

World Gastroenterology Organisation Global Guidelines

Probiotics and prebiotics

February 2023



Review Team

Francisco Guarner (Chair, Spain), Mary Ellen Sanders (Co-Chair, USA),
Hania Szajewska (Co-Chair, Poland), Henry Cohen (Uruguay),
Rami Eliakim (Israel), Claudia Herrera (Guatemala),
Tarkan Karakan (Turkey), Dan Merenstein (USA), Alejandro Piscoya (Peru),
Balakrishnan Ramakrishna (India), Seppo Salminen (Finland)

Contents

1	Probiotics and prebiotics—the concept	4
1.1	History and definitions	4
1.2	Prebiotics and synbiotics	6
1.3	Genera, species, and strains used as probiotics	7
1.4	Colonizing microbiota	8
1.5	Mechanisms of action of probiotics and prebiotics	9
2	Products, health claims, and commerce	11
2.1	Understanding the marketplace	11
2.2	Products: dosages and quality	12
2.3	Product safety	13
3	Clinical applications	13
3.1	Colorectal cancer prevention	13
3.2	Diarrhea treatment and prevention	14
3.2.1	Treatment of acute diarrhea	14
3.2.2	Prevention of acute diarrhea	14
3.2.3	Prevention of antibiotic-associated diarrhea	14
3.2.4	Prevention of <i>C. difficile</i> diarrhea	14
3.2.5	Prevention of radiation-induced diarrhea	14
3.3	<i>Helicobacter pylori</i> eradication	14
3.4	Hepatic encephalopathy prevention and treatment	15
3.5	Immune response	15
3.6	Inflammatory bowel disease (IBD)	15
3.6.1	Pouchitis	15
3.6.2	Ulcerative colitis	15
3.6.3	Crohn’s disease	15
3.7	Irritable bowel syndrome (IBS)	15
3.8	Colic	16
3.9	Lactose malabsorption	16
3.10	Necrotizing enterocolitis	16
3.11	Nonalcoholic fatty liver disease	16
3.12	Prevention of systemic infections	16
4	Summaries of evidence for probiotics and prebiotics in adult and pediatric conditions—the global picture	17
	References	40

List of tables

Table 1	Definitions	4
Table 2	New names for former <i>Lactobacillus</i> probiotic species	5
Table 3	Nomenclature used for probiotic microorganisms	8
Table 4	Human intestinal microbiota	9
Table 5	Mechanisms of probiotic and prebiotic host interaction	10
Table 6	Categories of products containing probiotics	11
Table 7	Levels of evidence for treatment benefits	18

Table 8	List of positive RCTs with probiotics/prebiotics (adult indications)	19
Table 9	List of positive RCTs with probiotics/prebiotics (pediatric indications)	34
Table 10	Abbreviations used in this guideline	40

List of figures

Fig. 1	<i>Ligilactobacillus salivarius</i> 118 adhering to Caco-2 cells	6
Fig. 2	Composition of complementary and synergistic synbiotics	7
Fig. 3	Mechanisms of microbiota and probiotic interaction with the host	10

1 Probiotics and prebiotics—the concept

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; Table 1) 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 saccharolytic microbes. He developed a diet with milk fermented with a bacterium 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 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. The resulting *Escherichia coli* strain Nissle 1917 is an example 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 *Lacticaseibacillus paracasei* strain Shirota to battle diarrheal outbreaks. A probiotic product with this strain has been commercially available since 1935.

These were early predecessors in a scientific field that has flourished. 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.

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [1] (Table 1). 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 2).

Table 1 Definitions. Adherence to these well-accepted definitions will lead to consistency in how the terms are used both scientifically and on products. Other terms, such as paraprobiotic, immunobiotic, and ghost probiotics, have emerged, but their use is discouraged due to lack of clear, well-considered definitions and their potential for confusion

Concept	Definition
Probiotics	Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host

Concept	Definition
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 two 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
Lactic acid bacteria (LAB)	A functional classification of nonpathogenic, nontoxicogenic, Gram-positive, fermentative bacteria that are associated with the production of lactic acid from carbohydrates, making them useful for food fermentation. Species of <i>Lactobacillus</i> , <i>Lacticaseibacillus</i> , <i>Lactiplantibacillus</i> , <i>Limosilactobacillus</i> , <i>Levilactobacillus</i> , <i>Lactococcus</i> , and <i>Streptococcus thermophilus</i> are included in this group. Many probiotics are also LAB, but some probiotics (such as strains of <i>E. coli</i> , <i>Akkermansia mucinophila</i> , bacterial 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

Table 2 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
<i>Lactobacillus casei</i>	<i>Lacticaseibacillus casei</i>
<i>Lactobacillus paracasei</i>	<i>Lacticaseibacillus paracasei</i>
<i>Lactobacillus rhamnosus</i>	<i>Lacticaseibacillus rhamnosus</i>
<i>Lactobacillus plantarum</i>	<i>Lactiplantibacillus plantarum</i>
<i>Lactobacillus brevis</i>	<i>Levilactobacillus brevis</i>
<i>Lactobacillus salivarius</i>	<i>Ligilactobacillus salivarius</i>
<i>Lactobacillus fermentum</i>	<i>Limosilactobacillus fermentum</i>
<i>Lactobacillus reuteri</i>	<i>Limosilactobacillus reuteri</i>

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>.

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. LAB, which have been used for preservation of food by fermentation (Table 1) 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.

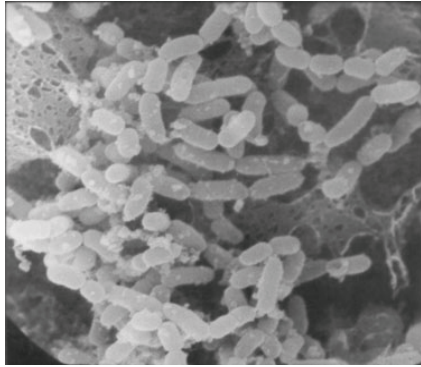


Fig. 1 Electron micrograph of *Ligilactobacillus salivarius* 118 adhering to Caco-2 cells. (Reproduced with permission from Blackwell Publishing Ltd.; journal via Copyright Clearance Center.)

