World Gastroenterology Organisation Global Guidelines

Probiotics and prebiotics

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1.1 History and definitions

Over a century ago, Elie Metchnikoff (a Russian scientist, Nobel laureate, and professor at the Pasteur Institute in Paris) postulated that lactic acid bacteria (LAB) offered health benefits capable of promoting longevity. He suggested that "intestinal auto-intoxication" and the resultant aging could be suppressed by modifying the gut microbiota and replacing proteolytic microbes—which produce toxic substances including phenols, indoles, and ammonia from the digestion of proteins—with useful microbes. He developed a diet with milk fermented with a bacterium that he called "Bulgarian bacillus."

Other early developments of this concept ensued. Disorders of the intestinal tract were frequently treated with viable nonpathogenic bacteria to change or replace the intestinal microbiota. In 1917, before Sir Alexander Fleming's discovery of penicillin, the German scientist 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. The resulting *Escherichia coli* strain Nissle 1917 is one of the few examples of a non-LAB probiotic.

Henry Tissier (of the Pasteur Institute) isolated a *Bifidobacterium* from a breast-fed infant with the goal of administering it to infants suffering from diarrhea. He hypothesized that it would displace proteolytic bacteria that cause diarrhea. In Japan, Dr. Minoru Shirota isolated *Lactobacillus casei* strain Shirota to battle diarrheal outbreaks. A probiotic product with this strain has been marketed since 1935.

These were early predecessors in a scientific field that has blossomed. Today, a search of PubMed for human clinical trials shows that over 1500 trials have been published on probiotics and close to 350 on prebiotics. Although these studies are heterogeneous with regard to strain(s), prebiotics tested, and populations included, accumulated evidence supports the view that benefits are measurable across many different outcomes.

Probiotics are live microorganisms that confer a health benefit on the host when administered in adequate amounts [1] (Table **1**). Species of *Lactobacillus* (Fig. **1**) and *Bifidobacterium* are most commonly used as probiotics, but the yeast *Saccharomyces boulardii* and some *E. coli* and *Bacillus* species are also used. Newcomers include also *Clostridium butyricum*, recently approved as a novel food in European Union. Lactic acid bacteria, including *Lactobacillus* species, which have been used for preservation of food by fermentation for thousands of years, can act as agents for food fermentation and, in addition, potentially impart health benefits. Strictly speaking, 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 (cereals, roots, tubers, fruit and vegetables, milk, meat, fish, etc.).

Table 1 Definitions

Concept	Definition
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	Products that contain both probiotics and prebiotics, with conferred health benefits
Lactic acid bacteria (LAB)	A functional classification of nonpathogenic, nontoxigenic, Gram-positive, fermentative bacteria that are associated with the production of lactic acid from carbohydrates, making them useful for food fermentation. Species of *Lactobacillus, Lactococcus,* and *Streptococcus thermophilus* are included in this group. Many probiotics are also LABs, but some probiotics (such as certain strains of *E. coli,* spore-formers, and yeasts used as probiotics) are not
Fermentation	A process by which a microorganism transforms food into other products, usually through the production of lactic acid, ethanol, and other metabolic end products

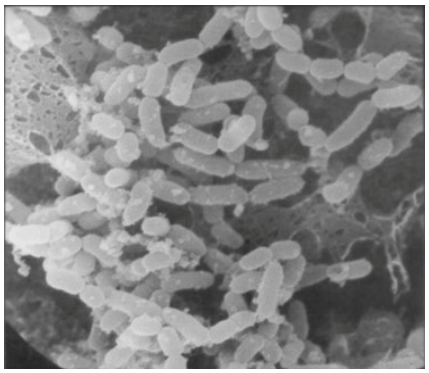


Fig. 1 Electron micrograph of *Lactobacillus salivarius UCC118* adhering to Caco-2 cells. Reproduced with permission of Blackwell Publishing Ltd.

1.2 Prebiotics and synbiotics

The prebiotic concept is a more recent one than probiotics and was first proposed by Gibson and Roberfroid in 1995 [2]. The key aspects of a prebiotic are that it is not digestible by the host and that it leads to health benefits for the individual through a positive influence on native beneficial microbes. The administration or use of prebiotics or probiotics is intended to influence the gut environment, which is dominated by trillions of commensal microbes, for the benefit of 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 are dietary substances (mostly consisting of nonstarch polysaccharides and oligosaccharides). Most prebiotics are used as food ingredients—in biscuits, cereals, chocolate, spreads, and dairy products, for example. Commonly known prebiotics are:

- Oligofructose
- Inulin
- Galacto-oligosaccharides

- Lactulose
- Breast milk oligosaccharides

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 results in a large number of physiologic effects, including:

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

The increase in colonic bifidobacteria has been assumed to benefit human health by producing compounds to inhibit potential pathogens, by reducing blood ammonia levels, and by producing vitamins and digestive enzymes.

