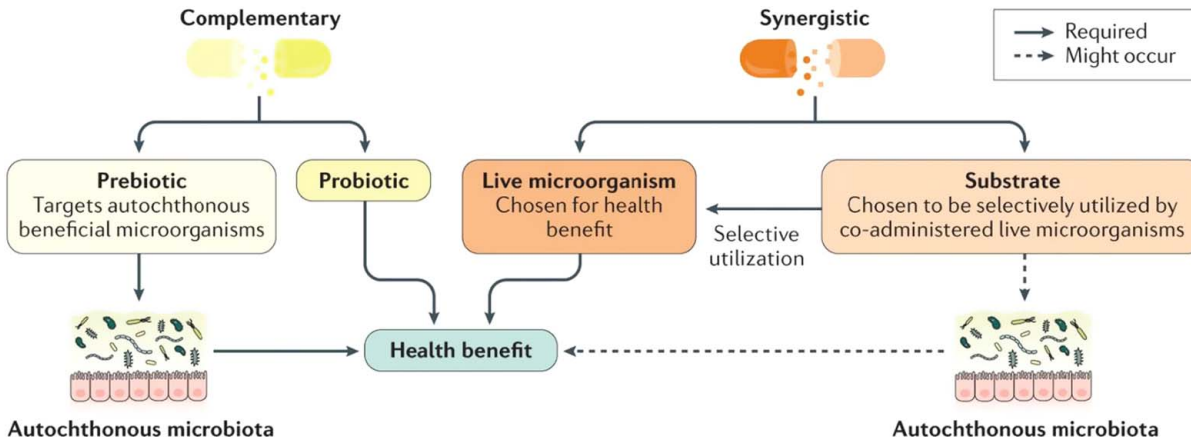

FIGURE 1. Composition of complementary and synergistic synbiotics. A complementary synbiotic combines a prebiotic and a probiotic, which work independently to elicit one or more health benefits. The prebiotic functions by modulating the resident microbiota to elicit a health benefit. The synergistic synbiotic is composed of a substrate that is utilized by the coadministered live microorganism, enhancing its functionality. Components of synergistic synbiotics work together (not independently) to bring about the resulting health benefits. (Reproduced from Swanson et al[4] CC BY 4.0).

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TABLE 2. Nomenclature Used for Probiotic Microorganisms

Genus	Species	Subsp.	Strain designation	International strain depository designation	Strain nickname	Product name
Lacticaseibacillus	*rhamnosus*	None	GG	ATCC 53103	LGG	Culturelle
Bifidobacterium	*animalis*	*lactis*	DN-173 010	CNCM I-2494	*Bifidus regularis*	Activia yogurt
Bifidobacterium	*longum*	*longum*	35624	NCIMB 41003	*Bifantis*	Align

ATCC (Manassas, Virginia, USA); CNCM (Institut Pasteur, Paris, France); NCIMB (Aberdeen, Scotland). The product commercial name shown in the table may only be used in some countries. ATCC indicates American Type Culture Collection; CNCM, Collection Nationale de Cultures de Microorganismes; NCIMB, National Collection of Industrial, Food and Marine Bacteria.

Organization (FAO; http://www.fao.org/3/a-a0512e.pdf), probiotic manufacturers should deposit their strains in an internationally recognized culture collection. Such depositories will give an additional designation to strains. Table 3 shows a few examples of commercial strains and the names associated with them.

Strain designations for probiotics are important because the most robust approach to probiotic evidence is to link benefits (such as the specific gastrointestinal targets discussed in this guideline) to specific strains or strain combinations of probiotics at the effective dose.

Recommendations of probiotics, especially in a clinical setting, should tie specific strains to the claimed benefits based on human studies. Some strains will have unique properties that may account for certain neurological, immunological, and antimicrobial activities. However, an emerging concept in the field of probiotics is to recognize that some mechanisms of probiotic activity are likely shared among different strains, species, or even genera. Many probiotics may function in a similar manner with regard to their ability to foster colonization resistance, regulate intestinal transit, or normalize perturbed microbiota. For example, the ability to enhance short-chain fatty acid production or reduce luminal pH in the colon may be a core benefit expressed by many different probiotic strains. Thus, some probiotic benefits may be delivered by different strains of certain well-studied species of probiotic genera.

TABLE 3. Mechanisms of Probiotic and Prebiotic Host Interaction. The Symbiosis Between Microbiota and the Host can be Optimized by Pharmacological or Nutritional Interventions in the Gut Microbial Ecosystem Using Probiotics or Prebiotics

Probiotics

Immunologic benefits
- Activate local macrophages to increase antigen presentation to B lymphocytes and increase secretory immunoglobulin A (IgA) production both locally and systemically
- Modulate cytokine profiles
- Induce tolerance to food antigens

Nonimmunologic benefits
- Digest food and compete for nutrients with pathogens
- Alter local pH to create an unfavorable local environment for pathogens
- Produce bacteriocins to inhibit pathogens
- Scavenge superoxide radicals
- Stimulate epithelial mucin production
- Enhance intestinal barrier function
- Compete for adhesion with pathogens
- Modify pathogen-derived toxins

Prebiotics
- Metabolic effects: production of short-chain fatty acids, absorption of ions (Ca, Fe, Mg)
- Enhancing host immunity (IgA production, cytokine modulation, etc.)

It is now common in the field of probiotics for systematic reviews and meta-analyses to include multiple strains. Such an approach is valid if shared mechanisms of action among the different strains included are demonstrated to be responsible for the benefit being assessed. Otherwise, such efforts should focus on strain-specific evidence.

Colonizing Microbiota

The functions of both probiotics and prebiotics for gastrointestinal end points are interwoven with the microbes that reside in the human gut. Prebiotics are utilized by beneficial members of the commensal microbial community, thereby promoting health. Crosstalk between probiotics and host cells or probiotics and resident microbes provides a key mechanism for influencing the host's health.

The intestine contains a large number of microbes, located mainly in the colon and comprising hundreds of species. Estimates suggest that over 40 trillion bacterial cells are harbored in the colon of an adult human being (including a small proportion of Archaea, less than 1%). Fungi and protists are also present, with a negligible contribution in terms of cell numbers, whereas viruses/phages may outnumber bacteria cells. Gut microbes add an average of 600,000 genes to each human being.[5]

At the level of species and strains, the microbial diversity between individuals is quite remarkable: each individual harbors his or her own distinctive pattern of bacterial composition, determined partly by the host genotype, by initial colonization at birth through vertical transmission, and by dietary habits.

In healthy adults, the fecal composition is stable over time. In the human gut ecosystem, the 2 bacterial divisions, Bacteroidetes and Firmicutes, predominate and account for more than 90% of microbes. The rest are *Actinobacteria, Proteobacteria, Verrucomicrobia,* and *Fusobacteria*.

The normal interaction between gut bacteria and their host is a symbiotic relationship. An important influence of intestinal bacteria on immune function is suggested by the presence of a large number of organized lymphoid structures in the mucosa of the small intestine (Peyer's patches) and large intestine (isolated lymphoid follicles). The epithelium over those structures is specialized for the uptake and sampling of antigens, and they contain lymphoid germinal centers for the induction of adaptive immune responses. In the colon, microorganisms proliferate by fermenting available substrates from diet or endogenous secretions and thereby contribute to host nutrition.

Many studies have shown that populations of colonizing microbes differ between healthy individuals and others with disease or unhealthy conditions. However, researchers are not able to define the composition of healthy human microbiota. Certain commensal bacteria (such as *Roseburia*, *Akkermansia*, *Bifidobacterium*, and *Faecalibacterium prausnitzii*) seem

to be associated more commonly with health, but it is a currently active area of research to determine whether supplementation with these bacteria will improve health or reverse disease.