1.2 Prebiotics and synbiotics

The prebiotic concept, first proposed by Gibson and Roberfroid in 1995 [2], 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 (Table 1). 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 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 (Table 1). A complementary synbiotic is defined simply as a mixture of probiotic(s) and prebiotic(s), where the two 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 lead to a documented health benefit. The components of a synergistic synbiotic do not need to independently meet the criteria for a probiotic or prebiotic.

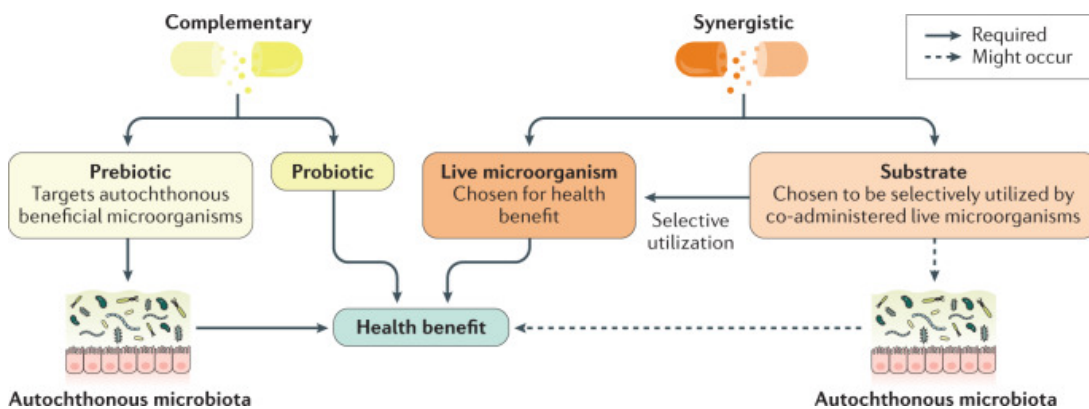


Fig. 2 Composition of complementary and synergistic synbiotics. A complementary synbiotic combines a prebiotic and a probiotic, which work independently to elicit one or more health benefits. The prebiotic functions by modulating the resident microbiota to elicit a health benefit. The synergistic synbiotic 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. [3]. CC BY 4.0.)

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 (Table 3). 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 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.

Table 3 Nomenclature used for probiotic microorganisms

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

ATCC, American Type Culture Collection (Manassas, Virginia, USA); CNCM, *Collection Nationale de Cultures de Microorganismes* (Institut Pasteur, Paris, France); NCIMB, National Collection of Industrial, Food and Marine Bacteria (Aberdeen, Scotland).

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.

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.

1.4 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 (Table 4). 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 [4].

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, the two 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 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 current active area of research to determine whether supplementation with these bacteria will improve health or reverse disease.

Table 4 Human intestinal microbiota. The gut microbiota form a diverse and dynamic ecosystem, including bacteria, Archaea, Eukarya, and viruses that have adapted to live on the intestinal mucosal surface or within the gut lumen

Stomach and duodenum	<ul style="list-style-type: none"> • Harbor very low numbers of microorganisms: < 10³ 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	<ul style="list-style-type: none"> • Numbers progressively increase from 10⁴ in the jejunum to 10⁷ cells per gram of contents in the distal ileum
Large intestine	<ul style="list-style-type: none"> • Heavily populated by anaerobes: up to 10¹² cells per gram of luminal contents

1.5 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. 3; Table 5). 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 reduction of the incidence and severity of diarrhea, which is one of the most widely recognized uses of probiotics.

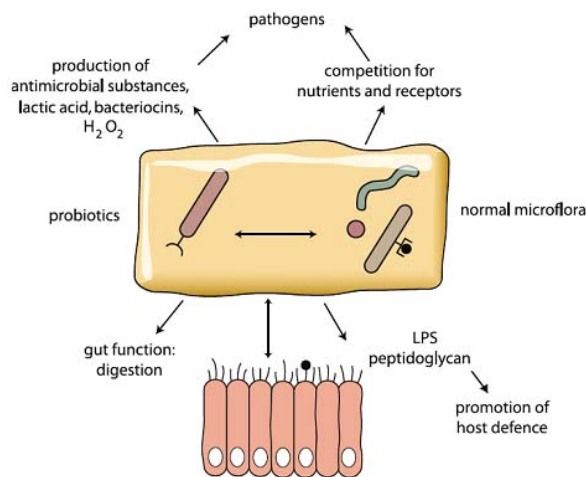


Fig. 3 Mechanisms of microbiota and probiotic interaction with the host. The normal microbiota and probiotics interact with the host in metabolic activities and immune function and prevent colonization of opportunistic and pathogenic microorganisms. (Reproduced with permission from Blackwell Publishing Ltd.; journal via Copyright Clearance Center.)

Table 5 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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

Probiotics

- 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 successfully marketed in many regions of the world. A range of product types—from conventional food through prescription drugs—is available commercially (Table 6).

Table 6 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 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.

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 for 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
- 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

2.2 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. One effort to do this for Canada and the United States, funded by unrestricted grants from commercial entities, 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 300–450 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. 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 probiotic strains have an 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.

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 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. [5]. Testing or use of newly isolated probiotics or known probiotics for new disease indications is 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.

3 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 8 and 9 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 8 and 9 detail individual probiotic preparations and clinical situations in which they have been found effective.

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 in animal models, there are limited data in humans showing any benefit of probiotics or prebiotics in 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.

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. A Cochrane meta-analysis based only on large trials with a low risk of bias [6] concluded that probiotics probably make little or no difference with diarrhea lasting 48 hours or longer. Early administration of probiotics may therefore be needed.

3.2.3 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 [7], adults [8], and elderly adults [9].

3.2.4 Prevention of *C. difficile* diarrhea

- A 2017 meta-analysis concluded with moderate certainty that probiotics are effective for preventing *C. difficile*-associated diarrhea in patients receiving antibiotics [10]. 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.

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 concluded that probiotics may be beneficial in the prevention and possibly in the treatment of radiation-induced diarrhea [11].