Synbiotics are appropriate combinations of prebiotics and probiotics. A synbiotic product exerts both a prebiotic and probiotic effect.

1.3 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. In the scientific community, there is an agreed nomenclature for microorganisms—for example, *Lactobacillus casei* DN-114 001 or *Lactobacillus rhamnosus* GG. Marketing and trade names are not controlled by the scientific community. According to WHO/FAO guidelines (http://www.fao.org/3/a-a0512e.pdf), probiotic manufacturers should register their strains with an international depository. Depositories will give an additional designation to strains. Table **2** shows a few examples of commercial strains and the names associated with them.

Table 2 Nomenclature used for probiotic microorganisms

Genus	Species	Subspecies	Strain designation	International strain depository designation	Strain nickname	Product name
Lactobacillus	*rhamnosus*	None	GG	ATTC 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, American Type Culture Collection; CNCM, National Collection of Microorganisms Cultures; NCIMB, National Collection of Industrial and Marine Bacteria.

Using strain designations for probiotics is important, since 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. Some probiotic benefits may therefore be delivered by many strains of certain well-studied species of *Lactobacillus* and *Bifidobacterium*. If the goal of probiotic consumption is to support digestive health, perhaps many different probiotic preparations containing adequate numbers of well-studied species will be sufficient.

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.

1.4 Colonizing microbiota

The functions of both probiotics and prebiotics are interwoven with the microbes that colonize humans. Prebiotics serve as a food source for beneficial members of the commensal microbial community, thereby promoting health. Cross-talk between probiotics and host cells, or probiotics and resident microbes, provides a key means of influencing host health.

The intestine contains a large number of microbes, located mainly in the colon, and comprising hundreds of species (Table **3**). Estimates suggest that over 40 trillion bacteria 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. Altogether, gut microbes add an average of 600,000 genes to each human being.

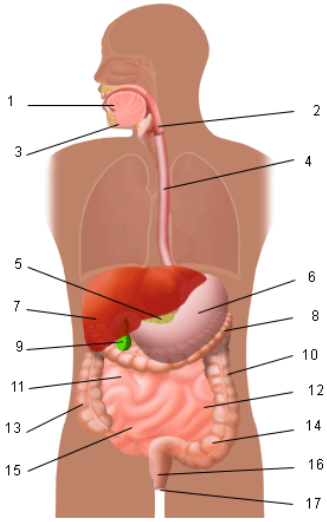
At the level of species and strains, the microbial diversity between individuals is quite remarkable: each individual harbors his or her own distinctive pattern of bacterial composition, determined partly by the host genotype, by initial colonization at birth via vertical transmission, and by dietary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

In healthy adults, the fecal composition is stable over time. In the human gut ecosystem, two bacterial divisions predominate—*Bacteroidetes* and *Firmicutes*—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 these structures is specialized for the uptake and sampling of antigens and contains lymphoid germinal centers for induction of adaptive immune responses. In the colon, microorganisms proliferate by fermenting available substrates from the diet or endogenous secretions and 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 still not able to define the composition of a healthy human microbiota. Certain commensal bacteria (such as *Roseburia*, *Akkermansia*, *Bifidobacterium*, and *Faecalibacterium prausnitzii*) appear to be associated more commonly with health, but it is a current active area of research to determine whether supplementation with these bacteria may improve health or reverse disease.

Table 3 Human intestinal microbiota. The gut microbiota form a diverse and dynamic ecosystem, including bacteria, archaea, eukaryotes, and viruses that have adapted to live on the intestinal mucosal surface or within the gut lumen

Stomach and duodenum	• Harbor very low numbers of microorganisms: < 10^3 cells per gram of contents • Mainly lactobacilli and streptococci • Acid, bile, and pancreatic secretions suppress most ingested microbes • Phasic propulsive motor activity impedes stable colonization of the lumen (also true for the small intestine)	
Jejunum and ileum	• Numbers progressively increase from 10^4 in the jejunum to 10^7 cells per gram of contents in the distal ileum	
Large intestine	• Heavily populated by anaerobes: up to 10^{12} cells per gram of luminal contents	

Key: 1, mouth; 2, pharynx; 3, tongue; 4, esophagus; 5, pancreas; 6, stomach; 7, liver; 8, transverse colon; 9, gallbladder; 10, descending colon; 11, duodenum; 12, jejunum; 13, ascending colon; 14, sigmoid colon; 15, ileum; 16, rectum; 17, anus.