Mechanisms of Action of Probiotics and Prebiotics

Prebiotics affect intestinal bacteria by enhancing the numbers or activities of beneficial bacteria. This may result in decreasing the population of potentially pathogenic microorganisms or reducing potentially deleterious metabolic activities of host microbiota. Prebiotics may also impact immune function.

Probiotic strains may mediate health effects through one or more of several identified mechanisms. Probiotics may affect the intestinal ecosystem by impacting mucosal immune mechanisms, by interacting with commensal or potential pathogenic microbes, by generating metabolic end products such as short-chain fatty acids, and by communicating with host cells through chemical signaling (Fig. 2; Table 3). These mechanisms can lead to antagonism of potential pathogens, an improved intestinal environment, bolstering the intestinal barrier, downregulation of inflammation, and upregulation of the immune response to antigenic challenges. These phenomena are thought to mediate the most beneficial effects, including reduction of the incidence and severity of diarrhea, which is one of the most widely recognized uses of probiotics.

Understanding the Marketplace

Probiotic-containing products have been successfully marketed in many regions of the world. A range of product types—from conventional food through prescription drugs—is available commercially (Table 4).

The claims that can be made on these types of products differ, depending on regulatory oversight in the region. Most commonly, probiotics and prebiotics are sold as foods or supplement-type products. Typically, no mention of disease or illness is allowed, claims tend to be general, and products are targeted at the generally healthy population. Natural health products represent a specific category in Canada, where the regulatory authorities approve claims and the labeling of the product for use in managing diseases is allowed.

From a scientific perspective, suitable descriptions of a probiotic product as reflected on the label should include:

- Genus, species (and subspecies, if applicable) identification, with nomenclature consistent with current scientifically recognized names
- Strain designation
- Viable count of each strain at the end of shelf-life
- Recommended storage conditions
- The recommended dose, which should be based on induction of the claimed physiological effect
- An accurate description of the physiological effect, as allowable by law
- Contact information for post-market surveillance

Products: Dosages and Quality

The global market for probiotics was valued at US$ 32.1 billion in 2013, according to a 2015 Grand View Research report. It is predicted that the worldwide probiotic market will progress rapidly at an annual growth rate of 8.1% to reach US $ 85.4 billion by 2027 ("Probiotics Market," https://www.marketsandmarkets.com/). Wading through the multitude of foods, supplements, and pharmaceutical products on the market is a daunting task. Most guidance from medical organizations is based on strains rather than product names, which can differ depending on the geographical region. It can be difficult to match probiotic strains to specific products, and not all products are suitably labeled. An effort to accomplish this has been undertaken in Canada and the United States, funded by unrestricted grants from commercial entities, and does link products to available evidence (see http://www.probioticchart.ca/ and http://usprobioticguide.com/).

The quality of probiotic products depends on the manufacturer concerned. Since most are not made to pharmaceutical standards, regulatory authorities may not oversee adherence to quality standards. The issues that are important specifically to probiotic quality include assurance of potency (maintenance of viability, typically indicated by colony-forming units, through the end of shelf-life), purity (manufacturing processes that sufficiently reduce any pathogens of concern), and identity (current nomenclature used to specify the genus, species, and subspecies, if applicable, and a strain designation for each strain in the product).

The dose needed for probiotics varies depending on the strain and product. Although many over-the-counter products deliver in the range of 1–10 billion cfu/dose, some products have been shown to be efficacious at lower levels, while some require substantially more. For example, *Bifidobacterium longum* subsp. *longum* 35624 was effective in alleviating the symptoms of IBS at 100 million cfu/day, whereas the effective dose of other probiotic products is 300 to 450 billion cfu 3 times daily. It is not possible to state a general dose that is needed for probiotics; the dosage should be based on human studies showing a health benefit.

Because probiotics are alive, they are susceptible to die-off during product storage. Manufacturers typically build in overages so that at the end of the product's shelf-life, it does not fall below the potency declared on the label. Responsible manufacturers will indicate the dose expected at the use-by date (not at the time of manufacture). Spore-forming

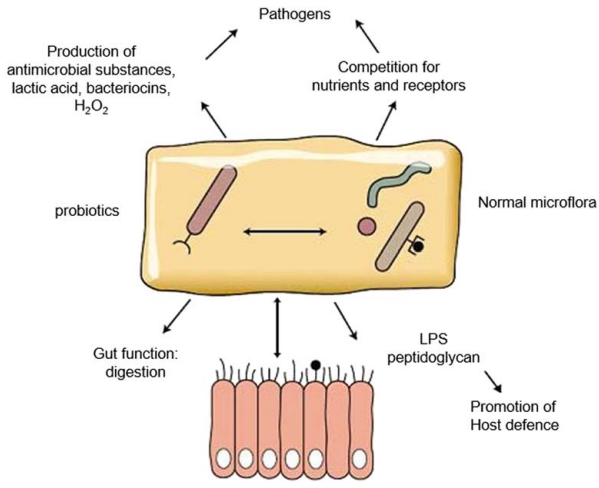

FIGURE 2. Mechanisms of microbiota and probiotic interaction with the host. The normal microbiota and probiotics interact with the host in metabolic activities and immune function and prevent colonization of opportunistic and pathogenic microorganisms. (Reproduced with permission from Blackwell Publishing Ltd.; journal through Copyright Clearance Center).

TABLE 4. Categories of Products Containing Probiotics

Product type	Target population	Type of claim possible
Food	Generally healthy	Improves or maintains health
Meal replacement	People with unique nutritional requirements	Healthy diet for the target consumer
Dietary supplement*	General population	Improves or maintains health
Natural health product†	Generally healthy or those with nonsevere medical conditions	Improves or maintains health or treats mild conditions
Over-the-counter drug	People needing to prevent or treat disease	Treats mild diseases
Prescription drug	People needing to prevent or treat disease	Treats or prevents disease

*Typically tablets, capsules, and sachets containing the bacteria in freeze-dried form.
†This category is specific to Canada.

probiotic strains have the advantage of superior resistance to environmental stress during shelf-life. However, robust evidence of the efficacy of spore-formers lags behind that for non–spore-forming probiotics. Probiotic products on the market have been shown in some cases to fail to meet label claims regarding the numbers and types of viable microbes present in the product. Purchasing products from reliable manufacturers is therefore essential.

Product Safety

Most probiotics in use today are derived either from fermented foods or from the microbes colonizing a healthy human and have been used in products for decades. On the basis of the prevalence of lactobacilli in fermented food, as normal colonizers of the human body, and the low level of infection attributed to them, their pathogenic potential is deemed to be quite low by experts in the field. *Bifidobacterium* species enjoy a similar safety record. Most products are intended by design for the generally healthy population, so use in persons with compromised immune function or serious underlying disease should be restricted to the strains and indications with proven safety and efficacy for these target patient populations, as described in section 4 below. Microbiological quality standards should meet the needs of at-risk patients, as reviewed by Sanders et al[6] . Testing or use of newly isolated probiotics or known probiotics for new disease indications are only acceptable after scrutiny and approval by an independent ethics committee. Traditional LAB, long associated with food fermentation, are generally considered safe for oral consumption as part of foods and supplements for the generally healthy population and at levels traditionally used.