3.3 *Helicobacter pylori* eradication

- The 2022 Maastricht VI/Florence Consensus Report on 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 [12]. 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*.

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. A 2017 Cochrane meta-analysis found that evidence from three studies on the benefits of probiotics for people with hepatic encephalopathy was of low quality [13]. Although no difference in the mortality rate was observed, the authors concluded that probiotics may improve recovery, quality of life, and plasma ammonia concentrations.

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 in studies that tested antibody responses to vaccines.

3.6 Inflammatory bowel disease (IBD)

3.6.1 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 [14].

3.6.2 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 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 disease [15].

3.6.3 Crohn's disease

- Studies of probiotics in Crohn's disease have indicated that there is no evidence to suggest that they are beneficial for induction or 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 persons with functional abdominal pain. Strain-specific effects of certain probiotics on IBS symptoms are shown in Tables 8 and 9.

3.8 Colic

- *L. reuteri* DSM17938 and *B. animalis* ssp. *lactis* BB12 have been shown to reduce crying time in breastfed infants with colic (Table 9).

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 [16].

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. Special attention to adequate quality in the probiotic product is important for this vulnerable group of patients [17]. There was moderate certainty for reduction of the mortality rate and late-onset invasive infection, but no effect was observed on severe neurodevelopmental impairment [18].

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 assessment (HOMA), blood cholesterol, TNF- α , and liver function tests (ALT and 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 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 [19]. 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

We have comprehensively evaluated the evidence for gastrointestinal conditions. Table 7 lists the criteria used to establish the level of evidence.

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 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 8 and 9, 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 (i.e., studies showing statistically significant results for its main outcome) were included. Negative (null) studies were not included (i.e., 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.

Table 7 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
Step 1*	Systematic review of randomized trials
Step 2*	Randomized trials with consistent effect, without systematic review
Step 3*	Supported by a single randomized controlled trial**
Step 4	Case-series, case-control studies, or historically controlled studies**
Step 5	Mechanism-based reasoning

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>).

* 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.

Table 8 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	<i>Lactobacillus rhamnosus</i> GG	50 g of probiotic cheese containing LGG	3	[20]	Reduction of prevalence of oral candida in the elderly
	<i>Lactobacillus reuteri</i> DSM 17938 and <i>L. reuteri</i> ATCC PTA 5289	1 × 10 ⁸ cfu of each strain, twice daily	3	[21]	Reduction of prevalence of oral candida in nursing homes
	<i>Lactobacillus rhamnosus</i> HS111, <i>L. acidophilus</i> HS101, and <i>Bifidobacterium bifidum</i>	1 capsule a day	3	[22]	Reduction of prevalence of oral candida in denture wearers
Treatment of acute diarrhea in adults	<i>Lactobacillus paracasei</i> B 21060 or <i>L. rhamnosus</i> GG	10 ⁹ cfu, twice daily	3	[23]	
	<i>Saccharomyces boulardii</i> CNCM I-745	5 × 10 ⁹ cfu or 250 mg, twice daily	3	[24]	
	<i>Enterococcus faecium</i> SF68	7.5 × 10 ⁷ cfu, three times daily	3	[25]	
Antibiotic-associated diarrhea (AAD)	Yogurt with <i>L. casei</i> DN114, <i>L. bulgaricus</i> and <i>Streptococcus thermophilus</i>	≥ 10 ¹⁰ cfu, twice daily	2	[26,27]	Prevention of AAD in hospitalized patients
	<i>Lactobacillus acidophilus</i> CL1285 and <i>L. casei</i> (Bio-K+ CL1285)	≥ 10 ¹⁰ cfu, once daily	2	[26,27]	Prevention of AAD in various clinical settings (hospitalized and outpatients)
	<i>Lactobacillus rhamnosus</i> GG	10 ¹⁰ cfu, twice daily	1	[26–28]	Prevention of AAD in various clinical settings (hospitalized and outpatients)

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
	<i>Saccharomyces boulardii</i> CNCM I-745	5 × 10e9 cfu or 250 mg, twice daily	1	[26–29]	Prevention of AAD in various clinical settings (hospitalized and outpatients)
	<i>Lactobacillus reuteri</i> DSM 17938	10e8 cfu, twice daily	3	[30]	Prevention of AAD in hospitalized patients
	<i>Lactobacillus acidophilus</i> NCFM, <i>L. paracasei</i> Lpc-37, <i>Bifidobacterium lactis</i> Bi-07, <i>B. lactis</i> BI-04	1.7 × 10e10 cfu, once daily	3	[27,31]	Prevention of AAD in hospitalized patients
	<i>Bifidobacterium bifidum</i> W23, <i>B. lactis</i> W18, <i>B. longum</i> W51, <i>Enterococcus faecium</i> W54, <i>Lactobacillus acidophilus</i> W37 and W55, <i>L. paracasei</i> W72, <i>L. plantarum</i> W62, <i>L. rhamnosus</i> W71, and <i>L. salivarius</i> W24	5 g of the mix containing 10e9 cfu/g, twice daily	3	[27,32]	Reduction of diarrhea-like bowel movements in healthy volunteers receiving amoxicillin
	<i>Lactobacillus rhamnosus</i> GG, <i>L. acidophilus</i> La5, and <i>B. animalis</i> subsp. <i>lactis</i> BB-12	2.5 × 10e10, 2.5×10e9, and 2.5 × 10e10 cfu, respectively, once daily	3	[33]	Prevention of AAD in hospitalized patients
	<i>Lactobacillus acidophilus</i> , <i>Lactobacillus plantarum</i> , <i>Lactobacillus casei</i> , and <i>Lactobacillus delbrueckii</i> subspecies <i>bulgaricus</i> , <i>Bifidobacterium breve</i> , <i>Bifidobacterium longum</i> , and <i>Bifidobacterium infantis</i> , and <i>Streptococcus salivarius</i> subsp. <i>thermophilus</i>	4.5 × 10e11 cfu, twice daily	3	[34]	Prevention of AAD in hospitalized patients