1.5 Mechanisms of action of probiotics

Prebiotics affect intestinal bacteria by increasing the numbers of beneficial anaerobic bacteria and decreasing the population of potentially pathogenic microorganisms. Probiotics 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 **4**). These mechanisms can lead to antagonism of potential pathogens, an improved intestinal environment, bolstering the intestinal barrier, down-regulation of inflammation, and up-regulation of the immune response to antigenic challenges. These phenomena are thought to mediate most beneficial effects, including a reduction in the incidence and severity of diarrhea, which is one of the most widely recognized uses of probiotics.

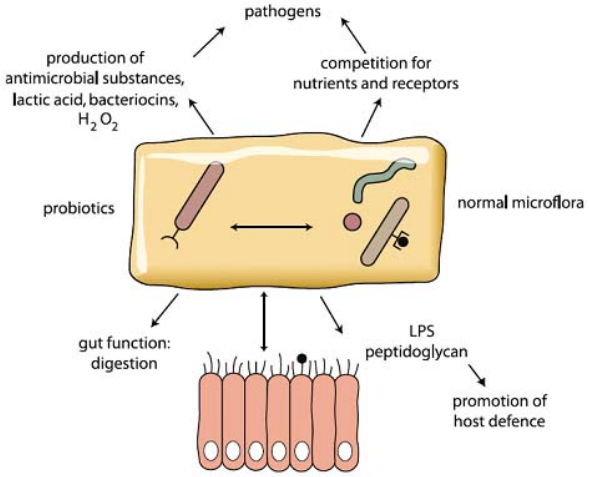


Fig. 2 Mechanisms of interaction between microbiota and probiotics with the host. The normal microbiota and probiotics interact with the host in metabolic activities and immune function and prevent colonization of opportunistic and pathogenic microorganisms. Reproduced with permission of Blackwell Publishing Ltd.

Table 4 Mechanisms of probiotic and prebiotic host interaction. 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.)	

2 Products, health claims, and commerce

2.1 Understanding the marketplace

Probiotic-containing products have been successful in many regions of the world. A range of product types—from conventional food through prescription drugs—is available commercially (Table **5**).

Table 5 Spectrum of products containing probiotics

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

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

The claims that can be made about these types of product differ depending on regulatory oversight in each 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 for the generally healthy population. "Natural health products" is a category specific to Canada, where the regulatory authorities approve claims and the use of the product to manage diseases is permitted.

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

- Genus and species 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
- Safety under the conditions of recommended use
- Recommended dose, which should be based on induction of the claimed physiological effect
- An accurate description of the physiological effect, as far as is allowable by law
- Contact information for post-market surveillance

The global market for probiotics was valued at US $32.06 billion in 2013, according to a 2015 Grand View Research report. Wading through the multitude of foods, supplements, and pharmaceutical products on the market is a daunting task. Some guidance is provided by the documents listed in Table **6**.

Table 6 Evidence-based lists of probiotic products and their associated benefits. Both lists have been funded by unrestricted grants from commercial entities

Organization	Title	Reference
European Society of Primary Care Gastroenterology	*Consensus Guidelines on Probiotics*	http://espcg.eu/wp-content/uploads/2013/09/ENGLISH-LEAFLET-ESPCG-2013-Consensus-Guidelines-on-Probiotics.pdf
Global Alliance for Probiotics	*Clinical Guide to Probiotic Supplements Available in Canada*	http://www.probioticchart.ca/
	Clinical Guide to Probiotic Supplements Available in the United States	http://usprobioticguide.com/

2.2 Products: dosages and quality

The quality of probiotic products depends on the manufacturer concerned. Since most are not made to pharmaceutical standards, the regulatory authorities may not oversee adherence to quality standards. The issues that are important specifically for probiotic quality include maintenance of viability (as indicated by colony-forming units, or CFU) through the end of the product's shelf-life and using the current nomenclature to identify the genus, species, and strain of all organisms included in the product.

The dose needed for probiotics varies greatly 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 inflammatory bowel syndrome (IBS) at 100 million CFU/day, whereas studies with VSL#3 (now branded as Vivomixx in some countries) have used sachets with 300–450 billion CFU three 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. Responsible manufacturers 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. Spore-forming probiotic strains, although not as well studied as others, do have the advantage of superior resistance to environmental stress during shelf-life. 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.

Note: A specified range of permissible colony-forming units should perhaps be required in order to minimize the risks of toxicity as well as loss of effect between production and the end of shelf-life [3,4].

2.3 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 designed for the generally healthy population, so use in persons with compromised immune function or serious underlying disease is best restricted to the strains and indications with proven efficacy, as described in section 4. Microbiological quality standards should meet the needs of at-risk patients, as reviewed by Sanders et al. [4]. Testing or use of newly isolated probiotics in other disease indications is only acceptable after approval by an independent ethics committee. Traditional lactic acid bacteria, 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.