CLINICAL APPLICATIONS

Current insights into the clinical applications (in alphabetical order) for probiotics or prebiotics in gastroenterology are summarized below. It should be noted that the description provides a general overview of clinical efficacy. However, the effects of probiotics are strain-specific and dose-specific, and for prebiotics, the effects are based on the particular formulation. For specific recommendations for different indications on the basis of levels of graded evidence, Tables 6 and 7 should be consulted. Meta-analyses are regarded as providing the highest level of evidence for evaluating clinical efficacy. However, applying meta-analysis to clinical trials with probiotics is fraught with problems due to the heterogeneity of trial designs, the heterogeneity of the probiotic interventions used, the heterogeneity of the populations studied, and the relatively small numbers included in each clinical trial. Such issues can plague meta-analyses conducted on any intervention, but the strain-specificity of effects needs to be carefully taken into account with meta-analyses on probiotics. Combining data on different probiotic strains without a rationale that similar underlying mechanisms of action are driving the effects observed should be avoided when using the results to make medical recommendations. While this section therefore deals with an overview of probiotic efficacy in clinical situations, Tables 6 and 7 detail individual probiotic preparations and clinical situations in which they have been found effective.

Treatment of Acute Diarrhea

- Some probiotic strains are useful in reducing the severity and duration of acute infectious diarrhea in children. Oral administration shortens the duration of acute diarrheal illness in children by ~1 day. Several meta-analyses of controlled clinical trials testing other probiotic strains have been published that show consistent results, suggesting that probiotics are likely to be safe and effective.

Prevention of Acute Diarrhea

- In the prevention of adult and childhood diarrhea, there is evidence that certain probiotics can be effective in some specific settings. A Cochrane meta-analysis based only on large trials with a low risk of bias[7] concluded that probiotics probably make little or no difference with diarrhea lasting 48 hours or longer. Early administration of probiotics may therefore be needed.

Prevention of Antibiotic-Associated Diarrhea

- In the prevention of antibiotic-associated diarrhea, there is evidence of efficacy in adults or children who are receiving antibiotic therapy. Meta-analyses concluded that probiotics may provide a moderate effect for preventing antibiotic-associated diarrhea in children,[8] adults,[9] and elderly adults.[10]

Prevention of *C. difficile* Diarrhea

A 2017 meta-analysis concluded with moderate certainty that probiotics are effective in preventing *C. difficile*-associated diarrhea in patients receiving antibiotics.[11] Probiotic use in patients who are not immunocompromised or severely debilitated appeared to be safe. The authors also cited the need for further research, but concluded that the data indicate that patients who are at high risk of developing *C. difficile*-associated diarrhea would benefit from being informed of the potential benefits and harms of probiotics.

TABLE 5. Levels of Evidence in Evidence-based Medicine for Treatment Benefits in Response to the Question "Does this Intervention Help?" (adapted from The Oxford 2011 Levels of Evidence, Oxford Centre for Evidence-Based Medicine)

Evidence level	Study type
Level 1*	A systematic review of randomized trials
Level 2*	Randomized trials with consistent effect, without systematic review
Level 3*	Supported by a single randomized controlled trial†
Level 4	Case-series, case–control studies, or historically controlled studies†
Level 5	Mechanism-based reasoning

*The level may be graded downward on the basis of study quality, imprecision, indirectness (the study's population, intervention, comparison, and outcome [PICO] does not match the question's PICO), because of inconsistency between studies, or because the absolute effect size is very small. The level may be graded upward if there is a large or very large effect size.

†A systematic review is considered to provide higher-quality evidence than an individual study.

Source: The Oxford 2011 Levels of Evidence, version 2.1 (OCEBM Levels of Evidence Working Group, Oxford Centre for Evidence-Based Medicine; http://www.cebm.net/index.aspx?o = 5653).

Prevention of Radiation-induced Diarrhea

The gut microbiota may play an important role in radiation-induced diarrhea by reinforcing intestinal barrier function, improving innate immunity, and stimulating intestinal repair mechanisms. A 2013 meta-analysis concluded that probiotics may be beneficial in the prevention and possibly in the treatment of radiation-induced diarrhea.[12]

Helicobacter Pylori Eradication

The 2022 Maastricht VI/Florence Consensus Report on the management of *H. pylori* infection concluded that certain probiotics have been shown to be effective in reducing gastrointestinal side effects caused by *Helicobacter pylori* eradication therapies and thus have a beneficial effect on the treatment. However, the quality of the evidence was weak, and the grade of recommendation was moderate.[13] There is no evidence to support the concept that a probiotic alone, without concomitant antibiotic therapy, would be effective. Instead, probiotics appear to increase the *H. pylori* eradication rate by reducing side effects related to eradication therapy rather than through direct effects on *H. pylori*.

Hepatic Encephalopathy Prevention and Treatment

Prebiotics such as lactulose are commonly used for the prevention and treatment of hepatic encephalopathy. Evidence for 1 probiotic mixture suggests that it can reverse minimal hepatic encephalopathy. A 2017 Cochrane meta-analysis found that evidence from 3 studies on the benefits of probiotics for people with hepatic encephalopathy was of low quality.[14] Although no difference in the mortality rate was observed, the authors concluded that probiotics may improve recovery, quality of life, and plasma ammonia concentrations.

Immune Response

There is suggestive evidence that several probiotic strains and the prebiotic oligofructose are useful in improving the immune response. Evidence suggestive of enhanced immune responses has been obtained in studies aimed at preventing acute infectious disease (nosocomial diarrhea in children, influenza episodes in winter) and in studies that tested antibody responses to vaccines.

Pouchitis

There is evidence for the usefulness of a probiotic mix in preventing an initial attack of pouchitis and in preventing further relapse after the induction of remission with antibiotics. The probiotic mix is recommended for adults and children with pouchitis of mild activity or as maintenance therapy for those in remission.[15]

Ulcerative Colitis

Individual studies show that certain probiotics may be safe and as effective as conventional therapy in response and remission rates in mild to moderately active ulcerative colitis in both adult and pediatric populations. However, a 2020 Cochrane meta-analysis concluded that evidence for the induction of remission in mild to moderate ulcerative colitis was of low certainty, and there was no evidence that probiotics were effective in more severe diseases.[16]

Crohn's Disease

Studies of probiotics in Crohn's disease have indicated that there is no evidence to suggest that they are beneficial for the induction or maintenance of remission of Crohn's disease.

Irritable Bowel Syndrome (IBS)

A reduction in abdominal bloating and flatulence as a result of probiotic treatments is a consistent finding in published studies; some strains may ameliorate pain and provide global relief. The literature suggests that certain probiotics may alleviate symptoms and improve the quality of life in persons with functional abdominal pain. Strain-specific effects of certain probiotics on IBS symptoms are shown in Tables 6 and 7.

Infant Colic

L. reuteri DSM 17938 and *B. animalis* ssp. *lactis* BB12 have been shown to reduce crying time in breastfed infants with colic (Table 7).

Lactose Malabsorption

Streptococcus thermophilus and *Lactobacillus delbrueckii* subsp. *bulgaricus* improves lactose digestion and reduces symptoms related to lactose intolerance. This was confirmed in a number of controlled studies with individuals consuming yogurt with live cultures.[17]

Necrotizing Enterocolitis

Probiotic supplementation reduces the risk of necrotizing enterocolitis in preterm neonates. Meta-analyses of randomized controlled trials have also shown a reduced risk of death in probiotic-treated groups, although not all probiotic preparations tested are effective. The number needed to treat to prevent 1 death from all causes by treatment with probiotics is 20. Special attention to adequate quality in the probiotic product is important for this vulnerable group of patients.[18] There was moderate certainty for reduction of the mortality rate and late-onset invasive infection, but no effect was observed on severe neurodevelopmental impairment.[19]

TABLE 6. List of Positive Randomized Controlled Trials With Probiotics and/or Prebiotics in Gastroenterology (Adult Indications)