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
Prevention of <i>Clostridium difficile</i> -associated diarrhea (or prevention of recurrence)	<i>Lactobacillus acidophilus</i> CL1285 and <i>L. casei</i> LBC80R	≥ 10e10 cfu, once daily	2	[10,35,36]	Primary prevention
	Yogurt with <i>L. casei</i> DN114 and <i>L. bulgaricus</i> and <i>Streptococcus thermophilus</i>	10e7–10e8 cfu twice daily	3	[10,35,36]	Primary prevention
	<i>Saccharomyces boulardii</i> CNCM I-745	10e9 cfu or 250 mg, twice daily	2	[10,35,36]	Primary prevention
	<i>Lactobacillus acidophilus</i> NCFM, <i>L. paracasei</i> Lpc-37, <i>Bifidobacterium lactis</i> Bi-07, <i>B. lactis</i> BI-04	1.7 × 10e10 cfu, once daily	3	[10,35,36]	Primary prevention
	<i>Lactobacillus acidophilus</i> + <i>Bifidobacterium bifidum</i> (Cultech strains)	2 × 10e10 cfu, once daily	3	[10,37]	Primary prevention
	Oligofructose	4 g, three times daily	3	[38]	Prevention of recurrence
Coadjuvant therapy for <i>Helicobacter pylori</i> eradication	<i>Lactobacillus rhamnosus</i> GG	6 × 10e9 cfu, twice daily	2	[39]	Improved eradication rate and treatment compliance
	<i>Bifidobacterium animalis</i> subsp. <i>lactis</i> Bb12, <i>Lactobacillus rhamnosus</i> GG	10e8–10e10 cfu, twice daily	2	[40]	Improved eradication rate and treatment compliance
	<i>Lactobacillus reuteri</i> DSM 17938 and <i>L. reuteri</i> ATCC 6475,	1 × 10e8 cfu of each strain, twice daily	2	[39]	Improved eradication rate and treatment compliance

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
	<i>Saccharomyces boulardii</i> CNCM I-745	10e9 cfu or 250 mg, twice daily	2	[39,41]	Reduction in therapy-related side effects and improved compliance
	<i>Bacillus clausii</i> (Enterogermina strains)	2 × 10e9 spores, three times daily	2	[42,43]	Reduction in therapy-related side effects and improved compliance
	Kefir	250 ml twice daily	3	[44]	
Prevention of diarrhea associated with radiotherapy	Mixture containing strains of <i>Lactobacillus plantarum</i> , <i>L. casei</i> , <i>L. acidophilus</i> , <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> , <i>Bifidobacterium infantis</i> , <i>B. longum</i> , <i>B. breve</i> , and <i>Streptococcus salivarius</i> subsp. <i>Thermophilus</i>	450 × 10e9 cfu, three times daily	3	[45–47]	Patients on radiotherapy after surgery for pelvic cancer
	<i>Lactobacillus acidophilus</i> plus <i>Bifidobacterium bifidum</i>	2 × 10e9 cfu, twice daily	3	[46–48]	Patients on radiotherapy after surgery for pelvic cancer
	<i>Lactobacillus acidophilus</i> LAC-361 and <i>Bifidobacterium longum</i> BB-536	1.3 × 10e9 cfu, twice daily	3	[46,47,49]	Patients on radiotherapy after surgery for pelvic cancer
	<i>Lactobacillus acidophilus</i> LA-5 plus <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> BB-12	1.75 × 10e9 cfu, three times daily	3	[50]	Patients on radiotherapy after surgery for pelvic cancer
Prevention of diarrhea associated with enteral nutrition	Shen Jia fiber plus <i>Bifidobacterium</i> and <i>Lactobacillus</i> in tablets	30 g plus 6g	3	[51]	Postoperative patients with gastric cancer

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
Liver disease Hepatic encephalopathy	<i>Bacillus cereus</i> A05	5 × 10e6 cfu, every 6 h	3	[52]	<i>B. cereus</i> A05 was more effective than fiber in reducing diarrhea among patients receiving enteral nutrition
	Mixture containing strains of <i>Lactobacillus plantarum</i> , <i>L. casei</i> , <i>L. acidophilus</i> , <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> , <i>Bifidobacterium infantis</i> , <i>B. longum</i> , <i>B. breve</i> and <i>Streptococcus salivarius</i> subsp. <i>Thermophilus</i>	450 × 10e9 cfu, twice daily	3	[53]	Reduction of incidence of liquid stool in critically ill patients receiving enteral nutrition
	Lactulose	45–90 g, daily	1	[54]	Prophylaxis of hepatic encephalopathy, and recovery from overt hepatic encephalopathy
	Mixture containing strains of <i>L. plantarum</i> , <i>L. casei</i> , <i>L. acidophilus</i> , <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> , <i>Bifidobacterium infantis</i> , <i>B. longum</i> , <i>B. breve</i> and <i>Streptococcus salivarius</i> subsp. <i>thermophilus</i>	110 × 10e9 cfu, three times daily	3	[13,55,56]	Prophylaxis of hepatic encephalopathy
	Mixture containing strains of <i>Lactobacillus plantarum</i> , <i>L. casei</i> , <i>L. acidophilus</i> , <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> , <i>Bifidobacterium infantis</i> , <i>B. longum</i> , <i>B. breve</i> and <i>Streptococcus salivarius</i> subsp. <i>thermophilus</i>	110 × 10e9 cfu, twice daily	3	[13,56,57]	Minimal hepatic encephalopathy reversal