3 Clinical applications

Current insights into the clinical applications for various probiotics or prebiotics in gastroenterology are summarized below. Specific recommendations for different indications are based on levels of graded evidence (Table **7**) and are summarized in Tables **8** and **9**.

3.1 Colorectal cancer prevention

- Although diet is thought to contribute to the onset of colorectal cancer, and both probiotics and prebiotics have been shown to improve biomarkers associated with colorectal cancer, there are limited data in humans showing any benefit of probiotics or prebiotics in the prevention of colorectal cancer.

3.2 Diarrhea treatment and prevention

3.2.1 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 approximately 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. However, the mechanisms of action may be strain-specific.

3.2.2 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.

3.2.3 Prevention of antibiotic-associated diarrhea

- In the prevention of antibiotic-associated diarrhea, there is strong evidence of efficacy in adults or children who are receiving antibiotic therapy.

3.2.4 Prevention of *Clostridium difficile* diarrhea

- A 2016 meta-analysis [5] concluded that probiotics can reduce the risk of developing *C. difficile*–associated diarrhea in patients receiving antibiotics. However, the authors caution that additional studies are needed in order to determine the best dosage and strain.

3.2.5 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 [6] concluded that probiotics may be beneficial in the prevention and possibly in the treatment of radiation-induced diarrhea.

3.3 *Helicobacter pylori* eradication

- The 2016 Maastricht V/Florence Consensus Report on management of *H. pylori* infection concluded that probiotics and prebiotics show promise in reducing side effects of treatment for *H. pylori*. However, the quality of the evidence and the grade of recommendation were low. A 2014 meta-analysis of randomized trials [7] suggests that supplementation of anti–*H. pylori* antibiotic regimens with certain probiotics may also be effective in increasing eradication rates and may be considered helpful for patients with eradication failure. There is no evidence to support the concept that a probiotic alone, without concomitant antibiotic therapy, would be effective.

3.4 Hepatic encephalopathy prevention and treatment

- Prebiotics such as lactulose are commonly used for the prevention and treatment of hepatic encephalopathy. Evidence for one probiotic mixture suggests that it can reverse minimal hepatic encephalopathy.

3.5 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 studies that tested antibody responses to vaccines.

3.6 Inflammatory bowel disease (IBD)

3.6.1 Pouchitis

- There is good evidence for the usefulness of certain probiotics in preventing an initial attack of pouchitis, and in preventing further relapse of pouchitis after the induction of remission with antibiotics. Probiotics can be recommended to patients with pouchitis of mild activity, or as maintenance therapy for those in remission.

3.6.2 Ulcerative colitis

- Certain probiotics have been found to be safe and as effective as conventional therapy in achieving higher response and remission rates in mild to moderately active ulcerative colitis in both adult and pediatric populations.

3.6.3 Crohn's disease

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

3.7 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 patients with functional abdominal pain.

3.8 Colic

- Certain probiotic strains have been shown to reduce crying time in breastfed infants with colic.

3.9 Lactose malabsorption

- *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaricus* improve lactose digestion and reduce symptoms related to lactose intolerance. This was confirmed in a number of controlled studies with individuals consuming yogurt with live cultures.

3.10 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 one death from all causes by treatment with probiotics is 20.

3.11 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 of assessment (HOMA) scores, blood cholesterol, tumor necrosis factor-α (TNF-α), and liver function tests—alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Further studies are needed to confirm long-term benefits.

3.12 Prevention of systemic infections

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

Although it is outside 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 non-gastrointestinal 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 lead to a World Allergy Organization recommendation on probiotic use during pregnancy, breastfeeding, and weaning in families with a high risk of allergic disease. 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.

4 Summaries of evidence for probiotics and prebiotics in adult and pediatric conditions—the global picture

Tables **8** and **9** summarize a number of gastrointestinal conditions for which there is evidence from at least one 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 for sale on the market may not have been tested.

The list may not be complete, as the publication of new studies is ongoing. The level of evidence may vary between the different indications. The doses shown are those used in the randomized controlled trials. 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 in accordance with the Oxford Centre for Evidence-Based Medicine criteria (Table **7**). Recommendations by medical associations are also shown.

Table 7 Oxford Centre for Evidence-Based Medicine levels of evidence for treatment benefits relative to the question "Does this intervention help?"

Evidence level	Study type
1*	Systematic review of randomized trials or *n*-of-1 trials
2*	Randomized trial or observational study with dramatic effect
3*	Nonrandomized controlled cohort / follow-up study †
4*	Case-series, case-control studies, or historically controlled studies †
5	Mechanism-based reasoning

Source: "2011 Levels of Evidence," Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/index.aspx?o=5653).