Disorder, action	Probiotic strain / prebiotic/synbiotic	Recommended dose	Evidence level	References	Comments
Prophylaxis and treatment of oral candidiasis	*Lactobacillus rhamnosus* GG	50 g of probiotic cheese containing LGG	3	21	Reduction of prevalence of oral candida in the elderly
	Lactobacillus reuteri DSM 17938 and *L. reuteri* ATCC PTA 5289	1 × 10e8 cfu of each strain, twice daily	3	22	Reduction of prevalence of oral candida in nursing homes
	Lactobacillus rhamnosus HS111, *L. acidophilus* HS101, and *Bifidobacterium bifidum*	1 capsule a day	3	23	Reduction of prevalence of oral candida in denture wearers
Treatment of acute diarrhea in adults	*Lactobacillus paracasei* B21060 or *L. rhamnosus* GG	10e9 cfu, twice daily	3	24	
	Saccharomyces boulardii CNCM I-745	5 × 10e9 cfu or 250 mg, twice daily	3	25	
	Enterococcus faecium SF68	7.5 × 10e7 cfu, three times daily	3	26	
Antibiotic-associated diarrhea (AAD)	Yogurt with *L. casei* DN114, *L. bulgaricus* and *Streptococcus thermophilus*	≥ 10e10 cfu, twice daily	2	27,28	Prevention of AAD in hospitalized patients
	Lactobacillus acidophilus CL1285 and *L. casei* (Bio-K+ CL1285)	≥ 10e10 cfu, once daily	2	27,28	Prevention of AAD in various clinical settings (hospitalized and outpatients)
	Lactobacillus rhamnosus GG	10e10 cfu, twice daily	1	27–29	Prevention of AAD in various clinical settings (hospitalized and outpatients)
	Saccharomyces boulardii CNCM I-745	5 × 10e9 cfu or 250 mg, twice daily	1	27–30	Prevention of AAD in various clinical settings (hospitalized and outpatients)
	Lactobacillus reuteri DSM 17938	10e8 cfu, twice daily	3	31	Prevention of AAD in hospitalized patients
	Lactobacillus acidophilus NCFM, *L. paracasei* Lpc-37, *Bifidobacterium lactis* Bi-07, *B. lactis* Bl-04	1.7 × 10e10 cfu, once daily	3	28,32	Prevention of AAD in hospitalized patients
	Bifidobacterium bifidum W23, *B. lactis* W18, *B. longum* W51, *Enterococcus faecium* W54, *Lactobacillus acidophilus* W37 and W55, *L. paracasei* W72, *L. plantarum* W62, *L. rhamnosus* W71, and *L. salivarius* W24	5 g of the mix containing 10e9 cfu/g, twice daily	3	28,33	Reduction of diarrhea-like bowel movements in healthy volunteers receiving amoxycillin
	Lactobacillus rhamnosus GG, *L. acidophilus* La-5, and *B. animalis* subsp. *lactis* BB-12	2.5 × 10e10, 2.5×10e9, and 2.5 × 10e10 cfu, respectively, once daily	3	34	Prevention of AAD in hospitalized patients
	Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, and *Lactobacillus delbrueckii* subspecies *bulgaricus*, *Bifidobacterium breve, Bifidobacterium longum*, and *Bifidobacterium infantis,* and *Streptococcus salivarius* subsp. *thermophilus*	4.5 × 10e11 cfu, twice daily	3	35	Prevention of AAD in hospitalized patients
Prevention of *Clostridium* difficile-associated diarrhea (or prevention of recurrence)	*Lactobacillus acidophilus* CL1285 and *L. casei* LBC80R	≥ 10e10 cfu, once daily	2	11,36,37	Primary prevention
	Yogurt with *L. casei* DN114 and *L. bulgaricus* and *Streptococcus thermophilus*	10e7–10e8 cfu twice daily	3	11,36,37	Primary prevention
	Saccharomyces boulardii CNCM I-745	10e9 cfu or 250 mg, twice daily	2	11,36,37	Primary prevention

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TABLE 6. (*continued*)

Disorder, action	Probiotic strain / prebiotic/synbiotic	Recommended dose	Evidence level	References	Comments
	Lactobacillus acidophilus NCFM, *L. paracasei* Lpc-37, *Bifidobacterium lactis* Bi-07, *B. lactis* Bl-04	1.7 × 10e10 cfu, once daily	3	11,36,37	Primary prevention
	Lactobacillus acidophilus + *Bifidobacterium bifidum* (Cultech strains)	2 × 10e10 cfu, once daily	3	11,38	Primary prevention
	Oligofructose	4 g, three times daily	3	39	Prevention of recurrence
Coadjuvant therapy for *Helicobacter pylori* eradication	*Lactobacillus rhamnosus* GG	6 × 10e9 cfu, twice daily	2	40	Improved eradication rate and treatment compliance
	Bifidobacterium animalis subsp. *lactis* Bb12, *Lactobacillus rhamnosus* GG	10e8–10e10 cfu, twice daily	2	41	Improved eradication rate and treatment compliance
	Lactobacillus reuteri DSM 17938 and *L. reuteri* ATCC 6475,	1 × 10e8 cfu of each strain, twice daily	2	40	Improved eradication rate and treatment compliance
	Saccharomyces boulardii CNCM I-745	10e9 cfu or 250 mg, twice daily	2	40,42	Reduction in therapy-related side effects and improved compliance
	Bacillus clausii (Enterogermina strains)	2 × 10e9 spores, three times daily	2	43,44	Reduction in therapy-related side effects and improved compliance
	Kefir	250 ml twice daily	3	45	
Prevention of diarrhea associated with radiotherapy	Mixture containing strains of *Lactobacillus plantarum, L. casei, L. acidophilus, L. delbrueckii* subsp. *bulgaricus, Bifidobacterium infantis, B. longum, B. breve,* and *Streptococcus salivarius* subsp. *Thermophilus*	450 × 10e9 cfu, three times daily	3	46–48	Patients on radiotherapy after surgery for pelvic cancer
	Lactobacillus acidophilus plus *Bifidobacterium bifidum*	2 × 10e9 cfu, twice daily	3	47–49	Patients on radiotherapy after surgery for pelvic cancer
	Lactobacillus acidophilus LAC-361 and *Bifidobacterium longum* BB-536	1.3 × 10e9 cfu, twice daily	3	47,48,50	Patients on radiotherapy after surgery for pelvic cancer
	Lactobacillus acidophilus LA-5 plus *Bifidobacterium animalis* subsp. *lactis* BB-12	1.75 × 10e9 cfu, three times daily	3	51	Patients on radiotherapy after surgery for pelvic cancer
Prevention of diarrhea associated with enteral nutrition	Shen Jia fiber plus *Bifidobacterium* and *Lactobacillus* in tablets	30 g plus 6g	3	52	Postoperative patients with gastric cancer
	Bacillus cereus A05	5 × 10e6 cfu, every 6 h	3	53	*B. cereus* A05 was more effective than fiber in reducing diarrhea among patients receiving enteral nutrition
	Mixture containing strains of *Lactobacillus plantarum, L. casei, L. acidophilus, L. delbrueckii* subsp. *bulgaricus, Bifidobacterium infantis, B. longum, B. breve* and *Streptococcus salivarius* subsp. *Thermophilus*	450 × 10e9 cfu, twice daily	3	54	Reduction of incidence of liquid stool in critically ill patients receiving enteral nutrition
Liver disease					
Hepatic encephalopathy	Lactulose	45–90 g, daily	1	55	Prophylaxis of hepatic encephalopathy, and recovery from overt hepatic encephalopathy
	Mixture containing strains of *L. plantarum, L. casei, L. acidophilus, L. delbrueckii* subsp. *bulgaricus, Bifidobacterium infantis, B. longum, B. breve* and *Streptococcus salivarius* subsp. *thermophilus*	110 × 10e9 cfu, three times daily	3	14,56,57	Prophylaxis of hepatic encephalopathy
	Mixture containing strains of *Lactobacillus plantarum, L. casei, L. acidophilus, L. delbrueckii* subsp. *bulgaricus, Bifidobacterium infantis, B. longum, B. breve* and *Streptococcus salivarius* subsp. *thermophilus*	110 × 10e9 cfu, twice daily	3	14,57,58	Minimal hepatic encephalopathy reversal