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
NAFLD	Yogurt with <i>Streptococcus thermophilus</i> , <i>Lactobacillus bulgaricus</i> , <i>L. acidophilus</i> , bifidobacteria and <i>L. casei</i>	12 ounces (340 g) daily	3	[13,56,58]	Minimal hepatic encephalopathy reversal
	<i>Lactobacillus acidophilus</i>	10e6 cfu, three times daily	3	[13,59]	Minimal hepatic encephalopathy reversal
	<i>Lactobacillus plantarum</i> 299v	10e10 cfu, twice a day	3	[13,60]	Prophylaxis of hepatic encephalopathy
	Yogurt (with <i>Lactobacillus bulgaricus</i> and <i>Streptococcus thermophilus</i>) enriched with <i>L. acidophilus</i> La5 and <i>Bifidobacterium lactis</i> Bb12	300 g daily	3	[61]	Improvement in aminotransferases
	<i>Lactobacillus casei</i> , <i>L. rhamnosus</i> , <i>Streptococcus thermophilus</i> , <i>Bifidobacterium breve</i> , <i>L. acidophilus</i> , <i>B. longum</i> , and <i>L. bulgaricus</i> , plus fructooligosaccharide	2 × 10e8 cfu plus 250 mg FOS, twice daily	3	[62,63]	Improvement in aminotransferases, along with improved HOMA-IR and reduction of fibrosis score (elastography)
	<i>Bifidobacterium longum</i> W11 plus fructooligosaccharide	5 × 10e9 cfu plus 2.5 g FOS, once daily		[64]	Improvement in aminotransferases and NASH histological activity score
	<i>Lactobacillus paracasei</i> DSM 24733, <i>L. plantarum</i> DSM 24730, <i>L. acidophilus</i> DSM 24735 and <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> DSM 24734, <i>Bifidobacterium longum</i> DSM 24736, <i>B. infantis</i> DSM 24737, <i>B. breve</i> DSM 24732, and <i>Streptococcus thermophilus</i> DSM 24731	225 × 10e9 cfu, three times daily	3	[65]	Improvement in aminotransferases and NASH histological activity score
Yogurt with <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> Bb12 and starter cultures, plus inulin	3 × 10e10 cfu Bb12 plus 1.5 g inulin in 300 g yogurt, once daily	3	[66]	Improvement in aminotransferases and steatosis score (ultrasonography)	

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
IBS	<i>Bifidobacterium bifidum</i> MIMBb75	1 × 10 ⁹ cfu, once daily	2	[67,68]	Improvement in global IBS symptoms and QoL. Heat-inactivated MIMBb75 also alleviates IBS symptoms [68]
	<i>Lactobacillus plantarum</i> 299v (DSM 9843)	1 × 10 ⁹ cfu, once daily	2	[69,70]	Improvement in severity of abdominal pain and bloating
	<i>Escherichia coli</i> DSM17252	1.5–4.5 × 10 ⁷ cfu, three times daily	3	[71]	Effect on persistence of symptoms
	<i>Lactobacillus rhamnosus</i> NCIMB 30174, <i>L. plantarum</i> NCIMB 30173, <i>L. acidophilus</i> NCIMB 30175 and <i>Enterococcus faecium</i> NCIMB 30176	10 × 10 ⁹ cfu, once daily	3	[72]	Improvement in IBS score, mainly in pain and bowel habit score
	<i>Lactobacillus animalis</i> subsp. <i>lactis</i> BB-12 [®] , <i>L. acidophilus</i> LA-5 [®] , <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> LBY-27, <i>Streptococcus thermophilus</i> STY-31	4 × 10 ⁹ cfu, twice daily	3	[73]	Effect on persistence of symptoms
	<i>Saccharomyces boulardii</i> CNCM I-745	2 × 10 ¹¹ cfu, twice daily	3	[74]	Improvement in IBS-QoL score
	<i>Bifidobacterium infantis</i> 35624	1 × 10 ¹⁰ cfu, once daily	2	[70]	Improvement in global assessment of IBS symptoms
	<i>Bifidobacterium animalis</i> DN-173 010 in fermented milk (with <i>Streptococcus thermophilus</i> and <i>Lactobacillus bulgaricus</i>)	1.25 × 10 ¹⁰ cfu, twice daily	3	[70]	Improvement in HRQoL in constipation-predominant IBS
<i>Lactobacillus acidophilus</i> SDC 2012, 2013	2 × 10 ⁹ cfu, twice daily	3	[70]	Effect on persistence of symptoms	

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
	<i>Lactobacillus rhamnosus</i> GG, <i>L. rhamnosus</i> LC705, <i>Propionibacterium freudenreichii</i> ssp. <i>shermanii</i> JS DSM 7067, <i>Bifidobacterium animalis</i> ssp. <i>lactis</i> Bb12 DSM 15954	10e10 cfu, once daily	2	[70]	Improvement in global assessment of IBS symptoms
	Short-chain fructooligosaccharides	5 g daily	3	[75]	Effect on persistence of symptoms
	Galactooligosaccharides	3.5 g daily	2	[76–78]	Effect on persistence of symptoms
	<i>Pediococcus acidilactici</i> CECT 7483, <i>Lactobacillus plantarum</i> CECT 7484, <i>L. plantarum</i> CECT 7485	1–3 × 10e10 or 3–6 × 10e9 cfu, once daily	3	[79]	Improvement in IBS-QoL score
	Mixture containing strains of <i>Lactobacillus plantarum</i> , <i>L. casei</i> , <i>L. acidophilus</i> , <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> , <i>Bifidobacterium infantis</i> , <i>B. longum</i> , <i>B. breve</i> and <i>Streptococcus salivarius</i> subsp. <i>Thermophilus</i>	4 capsules containing 110 × 10e9 cfu, twice daily	3	[80]	Improvement of IBS symptoms
	<i>Bifidobacterium longum</i> NCC3001	1 × 10e10 cfu, once daily	3	[81]	Reduction of depression scores and improvement of QoL in IBS patients
	<i>Bacillus coagulans</i> MTCC 5856	2 × 10e9 cfu, once daily	3	[82]	Decrease in bloating, diarrhea, abdominal pain and stool frequency in IBS-D patients
	<i>Lactobacillus acidophilus</i> PBS066 and <i>L. reuteri</i> PBS072	5 × 10e9 cfu, once daily	3	[83]	Effect on persistence of symptoms in IBS-C patients