* The level may be downgraded on the basis of study quality, imprecision, indirectness—the study's population, intervention, comparison, and outcome (PICO) criteria do not match the question's PICO; because of inconsistency between studies; or because the absolute effect size is very small. The level may be upgraded if there is a large or very large effect size.

† As always, a systematic review is generally better than an individual study.

Table 8 Evidence-based *adult* indications for probiotics, prebiotics, and synbiotics in gastroenterology. * Oxford Centre for Evidence-Based Medicine levels of evidence (see Table **7**)

ADULT Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
Diarrhea					
Treatment of acute diarrhea in adults	*Lactobacillus paracasei* B 21060 or *L. rhamnosus* GG	10^9 CFU, twice daily	3	[8]	–
	Saccharomyces boulardii CNCM I-745, strain of *S. cerevisiae*	10^9 CFU/capsule of 250 mg twice daily	2	[9,10]	–
Antibiotic-associated diarrhea	Yogurt with *Lactobacillus casei* DN114, *L. bulgaricus,* and *Streptococcus thermophilus*	≥ 10^{10} CFU daily	1	[11]	Prevention of AAD in various clinical settings (in-patients and outpatients)
	Lactobacillus acidophilus CL1285 and *L. casei* (Bio-K+ CL1285)	≥ 10^{10} CFU daily	1	[11]	
	Lactobacillus rhamnosus GG	10^{10} CFU/capsule twice daily	1	[11]	
	Saccharomyces boulardii CNCM I-745	10^9 CFU/capsule of 250 mg twice daily	1	[11,12]	
	Lactobacillus reuteri DSM 17938	1×10^8 CFU twice daily	3	[13]	Prevention of AAD in hospitalized patients
	Lactobacillus acidophilus NCFM, *L. paracasei* Lpc-37, *Bifidobacterium lactis* Bi-07, *B. lactis* Bl-04	1.70^{10} CFU	2	[14]	
	Ecologic® AAD (*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)	10^9 CFU/g (5 g twice daily)	2	[15]	–
Prevention of *Clostridium difficile*–associated diarrhea (or prevention of recurrence)	*Lactobacillus acidophilus* CL1285 and *L. casei* LBC80R	5×10^{10} CFU daily and $4–10 \times 10^{10}$ CFU daily	2	[16]	–
	Yogurt with *Lactobacillus casei* DN114 and *L. bulgaricus* and *Streptococcus thermophilus*	$10^7–10^8$ CFU twice daily	2	[17]	–

ADULT Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
	Saccharomyces boulardii CNCM I-745	10^9 CFU/capsule of 250 mg twice daily	3	[17]	–
	Lactobacillus rhamnosus HN001 + *L. acidophilus* NCFM	10^9 CFU once daily	3	[18]	Reduced fecal counts of *Clostridium difficile* in healthy elderly patients without diarrhea
	Lactobacillus acidophilus + *Bifidobacterium bifidum* (Cultech strains)	2×10^{10} CFU, once daily	3	[19]	–
	Oligofructose	4 g, three times daily	3	[20]	–
***Helicobacter pylori* (HP)**					
Coadjuvant therapy for HP eradication	*Lactobacillus rhamnosus* GG	6×10^9 twice daily	2	[7]	Reduction in therapy-related side effects in first line therapy
	Bifidobacterium animalis subsp. *lactis* (DSM15954), *Lactobacillus rhamnosus* GG	10^8–10^{10} living bacteria twice daily	2	[21]	Reduction in therapy-related side effects
	Lactobacillus reuteri DSM 17938	1×10^8, CFU three times daily	2	[22]	Reduction in therapy-related side effects in levofloxacin second-line therapy
	Mixture of *Lactobacillus acidophilus* and *L. bulgaricus* and *Bifidobacterium bifidum* and *Streptococcus thermophilus* and galacto-oligosaccharides	$5 \times 10^8 + 1 \times 10^9$, live cells twice daily	2	[23]	Improves treatment compliance in sequential therapy
	Lactobacillus acidophilus, Streptococcus faecalis, Bacillus subtilis	5×10^6, 2.5×10^6, 5×10^3	3	[24]	Improves eradication rates in first-line therapy
	Saccharomyces boulardii CNCM I-745	10^9 CFU/capsule of 250 mg, twice daily	2	[7]	Reduction in therapy-related side effects
	Kefir	250 mL twice daily	3	[25]	
	Bacillus clausii (Enterogermina strains)	2×10^9 spores, three times daily	2	[26]	