	Yogurt with *Streptococcus thermophilus, Lactobacillus bulgaricus, L. acidophilus,* bifidobacteria and *L. casei*	12 ounces (340 g) daily	3	14,57,59	Minimal hepatic encephalopathy reversal
	Lactobacillus acidophilus	10e6 cfu, three times daily	3	14,60	Minimal hepatic encephalopathy reversal
	Lactobacillus plantarum 299v	10e10 cfu, twice a day	3	14,61	Prophylaxis of hepatic encephalopathy
NAFLD	Yogurt (with *Lactobacillus bulgaricus* and *Streptococcus thermophilus*) enriched with *L. acidophilus* La-5 and *Bifidobacterium lactis* Bb12	300 g daily	3	62	Improvement in aminotransferases
	Lactobacillus casei, L. rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, L. acidophilus, B. longum, and *L. bulgaricus*, plus fructooligosaccharide	2 × 10e8 cfu plus 250 mg FOS, twice daily	3	63,64	Improvement in aminotransferases, along with improved HOMA-IR and reduction of fibrosis score (elastography)
	Bifidobacterium longum W11 plus fructooligosaccharide	5 × 10e9 cfu plus 2.5 g FOS, once daily		65	Improvement in aminotransferases and NASH histological activity score
	Lactobacillus paracasei DSM 24733, *L. plantarum* DSM 24730, *L. acidophilus* DSM 24735 and *L. delbrueckii* subsp. *bulgaricus* DSM 24734, *Bifidobacterium longum* DSM 24736, *B. infantis* DSM 24737, *B. breve* DSM 24732, and *Streptococcus thermophilus* DSM 24731	225 × 10e9 cfu, three times daily	3	66	Improvement in aminotransferases and NASH histological activity score
	Yogurt with *Bifidobacterium animalis* subsp. *lactis* Bb12 and starter cultures, plus inulin	3 × 10e10 cfu Bb12 plus 1.5 g inulin in 300 g yogurt, once daily	3	67	Improvement in aminotransferases and steatosis score (ultrasonography)
IBS					
	Bifidobacterium bifidum MIMBb75	1 × 10e9 cfu, once daily	2	68,69	Improvement in global IBS symptoms and QoL. Heat-inactivated MIMBb75 also alleviates IBS symptoms[68]
	Lactobacillus plantarum 299v (DSM 9843)	1 × 10e9 cfu, once daily	2	70,71	Improvement in severity of abdominal pain and bloating
	Escherichia coli DSM17252	1.5–4.5 × 10e7 cfu, three times daily	3	72	Effect on persistence of symptoms
	Lactobacillus rhamnosus NCIMB 30174, *L. plantarum* NCIMB 30173, *L. acidophilus* NCIMB 30175 and *Enterococcus faecium* NCIMB 30176	10 × 10e9 cfu, once daily	3	73	Improvement in IBS score, mainly in pain and bowel habit score
	Lactobacillus animalis subsp. *lactis* BB-12®, *L. acidophilus* LA-5®, *L. delbrueckii* subsp. *bulgaricus* LBY-27, *Streptococcus thermophilus* STY-31	4 × 10e9 cfu, twice daily	3	74	Effect on persistence of symptoms
	Saccharomyces boulardii CNCM I-745	2 × 10e11 cfu, twice daily	3	75	Improvement in IBS-QoL score
	Bifidobacterium longum ssp longum 35624	1 × 10e8 cfu, once daily	2	71	Improvement in global assessment of IBS symptoms
	Bifidobacterium animalis DN-173 010 in fermented milk (with *Streptococcus thermophilus* and *Lactobacillus bulgaricus*)	1.25 × 10e10 cfu, twice daily	3	71	Improvement in HRQoL in constipation-predominant IBS
	Lactobacillus acidophilus SDC 2012, 2013	2 × 10e9 cfu, twice daily	3	71	Effect on persistence of symptoms
	Lactobacillus rhamnosus GG, *L. rhamnosus* LC705, *Propionibacterium freudenreichii* ssp. *shermanii* JS DSM 7067, *Bifidobacterium animalis* ssp. *lactis* Bb12 DSM 15954	10e10 cfu, once daily	2	71	Improvement in global assessment of IBS symptoms
	Short-chain fructooligosaccharides	5 g daily	3	76	Effect on persistence of symptoms
	Galactooligosaccharides	3.5 g daily	2	77–79	Effect on persistence of symptoms
			3	80	Improvement in IBS-QoL score

TABLE 6. (*continued*)

Disorder, action	Probiotic strain / prebiotic/synbiotic	Recommended dose	Evidence level	References	Comments
	Pediococcus acidilactici CECT 7483, *Lactobacillus plantarum* CECT 7484, *L. plantarum* CECT 7485	1–3 × 10e10 or 3–6 × 10e9 cfu, once daily			
	Mixture containing strains of *Lactobacillus plantarum, L. casei, L. acidophilus, L. delbrueckii* subsp. *bulgaricus, Bifidobacterium infantis, B. longum, B. breve* and *Streptococcus salivarius* subsp. *Thermophilus*	4 capsules containing 110 × 10e9 cfu, twice daily	3	81	Improvement of IBS symptoms
	Bifidobacterium longum NCC3001	1 × 10e10 cfu, once daily	3	82	Reduction of depression scores and improvement of QoL in IBS patients
	Bacillus coagulans MTCC 5856	2 × 10e9 cfu, once daily	3	83	Decrease in bloating, diarrhea, abdominal pain, and stool frequency in IBS-D patients
	Lactobacillus acidophilus PBS066 and *L. reuteri* PBS072	5 × 10e9 cfu, once daily	3	84	Effect on persistence of symptoms in IBS-C patients
	Lactobacillus rhamnosus LRH020, *L. plantarum* PBS067, and *Bifidobacterium animalis* subsp. *lactis* BL050	5 × 10e9 cfu, once daily	3	84	Effect on persistence of symptoms in IBS-C patients
	Saccharomyces cerevisiae CNCM I-3856	2–8 × 10e9 cfu, once daily	3	85	Improvement of symptoms in IBS overall population and IBS-C subpopulation
	Bacillus subtilis PXN 21, *Bifidobacterium bifidum* PXN 23, *B. breve* PXN 25, *B. infantis* PXN 27, *B. longum* PXN 30, *Lactobacillus acidophilus* PXN 35, *L. delbrueckii* spp. *bulgaricus* PXN39, *L. casei* PXN 37, *L. plantarum* PXN 47, *L. rhamnosus* PXN 54, *L. helveticus* PXN 45, *L. salivarius* PXN 57, *Lactococcus lactis* PXN 63, and *Streptococcus thermophilus* PXN 66	2 capsules containing 2×10e9 cfu, twice daily	3	86	Improvement of symptoms in patients with IBS-D
	Lactobacillus acidophilus DDS-1	1 × 10e10 cfu, once daily	3	87	Improvement of abdominal pain
	Bifidobacterium lactis UABla-12	1 × 10e10 cfu, once daily	3	87	Improvement of abdominal pain
	Lactobacillus acidophilus NCFM ATCC SD5221 and *L. acidophilus* subsp. *helveticus* LAFTI L10 CBS 116.411	5 × 10e9 cfu, twice daily	3	88	Decreases of abdominal pain, flatus, and composite scores
	Lactobacillus casei LMG 101/37 P-17504 (5×10e9 cfu/sachet), *L. plantarum* CECT 4528 (5×10e9 cfu/sachet), *Bifidobacterium animalis* subsp. *lactis* Bi1 LMG-P-17502 (10×10e9 cfu/sachet), *B. breve* Bbr8 LMG-P-17501 (10×10e9 cfu/sachet), *B. breve* Bl10 LMG-P-17500 (10×10e9 cfu/sachet).	One sachet once daily	3	89	Improvement of IBS-type symptoms in celiac disease patients on the strict gluten-free diet
	Bifidobacterium infantis NLS-SS	4 × 10e9 cfu, thrice daily	3	90	Improvement of IBS-type symptoms in celiac disease patients on the strict gluten-free diet
Functional constipation	*Bifidobacterium bifidum* (KCTC 12199BP), *B. lactis* (KCTC 11904BP), *B. longum* (KCTC 12200BP), *Lactobacillus acidophilus* (KCTC 11906BP), *L. rhamnosus* (KCTC 12202BP), and *Streptococcus thermophilus* (KCTC 11870BP)	2.5 × 10e8 cfu, once daily	3	91	Improvement of defecation frequency and symptoms in elderly nursing home residents
	Lactobacillus reuteri DSM 17938	1 × 10e8 cfu, twice daily	2	92,93	Improvement of defecation frequency and symptoms
	Lactulose	20–30 g/day	1	94	Prebiotics are commonly used as laxatives
	Oligofructose	12 g/day	1	95	Maintenance of normal defecation by increasing stool frequency