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
	<i>Lactobacillus rhamnosus</i> LRH020, <i>L. plantarum</i> PBS067, and <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> BL050	5 × 10e9 cfu, once daily	3	[83]	Effect on persistence of symptoms in IBS-C patients
	<i>Saccharomyces cerevisiae</i> CNCM I-3856	2–8 × 10e9 cfu, once daily	3	[84]	Improvement of symptoms in IBS overall population and IBS-C subpopulation
	<i>Bacillus subtilis</i> PXN 21, <i>Bifidobacterium bifidum</i> PXN 23, <i>B. breve</i> PXN 25, <i>B. infantis</i> PXN 27, <i>B. longum</i> PXN 30, <i>Lactobacillus acidophilus</i> PXN 35, <i>L. delbrueckii</i> spp. <i>bulgaricus</i> PXN39, <i>L. casei</i> PXN 37, <i>L. plantarum</i> PXN 47, <i>L. rhamnosus</i> PXN 54, <i>L. helveticus</i> PXN 45, <i>L. salivarius</i> PXN 57, <i>Lactococcus lactis</i> PXN 63, and <i>Streptococcus thermophilus</i> PXN 66	2 capsules containing 2×10e9 cfu, twice daily	3	[85]	Improvement of symptoms in patients with IBS-D
	<i>Lactobacillus acidophilus</i> DDS-1	1 × 10e10 cfu, once daily	3	[86]	Improvement of abdominal pain
	<i>Bifidobacterium lactis</i> UABla-12	1 × 10e10 cfu, once daily	3	[86]	Improvement of abdominal pain
	<i>Lactobacillus acidophilus</i> NCFM ATCC SD5221 and <i>L. acidophilus</i> subsp. <i>helveticus</i> LAFTI L10 CBS 116.411	5 × 10e9 cfu, twice daily	3	[87]	Decreases of abdominal pain, flatus and composite scores

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
	<i>Lactobacillus casei</i> LMG 101/37 P-17504 (5×10 ⁹ cfu/sachet), <i>L. plantarum</i> CECT 4528 (5×10 ⁹ cfu/sachet), <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> Bi1 LMG P-17502 (10×10 ⁹ cfu/sachet), <i>B. breve</i> Bbr8 LMG P-17501 (10×10 ⁹ cfu/sachet), <i>B. breve</i> Bl10 LMG P-17500 (10×10 ⁹ cfu/sachet).	One sachet once daily	3	[88]	Improvement of IBS-type symptoms in celiac disease patients on strict gluten-free diet
	<i>Bifidobacterium infantis</i> NLS-SS	4 × 10 ⁹ cfu, thrice daily	3	[89]	Improvement of IBS-type symptoms in celiac disease patients on strict gluten-free diet
Functional constipation	<i>Bifidobacterium bifidum</i> (KCTC 12199BP), <i>B. lactis</i> (KCTC 11904BP), <i>B. longum</i> (KCTC 12200BP), <i>Lactobacillus acidophilus</i> (KCTC 11906BP), <i>L. rhamnosus</i> (KCTC 12202BP), and <i>Streptococcus thermophilus</i> (KCTC 11870BP)	2.5 × 10 ⁸ cfu, once daily	3	[90]	Improvement of defecation frequency and symptoms in elderly nursing home residents
	<i>Lactobacillus reuteri</i> DSM 17938	1 × 10 ⁸ cfu, twice daily	2	[91,92]	Improvement of defecation frequency and symptoms
	Lactulose	20–30 g/day	1	[93]	Prebiotic commonly used as laxative
	Oligofructose	12 g/day	1	[94]	Maintenance of normal defecation by increasing stool frequency

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
	Fructooligosaccharide (FOS) and <i>Lactobacillus paracasei</i> (Lpc-37), <i>L. rhamnosus</i> (HN001), <i>L. acidophilus</i> (NCFM), and <i>Bifidobacterium lactis</i> (HN019)	6 g FOS plus 10e8–10e9 cfu, once daily	3	[95]	Improved evacuation in constipated women
	Pectin and Bifico strains (<i>Bifidobacterium longum</i> , <i>Lactobacillus acidophilus</i> , and <i>Enterococcus faecalis</i>)	8 g pectin plus 1 × 10e9 cfu of each strain, twice daily	3	[96]	Increased stool frequency, improved stool consistency, decreased colonic transit time, and improved constipation-related symptoms in patients with slow-transit constipation
	<i>Lactococcus lactis</i> subsp. <i>cremoris</i> FC	100 mg capsule, once daily	3	[97]	Increased stool frequency
	<i>Bifidobacterium animalis</i> subsp. <i>lactis</i> HN019	1 × 10e9 or 1 × 10e10 cfu, once daily	3	[98]	Increase in bowel movement frequency in participants with fewer than 3 bowel movements per week
	Lactulose plus <i>Bacillus coagulans</i> Unique IS2	10 g plus 2 × 10e9 cfu, once daily	3	[99]	<i>B. coagulans</i> Unique IS2 addition to lactulose reduced time required to relieve constipation as compared to lactulose alone
	<i>Lactobacillus acidophilus</i> BCMC 12130, <i>L. casei</i> BCMC 12313, <i>L. lactis</i> BCMC 12451, <i>B. bifidum</i> BCMC 02290, <i>B. infantis</i> BCMC 02129 and <i>B. longum</i> BCMC 02120 with fructo-oligosaccharide	3 × 10e10 cfu plus 60 mg fructo-oligosaccharide, twice daily	3	[100]	Increased stool frequency and decreased colonic transit time in Parkinson's disease patients with constipation

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
	<i>Lactobacillus casei</i> strain Shirota in fermented milk	6.5 × 10e9, once daily	3	[101]	Reduces incidence of hard or lumpy stools in healthy population
Uncomplicated symptomatic diverticular disease	<i>Lactobacillus casei</i> subsp. DG	2.4 × 10e10 cfu, once daily	2	[102]	Improvement in symptoms in uncomplicated diverticular disease
	<i>Lactobacillus paracasei</i> B21060	5 × 10e9 cfu, once daily	3	[103]	Improvement in symptoms in uncomplicated diverticular disease
	<i>Bifidobacterium lactis</i> LA 304, <i>Lactobacillus salivarius</i> LA 302, <i>L. acidophilus</i> LA 201	4 × 10e10 cfu, twice daily	3	[104]	The probiotic mix in combination with the standard antibiotic therapy reduced abdominal pain and CRP significantly more than antibiotic treatment alone
	<i>Lactobacillus reuteri</i> ATCC PTA 4659	1 × 10e8 cfu, twice daily	3	[105]	Reduced abdominal pain and inflammatory markers compared with antibiotics alone, and resulted in shorter hospitalization
Prevention of postoperative complications	<i>Lactobacillus plantarum</i> CGMCC 1258, <i>L. acidophilus</i> 11 and <i>Bifidobacterium longum</i> 88	Total daily dose of 2.6 × 10e14 cfu	3	[106,107]	Reduced rate of postoperative septicemia