ADULT Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
	Lactobacillus reuteri DSM 17938 and *L. reuteri* ATCC 6475,	1×10^8 CFU of each strain, twice daily	2	[27,28]	–
Liver disease					
Hepatic encephalopathy	Nonabsorbable disaccharides (lactulose)	45–90 g/daily	1	[29]	–
	VSL#3 (mixture of eight strains: 1 *Streptococcus thermophilus*, 4 *Lactobacillus*, 3 *Bifidobacterium*)	1×10^8 CFU three times daily	2	[30]	Primary prophylaxis of HE
	VSL#3 (mixture of eight strains: 1 *Streptococcus thermophilus*, 4 *Lactobacillus,* 3 *Bifidobacterium*)	1×10^8 CFU three times daily	2	[31,32]	Secondary prophylaxis of HE
	Yogurt with *Streptococcus thermophilus, Lactobacillus bulgaricus, L. acidophilus,* bifidobacteria, and *L. casei*	12 ounces daily	2	[33]	Improvement in minimal hepatic encephalopathy
NAFLD	Yogurt (with *Lactobacillus bulgaricus* and *Streptococcus thermophilus*) enriched with *L. acidophilus* La5 and *Bifidobacterium lactis* Bb12	300 g daily	3	[34]	Improvement in aminotransferases
	Mixture of *Lactobacillus casei, L. rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, L. acidophilus, B. longum,* and *L. bulgaricus* + fructo-oligosaccharides	At least 10^7 CFU twice daily	3	[35,36]	Improvement in aminotransferases, along with improve HOMA-IR and transient elastography
NASH	*Lactobacillus bulgaricus* and *Streptococcus thermophilus*	A tablet with 500 million, once daily	3	[37]	Improvement in aminotransferases
	Bifidobacterium longum W11 + FOS	5,000 million live bacteria once daily	2	[38]	Improvement in aminotransferases and NASH histological activity score
IBS					
	Bifidobacterium bifidum MIMBb75	1×10^9 CFU once daily	3	[39]	Improvement in global IBS symptoms and QOL

ADULT Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
	Lactobacillus plantarum 299v (DSM 9843)	5×10^7 billion CFU once daily	2	[40,41]	Improvement in severity of abdominal pain
	Escherichia coli DSM17252	10^7 CFU three times daily	2	[41]	–
	Lactobacillus rhamnosus NCIMB 30174, *L. plantarum* NCIMB 30173, *L. acidophilus* NCIMB 30175, and *Enterococcus faecium* NCIMB 30176.	10 billion bacteria	2	[42]	Improvement in IBS score, mainly in pain and bowel habit score
	Bacillus coagulans and fructo-oligosaccharides	15×10^7, three times daily	2	[43]	Decrease pain, improve constipation
	Lactobacillus animalis subsp. *lactis* BB-12®, *L. acidophilus* LA-5®, *L. delbrueckii* subsp. *bulgaricus* LBY-27, *Streptococcus thermophilus* STY-31	4 billion CFU, twice daily	3	[44]	Improvement in abdominal pain and bloating
	Saccharomyces boulardii CNCM I-745	10^9 CFU/capsule of 250 mg twice daily	2	[45]	Improvement in IBS QOL score
	Bifidobacterium infantis 35624	10^8 CFU, once daily	2	[46,47]	Improvement in subjects global assessment of IBS symptoms
	Bifidobacterium animalis DN-173 010 in fermented milk (with *Streptococcus thermophilus* and *Lactobacillus bulgaricus*)	10^{10} CFU, twice daily	2	[48,49]	Improvement in HRQOL in constipation-predominant IBS
	Lactobacillus acidophilus SDC 2012, 2013	10^{10} CFU, once daily	3	[41,50]	–
	Lactobacillus rhamnosus GG, *L. rhamnosus* LC705, *Propionibacterium freudenreichii* subsp. *shermanii* JS DSM 7067, *Bifidobacterium animalis* subsp. *lactis* Bb12 DSM 15954	10^{10} CFU, once daily	2	[41,51]	–
	Short-chain fructo-oligosaccharides	5 g/daily	3	[52]	–
	Galacto-oligosaccharides	3.5 g/daily	2	[53]	–
	Bacillus coagulans GBI-30, 6086	2×10^9 CFU, once daily	3	[54]	–