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	Fructooligosaccharide (FOS) and *Lactobacillus paracasei* (Lpc-37), *L. rhamnosus* (HN001), *L. acidophilus* (NCFM), and *Bifidobacterium lactis* (HN019)	6 g FOS plus 10e8–10e9 cfu, once daily	3	96	Improved evacuation in constipated women
	Pectin and Bifico strains (*Bifidobacterium longum, Lactobacillus acidophilus*, and *Enterococcus faecalis*)	8 g pectin plus 1 × 10e9 cfu of each strain, twice daily	3	97	Increased stool frequency, improved stool consistency, decreased colonic transit time, and improved constipation-related symptoms in patients with slow-transit constipation
	Lactococcus lactis subsp. *cremoris* FC	100 mg capsule, once daily	3	98	Increased stool frequency
	Bifidobacterium animalis subsp. *lactis* HN019	1 × 10e9 or 1 × 10e10 cfu, once daily	3	99	Increase in bowel movement frequency in participants with fewer than 3 bowel movements per week
	Lactulose plus *Bacillus coagulans* Unique IS2	10 g plus 2 × 10e9 cfu, once daily	3	100	*B. coagulans* Unique IS2 addition to lactulose reduced the time required to relieve constipation as compared to lactulose alone
	Lactobacillus acidophilus BCMC 12130, *L. casei* BCMC 12313, *L. lactis* BCMC 12451, *B. bifidum* BCMC 02290, *B. infantis* BCMC 02129 and *B. longum* BCMC 02120 with fructooligosaccharide	3 × 10e10 cfu plus 60 mg fructooligosaccharide, twice daily	3	101	Increased stool frequency and decreased colonic transit time in Parkinson's disease patients with constipation
	Lactobacillus casei strain Shirota in fermented milk	6.5 × 10e9, once daily	3	102	Reduces incidence of hard or lumpy stools in the healthy population
Uncomplicated symptomatic diverticular disease	*Lactobacillus casei* subsp. DG	2.4 × 10e10 cfu, once daily	2	103	Improvement in symptoms in uncomplicated diverticular disease
	Lactobacillus paracasei B21060	5 × 10e9 cfu, once daily	3	104	Improvement in symptoms in uncomplicated diverticular disease
	Bifidobacterium lactis LA 304, *Lactobacillus salivarius* LA 302, *L. acidophilus* LA 201	4 × 10e10 cfu, twice daily	3	105	The probiotic mix, in combination with the standard antibiotic therapy, reduced abdominal pain and CRP significantly more than antibiotic treatment alone
	Lactobacillus reuteri ATCC PTA 4659	1 × 10e8 cfu, twice daily	3	106	Reduced abdominal pain and inflammatory markers compared with antibiotics alone and resulted in shorter hospitalization
Prevention of postoperative complications	*Lactobacillus plantarum* CGMCC 1258, *L. acidophilus* 11 and *Bifidobacterium longum* 88	Total daily dose of 2.6 × 10e14 cfu	3	107,108	Reduced rate of postoperative septicemia
	Lactobacillus acidophilus NCFM, *L. rhamnosus* HN001, *L. paracasei* LPC-37, *Bifidobacterium lactis* HN019, and fructooligosaccharides	6 g FOS plus 4 × 10e9 cfu, twice daily	3	108,109	Reduced rate of postoperative infections
Small-bowel injury due to NSAIDs	*Lactobacillus casei* strain Shirota in fermented milk	6.5 × 10e9, once daily	3	110	Decreased the incidence of low-dose aspirin-associated small bowel injury
	Lactobacillus gasseri OLL2716 in fermented milk	112 mL of yogurt, twice daily	3	111	Decreased the incidence of low-dose aspirin-associated small-bowel injury
	Bifidobacterium breve Bif195	5 × 10e10, twice daily	3	112	Decreased the incidence of low-dose aspirin-associated small bowel injury
IBD Pouchitis					
	Mixture containing strains of *Lactobacillus plantarum, L. casei, L. acidophilus, L. delbrueckii* subsp. *bulgaricus, Bifidobacterium infantis, B. longum, B. breve* and *Streptococcus salivarius* subsp. *thermophilus*	1800 billion bacteria daily	2	113,114	Treatment of active pouchitis

TABLE 6. (*continued*)

Disorder, action	Probiotic strain / prebiotic/synbiotic	Recommended dose	Evidence level	References	Comments
	Mixture containing strains of *Lactobacillus plantarum, L. casei, L. acidophilus, L. delbrueckii* subsp. *bulgaricus, Bifidobacterium infantis, B. longum, B. breve* and *Streptococcus salivarius* subsp. *thermophilus*	1800 billion bacteria daily	2	114	Maintenance of clinical remission in pouchitis
	Mixture containing strains of *Lactobacillus plantarum, L. casei, L. acidophilus, L. delbrueckii* subsp. *bulgaricus, Bifidobacterium infantis, B. longum, B. breve* and *Streptococcus salivarius* subsp. *thermophilus*	1800 billion bacteria daily	2	114,115	Prevention of pouchitis in UC patients undergoing total colectomy
	Clostridium butyricum Miyairi	20 mg spores per tablet, 3 tablets three times per day	3	114,116	Prevention of pouchitis in UC patients undergoing total colectomy
Ulcerative colitis					
	Mixture containing strains of *Lactobacillus plantarum, L. casei, L. acidophilus, L. delbrueckii* subsp. *bulgaricus, Bifidobacterium infantis, B. longum, B. breve* and *Streptococcus salivarius* subsp. *thermophilus*	1800 billion bacteria twice daily	3	117	Induction of remission
	Escherichia coli Nissle 1917	5 × 10e10 viable bacteria 2 times daily	2	118,119	Maintenance of remission
	Bifid triple viable (Bifico strains: *Bifidobacterium longum*, *Lactobacillus acidophilus*, and *Enterococcus faecalis*)	420–630 mg, three times per day	2	120	Significant improvement in the clinical response to aminosalicylates
Reducing symptoms associated with lactose maldigestion	Yogurt with live cultures of *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus*	At least 10e8 cfu of each strain per gram of product	1	121	
	Lactobacillus acidophilus DDS-1	1 × 10e10, once daily	3	122	
	Bifidobacterium longum BB536 and *Lactobacillus rhamnosus* HN001 plus vitamin B6	4 × 10e9 plus 1 × 10e9 plus 1.4 mg	3	123	
	Pediococcus acidilactici CECT 7483, *Lactobacillus plantarum* CECT 7484, *L. plantarum* CECT 7485	3 × 10e9 cfu, once daily	3	124	

AAD indicates antibiotic-associated diarrhea; cfu, colony-forming unit; HOMA-IR, homeostasis model assessment of insulin resistance; HRQoL, health-related quality of life; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NSAID, nonsteroidal anti-inflammatory drug; QoL, quality of life; UC, ulcerative colitis.