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
	<i>Lactobacillus acidophilus</i> NCFM, <i>L. rhamnosus</i> HN001, <i>L. paracasei</i> LPC-37, <i>Bifidobacterium lactis</i> HN019, and fructo-oligosaccharides	6 g FOS plus 4 × 10e9 cfu, twice daily	3	[107,108]	Reduced rate of postoperative infections
Small-bowel injury due to NSAIDs	<i>Lactobacillus casei</i> strain Shirota in fermented milk	6.5 × 10e9, once daily	3	[109]	Decreased the incidence of low-dose aspirin-associated small bowel injury
	<i>Lactobacillus gasseri</i> OLL2716 in fermented milk	112 mL of yogurt, twice daily	3	[110]	Decreased the incidence of low-dose aspirin-associated small-bowel injury
	<i>Bifidobacterium breve</i> Bif195	5 × 10e10, twice daily	3	[111]	Decreased the incidence of low-dose aspirin-associated small bowel injury
IBD					
Pouchitis	Mixture containing strains of <i>Lactobacillus plantarum</i> , <i>L. casei</i> , <i>L. acidophilus</i> , <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> , <i>Bifidobacterium infantis</i> , <i>B. longum</i> , <i>B. breve</i> and <i>Streptococcus salivarius</i> subsp. <i>thermophilus</i>	1800 billion bacteria daily	2	[112,113]	Treatment of active pouchitis

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
Ulcerative colitis	Mixture containing strains of <i>Lactobacillus plantarum</i> , <i>L. casei</i> , <i>L. acidophilus</i> , <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> , <i>Bifidobacterium infantis</i> , <i>B. longum</i> , <i>B. breve</i> and <i>Streptococcus salivarius</i> subsp. <i>thermophilus</i>	1800 billion bacteria daily	2	[113]	Maintenance of clinical remission in pouchitis
	Mixture containing strains of <i>Lactobacillus plantarum</i> , <i>L. casei</i> , <i>L. acidophilus</i> , <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> , <i>Bifidobacterium infantis</i> , <i>B. longum</i> , <i>B. breve</i> and <i>Streptococcus salivarius</i> subsp. <i>thermophilus</i>	1800 billion bacteria daily	2	[113,114]	Prevention of pouchitis in UC patients undergoing total colectomy
	<i>Clostridium butyricum</i> Miyairi	20 mg spores per tablet, 3 tablets three times per day	3	[113,115]	Prevention of pouchitis in UC patients undergoing total colectomy
	Mixture containing strains of <i>Lactobacillus plantarum</i> , <i>L. casei</i> , <i>L. acidophilus</i> , <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> , <i>Bifidobacterium infantis</i> , <i>B. longum</i> , <i>B. breve</i> and <i>Streptococcus salivarius</i> subsp. <i>thermophilus</i>	1800 billion bacteria twice daily	3	[116]	Induction of remission
	<i>Escherichia coli</i> Nissle 1917	5 × 10 ¹⁰ viable bacteria 2 times daily	2	[117,118]	Maintenance of remission
	Bifid triple viable (Bifico strains: <i>Bifidobacterium longum</i> , <i>Lactobacillus acidophilus</i> , and <i>Enterococcus faecalis</i>)	420–630 mg, three times per day	2	[119]	Significant improvement of the clinical response to aminosalicylates

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
Reducing symptoms associated with lactose maldigestion	Yogurt with live cultures of <i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i> and <i>Streptococcus thermophilus</i>	At least 10e8 cfu of each strain per gram of product	1	[120]	
	<i>Lactobacillus acidophilus</i> DDS-1	1 × 10e10, once daily	3	[121]	
	<i>Bifidobacterium longum</i> BB536 and <i>Lactobacillus rhamnosus</i> HN001 plus vitamin B6	4 × 10e9 plus 1 × 10e9 plus 1.4 mg	3	[122]	
	<i>Pediococcus acidilactici</i> CECT 7483, <i>Lactobacillus plantarum</i> CECT 7484, <i>L. plantarum</i> CECT 7485	3 × 10e9 cfu, once daily	3	[123]	

AAD, 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 9 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	[6]	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)
	<i>L. rhamnosus</i> GG	$\geq 10^{10}$ cfu/day, for 5–7 days	1	[6,124,125]	Reduced duration of diarrhea, length of hospitalization, and stool output. ESPGHAN 2022 [124]
	<i>S. boulardii</i> *	250–750 mg/day, for 5–7 days	1	[6,124,126]	Reduced duration of diarrhea. ESPGHAN 2022 [124]
	<i>L. reuteri</i> DSM 17938	1×10^8 to 4×10^8 cfu/day, for 5 days	1	[6,124,127]	Reduced duration of diarrhea. ESPGHAN 2022 [124]
	<i>L. rhamnosus</i> 19070-2 & <i>L. reuteri</i> DSM 12246	2×10^{10} cfu for each strain/day, for 5 days	1	[124,128,129]	Reduced duration of diarrhea. ESPGHAN 2022 [124]
	<i>B. lactis</i> B94 + inulin	5×10^{10} cfu plus 900 mg once daily, respectively, for 5 days	3	[130]	Reduced duration of acute watery diarrhea
	<i>L. paracasei</i> B21060, plus arabinogalactan, and xylooligosaccharides	2.5×10^9 cfu plus 500 mg plus 700 mg, respectively, twice daily, for 5 days	3	[131]	Reduced duration of diarrhea
	<i>L. rhamnosus</i> strains 573L/1; 573L/2; 573L/3	1.2×10^{10} cfu or placebo, twice daily, for 5 days	3	[132]	Reduced duration of rotaviral diarrhea but not of diarrhea of any etiology