ADULT Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
	Pediococcus acidilactici CECT 7483, *Lactobacillus plantarum* CECT 7484, *L. plantarum* CECT 7485	3–6 × 10^9 CFUs/capsule, once daily	3	[55]	–
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 × 10^8 viable cells once daily	3	[56]	Improvement in elderly, in nursing-home population
	Lactobacillus reuteri DSM 17938	1 × 10^8, CFU twice daily	3	[57]	Improvement in bowel movement frequency per week
	Lactulose	20–40 g/d	2	[58]	–
	Oligofructose	20 g/d	3	[59]	–
	Fructo-oligosaccharide (FOS) and *Lactobacillus paracasei* (Lpc-37), *L. rhamnosus* (HN001), *L. acidophilus* (NCFM) and *Bifidobacterium lactis* (HN019)	6 g (FOS) + 10^8–10^9 CFU once daily	3	[60]	–
Uncomplicated symptomatic diverticular disease					
	Lactobacillus casei subsp. DG	24 billion viable lyophilized bacteria daily	2	[61]	Improvement in symptoms in uncomplicated diverticular disease
	Lactobacillus paracasei B21060	5 × 10^9 CFU daily	3	[62]	Improvement in symptoms in uncomplicated diverticular disease
Postoperative sepsis in elective gastrointestinal surgery patients					
	Lactobacillus acidophilus, L. plantarum, and *Bifidobacterium longum* 88	2.6 × 10^{14} CFU daily	1	[63]	–
Small-bowel injury from NSAIDs					

ADULT Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
	Lactobacillus casei strain Shirota	45×10^8 to 63×10^9 CFU, once daily	3	[64]	Decreased the incidence and severity of low-dose aspirin-associated small-bowel injury
IBD—pouchitis					
Treatment of active pouchitis	VSL#3 (mixture of eight strains: 1 *Streptococcus thermophilus,* 4 *Lactobacillus,* 3 *Bifidobacterium*)	900 billion bacteria daily	2	[65]	–
Maintenance of clinical remission	VSL#3 (mixture of eight strains: 1 *Streptococcus thermophilus,* 4 *Lactobacillus,* 3 *Bifidobacterium*)	1800 billion bacteria daily	1	[66]	–
IBD—ulcerative colitis					
Inducing remission	VSL#3 (mixture of eight strains: 1 *Streptococcus thermophilus,* 4 *Lactobacillus,* 3 *Bifidobacterium*)	1800 billion bacteria twice daily	3	[67]	–
Maintenance of clinical remission	*Escherichia coli* Nissle 1917	5×10^{10} viable bacteria twice daily	2	[68,69]	–
Lactose maldigestion—reducing associated symptoms					
	Yogurt with live cultures of *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus*	At least 10^8 CFU of each strain per gram of product	1	[70]	–
Healthy population—reducing incidence of hard or lumpy stools					
	Lactobacillus casei strain Shirota	6.5×10^9 in fermented milk, once daily	3	[71]	–

N.B.: VSL#3 is now branded as Vivomixx in some countries.

AAD, antibiotic-associated diarrhea; CFU, colony-forming unit(s); HE, hepatic encephalopathy; HRQOL, Health-Related Quality of Life (score); IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NSAID, nonsteroidal anti-inflammatory drug; QOL, quality of life.

Table 9 Evidence-based *pediatric* indications for probiotics, prebiotics, and synbiotics in gastroenterology. * Oxford Centre for Evidence-Based Medicine levels of evidence (see Table **7**)

PEDIATRIC **Disorder, action**	**Probiotic strain, prebiotic, synbiotic**	**Recommended dose**	**Evidence level***	**Refs.**	**Comments**
Treatment of acute gastroenteritis	LGG	≥ 10^{10} CFU/day (typically 5–7 days)	1	[72,73]	ESPGHAN/ESPID recommendations 2014; ESPGHAN Working Group on Probiotics. Meta-analysis of RCTs
	Saccharomyces boulardii CNCM I-745	250–750 mg/day (typically 5–7 days)	1	[72,74]	
	Lactobacillus reuteri DSM 17938	10^8 to 4 × 10^8 CFU (typically 5–7 days)	2	[72,73,75,76]	
	Escherichia coli Nissle 1917		3	[72]	ESPGHAN/ESPID: insufficient evidence to make a recommendation (methodological issues)
	Lactobacillus acidophilus	10 × 10^9 CFU	3	[72,77]	ESPGHAN/ESPID: Insufficient evidence to make a recommendation (no strain specification)
	Lactobacillus acidophilus and *Bifidobacterium bifidum*	3 × 10^9 CFU, for 5 days	3	[72,78]	
	Lactobacillus acidophilus and *Bifidobacterium infantis*	3 × 10^9 CFU of each organism for 4 days	3	[72,79]	
	Lactobacillus acidophilus rhamnosus 573L/1, 573L/2, 573L/3	1.2 × 10^{10} CFU twice daily, for 5 days)—effect only in RV diarrhea	2	[72,80]	ESPGHAN/ESPID: Insufficient evidence to make a recommendation (only one RCT available)
	Lactobacillus helveticus R0052 and *L. rhamnosus* R0011		2	[72,81]	
	Lactobacillus delbrueckii var. *bulgaricus, L. acidophilus, Streptococcus thermophilus, Bifidobacterium bifidum* (strains LMG-P17550, LMG-P 17549, LMG-P 17503, and LMG-P 17500)	10^9 CFU, 10^9 CFU, 10^9 CFU, and 5 × 10^8 CFU	2	[72,82]	