TABLE 7. List of Positive Randomized Controlled Trials With Probiotics and/or Prebiotics in Gastroenterology (Pediatric Indications)

Disorder, action	Probiotic strain / prebiotic/synbiotic	Recommended dose	Evidence level	References	Comments
Acute gastro-enteritis	Probiotics as a general group	N/A	1	7	Reduced the risk of diarrhea lasting ≥ 48 h; reduced the mean duration of diarrhea (based on an updated Cochrane review including 82 RCTs (n = 12,127 participants), mainly in children (n = 11,526)
	L. rhamnosus GG	$\geq 10^{10}$ cfu/day, for 5–7 days	1	7,125,126	Reduced duration of diarrhea, length of hospitalization, and stool output. ESPGHAN 2022[125]
	*S. boulardii**	250–750 mg/day, for 5–7 days	1	7,125,127	Reduced duration of diarrhea. ESPGHAN 2022[125]
	L. reuteri DSM 17938	1×10^8 to 4×10^8 cfu/day, for 5 days	1	7,125,128	Reduced duration of diarrhea. ESPGHAN 2022[125]
	L. rhamnosus 19070-2 & *L. reuteri* DSM 12246	2×10^{10} cfu for each strain/day, for 5 days	1	125,129,130	Reduced duration of diarrhea. ESPGHAN 2022[125]
	B. lactis B94 + inulin	5×10^{10} cfu plus 900 mg once daily, respectively, for 5 days	3	131	Reduced duration of acute watery diarrhea
	L. paracasei B21060, plus arabinogalactan, and xylooligosaccharides	2.5×10^9 cfu plus 500 mg plus 700 mg, respectively, twice daily, for 5 days	3	132	Reduced duration of diarrhea
	L. rhamnosus strains 573L/1; 573L/2; 573L/3	1.2×10^{10} cfu or placebo, twice daily, for 5 days	3	133	Reduced duration of rotaviral diarrhea but not of diarrhea of any etiology
	L. delbrueckii var. bulgaricus, L. acidophilus, Streptococcus thermophilus, B. bifidum (LMG-P17550, LMG-P 17549, LMG-P 17503, LMG-P 17500)	10^9 cfu, 10^9 cfu, 10^9 cfu, 5×10^8 cfu/dose, for 5 days	3	134	Reduced duration of diarrhea
	B. lactis Bi-07, *L. rhamnosus* HN001, and *L. acidophilus* NCFM	Then 1.0×10^{10} cfu once a day, for the duration of diarrhea plus 7 days	3	135	Reduced duration of diarrhea and reduced hospital stay
Prevention of AAD	Probiotics as a general group	N/A	1	8	Reduced risk of AAD (a 2019 Cochrane review; 33 RCTs involving 6352 participants)
	*S. boulardii**	≥ 5 billion cfu per day, for the duration of antibiotic treatment	1	8,30,136	Reduced risk of AAD/diarrhea. ESPGHAN 2016[136] and 2022[125]
	L. rhamnosus GG	≥ 5 billion cfu per day, for the duration of antibiotic treatment	1	8,136,137	Reduced risk of AAD/diarrhea. ESPGHAN 2016[136] and 2022[125]
	Multispecies probiotic *(Bifidobacterium bifidum W23, B. lactis W51, Lactobacillus acidophilus W37, Lactobacillus acidophilus W55, Lacticaseibacillus paracasei W20, Lactoplantibacillus plantarum W62, Lacticaseibacillus rhamnosus W71, and Ligilactobacillus salivarius W24]*	10 billion cfu per day, for the duration of antibiotic treatment and for 7 days after	3	138	Reduced risk of diarrhea but not AAD. The definition of diarrhea/AAD matters
	L. rhamnosus (strains E/N, Oxy, and Pen)	2 × 10 (10) cfu, twice daily, for the duration of antibiotic treatment	3	139	Reduced risk of diarrhea

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TABLE 7. (*continued*)

Disorder, action	Probiotic strain / prebiotic/synbiotic	Recommended dose	Evidence level	References	Comments
Prevention of *C. difficile* diarrhea	*S. boulardii**	250–500 mg	1	136	ESPGHAN 2016[136] and 2022;[125] AGA 2020;[15] reduced risk of *C. difficile*-associated diarrhea
Prevention of nosocomial diarrhea	*L. rhamnosus GG*	At least 10^9 cfu/day, for the duration of the hospital stay	1	140,141	ESPGHAN 2022;[125] reduced risk of nosocomial diarrhea
Prevention of necrotizing enterocolitis	Systematic reviews and meta-analyses (> 10,000 neonates) of RCTs		1	19,142–144	Some specific strains of probiotic may be effective for preventing NEC among preterm infants
	L. rhamnosus GG	From 1×10^9 cfu to 6×10^9 cfu	1	18,145	ESPGHAN 2020[18] and 2022;[125] AGA 2020[15]
	B. infantis BB-02, *B. lactis* BB-12, and *S. thermophilus* TH-4	3.0 to 3.5×10^8 cfu (of each strain)	1	18,145	ESPGHAN 2020[18] and 2022[125]
	B. animalis subsp. *lactis* Bb-12 or B94	5×10^9 cfu	3	142,145	
	L. reuteri ATCC 55730 or DSM 17938	1×10^8 cfu (various regimens)	1	142,145,146	ATCC 55730; this strain is no longer available. Recommended by AGA 2020,[15] but not ESPGHAN 2020[18] or 2022[125]
	B. longum subsp. *infantis* ATCC 15697 + *L. acidophilus* ATCC 4356	125 mg/kg/dose twice daily with breast milk until discharge	3	145,147	
	B. longum subsp. *longum* 35624 + *L. rhamnosus* GG	5×10^8 cfu and 5×10^8 cfu, respectively	3	145	
Helicobacter pylori infection	Probiotics as a general group		1	148–152	Improved eradication rates and/or reduced side effects of anti–*H. pylori* treatment
	*S. boulardii**	500 mg	1	150,151,153,154	Increased eradication rate (however, it was still below the desired level [≥ 90%] of success) and in reducing gastrointestinal adverse effects associated with *H. pylori* infection therapies. ESPGHAN 2022[125]
	*Lactobacillus (*now *Lactiplantibacillus) plantarum* (UBLP 40), *L acidophilus* (LA-5), *B animalis* subsp. *lactis* BB-12, and *S. boulardii* Unique-28	Per capsule: *L. plantarum* (0.5×10^9 cfu), *L. acidophilus* LA-5 (1.75×10^9 cfu), BB-12 (1.75×10^9 cfu), and *S. boulardii* (1.5×10^9 cfu), twice daily for 15 days	3	155	Increased eradication rate and decreased side effects
	Fermented milk containing *L. casei DN114 001*	10^{10} cfu/day for 14 days	3		
Infantile colic	Probiotics as a general group	N/A	1	156–165	
Infantile colic—management	*L. reuteri* DSM 17938	10^8 cfu/day for at least 21 days	1	156,160,162,166	Reduced crying and/or fussing time in breastfed infants, but its role in formula-fed infants is less clear. ESPGHAN 2022[125]
	B. lactis Bb12	10^8 cfu/day, for 21–28 days	2	167,168	Reduced crying and/or fussing time in breastfed infants with infantile colic. ESPGHAN 2022[125]
	L. rhamnosus 19070-2 and *L. reuteri* 12246 in a daily dose of 250 × 10â ¶ cfu, 3.33 mg of fructooligosaccharide	250 × 10â ¶ cfu, respectively, plus 3.33 mg of fructooligosaccharide, for 28 days	3	169	Reduced crying and/or fussing time in breastfed infants