PEDIATRIC Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
	Bacillus mesentericus and *Clostridium butyricum* and *Enterococcus faecalis*	1.1 × 10^7 CFU) & *Clostridium butyricum* (2.0 × 10^7 CFU) and *Enterococcus faecalis* (3.17 × 10^8 CFU)	3	[72,83]	
	Lactobacillus acidophilus, L. paracasei, L. bulgaricus, L. plantarum, Bifidobacterium breve, B. infantis, B. longum, Streptococcus thermophilus (VSL#3)		3	[72,84]	ESPGHAN/ESPID: Insufficient evidence to make a recommendation (only one RCT available and no strain identification))
	Lactobacillus acidophilus & *L. rhamnosus* & *Bifidobacterium longum* & *Saccharomyces boulardii* CNCM I-745		3	[72,85]	
Prevention of antibiotic-associated diarrhea	LGG	1–2 × 10^{10} CFU	1	[86,87]	ESPGHAN Working Group on Probiotics
	Saccharomyces boulardii	250–500 mg	1	[12]	
Prevention of nosocomial diarrhea	LGG	10^{10}–10^{11} CFU, twice daily	1	[12]	Meta-analysis of RCT
	Bifidobacterium bifidum and *Streptococcus thermophilus*		2	[88]	–
Infections in children attending day-care centers	LGG		1	[89–91]	Prevention of AAD in hospitalized patients
	Lactobacillus reuteri DSM 17938	1 × 10^8 CFU/day for 3 months	2	[92,93]	
	Lactobacillus casei DN-114 001 in fermented milk	10^{10} CFU, once daily	2	[94–96]	–
	Lactobacillus casei Shirota in fermented milk	10^{10} CFU, once daily	2	[97]	–

PEDIATRIC Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
Eczema (prevention)	(Probiotics) There is no clear indication yet regarding which probiotic(s) to use.			[98,99]	WAO suggests the use of probiotics in high-risk populations to reduce the risk of eczema
Necrotizing enterocolitis (prevention)	(Probiotics) No clear indications from scientific societies regarding which probiotic strain(s) should be recommended. The following strains are found NOT to be effective: *Saccharomyces boulardii* CNCM I-745, *Bifidobacterium breve* BBG-001, Bb12			[100,101]	Reduced risk of NEC and mortality in infants with birth weight < 1500 g
	Lactobacillus reuteri DSM 17938		2	[102]	–
H. pylori infection	*Saccharomyces boulardii* CNCM I-745	500 mg (in two doses, for 2–4 weeks)	2	[103]	Reduced risk of side effects and increased eradication rate
	Lactobacillus casei DN-114 001 in fermented milk	10^{10} CFU daily, for 14 days	2	[104]	–
Infantile colic—management	*Lactobacillus reuteri* DSM 17938	10^{8} CFU, once daily, for 21 days	1	[105–110]	Reduced crying time (documented mainly in breastfed infants). Meta-analysis of RCTs
Infantile colic—prevention	*Lactobacillus reuteri* DSM 17938	10^{8} CFU, once daily, up to 3 months of age	1	[111]	–
Abdominal pain–related functional gastrointestinal disorders	LGG	10^{10}–10^{11} CFU, twice daily	1	[112]	Meta-analysis of RCTs
	VSL#3	1 sachet of VSL#3 (once per day for children 4–11 years of age; twice per day for those 12–18 years old)	3	[113]	–
	Lactobacillus reuteri DSM 17938	10^{8} CFU/d for 4 weeks	1	[114,115]	–

PEDIATRIC Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
Induction of remission in ulcerative colitis	*Escherichia coli* Nissle 1917		2	[116,117]	ESPGHAN/ECCO: Limited evidence suggests that probiotics added to standard therapy may provide modest benefit
	VSL#3	4 to 9 × 10^{11} CFU, twice daily	2	[118,119]	–

N.B.: VSL#3 is now branded as Vivomixx in some countries.

AAD, antibiotic-associated diarrhea; CFU, colony-forming unit(s) ECCO, European Crohn's and Colitis Organization; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; ESPID, European Society for Paediatric Infectious Diseases; LGG, *Lactobacillus rhamnosus* GG ; NEC, necrotizing enterocolitis; RCT, randomized controlled trial.

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