	L. paracasei DSM 24733, *L. plantarum* DSM 24730, *L. acidophilus* DSM 24735, *L. delbrueckii* subsp. *bulgaricus* DSM 24734), *B. longum* DSM 24736, *B. breve* DSM 24732, and *B. infantis* DSM 24737, and *S. thermophilus* DSM 24731	5 billion cfu, for 21 days	3	170	Reduced crying in exclusively breastfed infants
Infantile colic – prevention	*L. reuteri* DSM 17938	10^8 cfu/day, to newborns each day for 90 days	1	158,171	Reduced crying time in both breastfed and formula fed infants
Functional abdominal pain disorders		N/A	1	172–174	No firm evidence for the use of probiotics (as a group) in children with FAPD
Functional abdominal pain / IBS	*L. reuteri* DSM 17938	10^8 cfu to 2 $\times 10^8$ cfu/day	1	172,174,175	ESPGHAN 2022[125]
	L. rhamnosus GG	10^9 cfu to 3×10^9 cfu twice daily	1	174,176	ESPGHAN 2022[125]
Ulcerative colitis	Probiotics as a group	N/A	1	16	May induce clinical remission in patients with active ulcerative colitis
	A mixture of 8 strains (*L. paracasei* DSM 24733, *L. plantarum* DSM 24730, *L. acidophilus* DSM 24735, *L. delbrueckii* subsp. *bulgaricus* DSM 24734, *B. longum* DSM 24736, *B. infantis* DSM 24737, *B. breve* DSM 24732, and *S. thermophilus* DSM 247), as adjuvant therapy or in those intolerant to 5-ASA	Daily dosages: 4–6 y (17–23 kg) 1 sachet (450 billion); 7–9 y (24–33 kg) 2 sachets (900 billion); 11–14 y (34–53 kg) 3 sachets (1350 billion); 15–17 y (54–66 kg) 4 sachets (1800 billion)	3	177	For induction and maintenance of remission. ESPGHAN & ECCO 2018[178]
	Escherichia coli Nissle 1917 (as adjuvant therapy or in those intolerant to 5-ASA)	200 mg/day (in adults and adolescents; no dosing is available for young children)	3	118,119,179	For induction and maintenance of remission. ESPGHAN & ECCO 2018[178]
Pouchitis	A mixture of 8 strains (*L. paracasei* DSM 24733, *L. plantarum* DSM 24730, *L. acidophilus* DSM 24735, *L. delbrueckii* subsp. *bulgaricus* DSM 24734, *B. longum* DSM 24736, *B. infantis* DSM 24737, *B. breve* DSM 24732, and *S. thermophilus* DSM 247)	Daily dosages: 4–6 y (17–23 kg) 1 sachet (450 billion); 7–9 y (24–33 kg) 2 sachets (900 billion); 11–14 y (34–53 kg) 3 sachets (1350 billion); 15–17 y (54–66 kg) 4 sachets (1800 billion)	3	180,181	Maintaining remission (but in adult patients) with chronic pouchitis ESPGHAN & ECCO 2018[178] and AGA 2020[15]
Nonalcoholic fatty liver disease	*Lactobacillus acidophilus* in combination with other strains of *Bifidobacterium* or *Lactobacillus* may be beneficial for improving levels of transaminases and lipid parameters, ultrasonographic and anthropometric characteristics in children with NAFLD. However, current evidence does not allow specification of the exact beneficial strain of probiotic		1	182	

*Most studies with the strain *S. boulardii* CNCM I-745.

AAD indicates antibiotic-associated diarrhea; AGA, American Gastroenterological Association; cfu, colony-forming unit; ECCO, European Crohn's and Colitis Organization; ESPGHAN, European Society for Paediatric Gastroenterology Hepatology and Nutrition; FAPD, functional abdominal pain disorder; IBS, irritable bowel syndrome; N/A, not available; NEC, necrotizing enterocolitis; RCT, randomized controlled trial.

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Nonalcoholic Fatty Liver Disease

The usefulness of certain probiotics as a treatment option to mitigate steatohepatitis has been proven through a number of randomized clinical trials in adults and children. Probiotics provided improvements in the outcomes of homeostasis model assessment (HOMA), blood cholesterol, TNF-α, and liver function tests (ALT and AST). Further studies are needed to confirm long-term benefits.

Prevention of Systemic Infections

There is insufficient evidence to support the use of probiotics or synbiotics in critically ill adult patients in intensive-care units.

Although it is beyond the scope of this guideline, it may be of interest to readers to note that probiotics and prebiotics have been shown to affect several clinical outcomes that are outside the normal spectrum of gastrointestinal disease. Emerging evidence suggests that gut microbiota may affect several nongastrointestinal conditions, thereby establishing a link between these conditions and the gastrointestinal tract. Numerous studies have shown that probiotics can reduce bacterial vaginosis, prevent atopic dermatitis in infants, reduce oral pathogens and dental caries, and reduce the incidence and duration of common upper respiratory tract infections. The net benefit of probiotics during the perinatal period in preventing allergic disease has led to a World Allergy Organization recommendation on probiotic use during pregnancy, breastfeeding, and weaning in families with a high risk of allergic disease.[20] Probiotics and prebiotics are also being tested for the prevention of some manifestations of the metabolic syndrome, including excess weight, type 2 diabetes, and dyslipidemia.

Summaries of Evidence for Probiotics and Prebiotics in Adult and Pediatric Conditions—the Global Picture

We have comprehensively evaluated the evidence for gastrointestinal conditions. Table 5 lists the criteria used to establish the level of evidence.

Tables 6 and 7 summarize a number of gastrointestinal conditions for which there is evidence from at least 1 well-designed clinical trial that oral administration of a specific probiotic strain or a prebiotic is effective. The purpose of these tables is to inform the reader about the existence of studies that support the efficacy and safety of the products listed, as some other products on sale in the market may not have been tested. The column headed "Comments" includes the most recent (2020–2022) recommendations from major pediatric gastroenterology societies such as the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition and the American Gastroenterological Association.

For Tables 6 and 7, probiotics had to be described by genus, species, and strain designations in studies reporting the benefit. If the strain was not given, the strain designation was not included. Only positive studies (ie, studies showing statistically significant results for its main outcome) were included. Negative (null) studies were not included (ie, studies in which the results for the main outcome were not statistically significant). For each condition, a list of the probiotic strains or prebiotics found to have a beneficial effect is presented.

For clinical decisions, however, only evidence related to a specific probiotic strain and/or prebiotic is relevant. Each study should be considered within the context of the totality of the relevant evidence. The risk of bias in the included trials was not assessed.

The list may not be complete, as the publication of new studies is ongoing. Locally, other probiotics and/or prebiotics evaluated in randomized controlled trials (RCTs) may be available. The level of evidence may vary among the different indications. Doses shown are those used in the RCTs. The order of the products listed is random.

There is no evidence from comparative studies to rank the products in terms of efficacy. The tables do not provide grades of recommendation but only levels of evidence according to evidence-based medicine criteria.

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