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
	<i>L. delbrueckii</i> var. <i>bulgaricus</i> , <i>L. acidophilus</i> , <i>Streptococcus thermophilus</i> , <i>B. bifidum</i> (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	[133]	Reduced duration of diarrhea
	<i>B. lactis</i> Bi-07, <i>L. rhamnosus</i> HN001, and <i>L. acidophilus</i> NCFM	Then 1.0 × 10 ¹⁰ cfu once a day, for the duration of diarrhea plus 7 days	3	[134]	Reduced duration of diarrhea and reduced hospital stay
Prevention of AAD	Probiotics as a general group	N/A	1	[7]	Reduced risk of AAD (a 2019 Cochrane review; 33 RCTs involving 6352 participants)
	<i>S. boulardii</i> *	≥ 5 billion cfu per day, for the duration of antibiotic treatment	1	[7,29,135]	Reduced risk of AAD/diarrhea. ESPGHAN 2016 [135] and 2022 [124]
	<i>L. rhamnosus</i> GG	≥ 5 billion cfu per day, for the duration of antibiotic treatment	1	[7,135,136]	Reduced risk of AAD/diarrhea. ESPGHAN 2016 [135] and 2022 [124]
	Multispecies probiotic (<i>Bifidobacterium bifidum</i> W23, <i>B. lactis</i> W51, <i>Lactobacillus acidophilus</i> W37, <i>Lactobacillus acidophilus</i> W55, <i>Lacticaseibacillus paracasei</i> W20, <i>Lactoplantibacillus plantarum</i> W62, <i>Lacticaseibacillus rhamnosus</i> W71, and <i>Ligilactobacillus salivarius</i> W24]	10 billion cfu per day, for the duration of antibiotic treatment and for 7 days after	3	[137]	Reduced risk of diarrhea but not AAD. The definition of diarrhea/AAD matters
	<i>L. rhamnosus</i> (strains E/N, Oxy, and Pen)	2 × 10 (10) cfu, twice daily, for the duration of antibiotic treatment	3	[138]	Reduced risk of diarrhea
Prevention of <i>C. difficile</i> diarrhea	<i>S. boulardii</i> *	250–500 mg	1	[135]	ESPGHAN 2016 [135] and 2022 [124]; AGA 2020 [14]; reduced risk of <i>C. difficile</i> -associated diarrhea

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
Prevention of nosocomial diarrhea	<i>L. rhamnosus GG</i>	At least 10^9 cfu/day, for the duration of the hospital stay	1	[139,140]	ESPGHAN 2022 [124]; reduced risk of nosocomial diarrhea
Prevention of necrotizing enterocolitis	Systematic reviews and meta-analyses (> 10,000 neonates) of RCTs		1	[18,141–143]	Some specific strains of probiotic may be effective for preventing NEC among preterm infants
	<i>L. rhamnosus GG</i>	From 1×10^9 cfu to 6×10^9 cfu	1	[17,144]	ESPGHAN 2020 [17] and 2022 [124]; AGA 2020 [14]
	<i>B. infantis</i> BB-02, <i>B. lactis</i> BB-12, and <i>S. thermophilus</i> TH-4	3.0 to 3.5×10^8 cfu (of each strain)	1	[17,144]	ESPGHAN 2020 [17] and 2022 [124]
	<i>B. animalis</i> subsp. <i>lactis</i> Bb-12 or B94	5×10^9 cfu	3	[141,144]	
	<i>L. reuteri</i> ATCC 55730 or DSM 17938	1×10^8 cfu (various regimens)	1	[141,144,145]	ATCC 55730; this strain is no longer available. Recommended by AGA 2020 [14], but not ESPGHAN 2020 [17] or 2022 [124]
	<i>B. longum</i> subsp. <i>infantis</i> ATCC 15697 + <i>L. acidophilus</i> ATCC 4356	125 mg/kg/dose twice daily with breast milk until discharge	3	[144,146]	
	<i>B. longum</i> subsp. <i>longum</i> 35624 + <i>L. rhamnosus GG</i>	5×10^8 cfu and 5×10^8 cfu, respectively	3	[144]	
<i>Helicobacter pylori</i> infection	Probiotics as a general group		1	[147–151]	Improved eradication rates and/or reduced side effects of anti- <i>H. pylori</i> treatment
	<i>S. boulardii</i> *	500 mg	1	[149,150,152,153]	Increased eradication rate (however, it was still below the desired level $\geq 90\%$) of

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
					success) and in reducing gastrointestinal adverse effects associated with <i>H. pylori</i> infection therapies. ESPGHAN 2022 [124]
	<i>Lactobacillus</i> (now <i>Lactiplantibacillus</i>) <i>plantarum</i> (UBLP 40), <i>L. acidophilus</i> (LA-5), <i>B. animalis</i> subsp. <i>lactis</i> BB-12, and <i>S. boulardii</i> Unique-28	Per capsule: <i>L. plantarum</i> (0.5×10^9 cfu), <i>L. acidophilus</i> LA-5 (1.75×10^9 cfu), BB-12 (1.75×10^9 cfu), and <i>S. boulardii</i> (1.5×10^9 cfu), twice daily for 15 days	3	[154]	Increased eradication rate and decreased side effects
	Fermented milk containing <i>L. casei</i> DN-114 001	10^{10} cfu/day for 14 days	3		
Infantile colic	Probiotics as a general group	N/A	1	[155–164]	
Infantile colic—management	<i>L. reuteri</i> DSM 17938	10^8 cfu/day for at least 21 days	1	[155,159,161,165]	Reduced crying and/or fussing time in breastfed infants, but its role in formula-fed infants is less clear. ESPGHAN 2022 [124]
	<i>B. lactis</i> Bb12	10^8 cfu/day, for 21–28 days	2	[166,167]	Reduced crying and/or fussing time in breastfed infants with infantile colic. ESPGHAN 2022 [124]
	<i>L. rhamnosus</i> 19070-2 and <i>L. reuteri</i> 12246 in a daily dose of 250×10^6 cfu, 3.33 mg of fructooligosaccharide	250×10^6 cfu, respectively, plus 3.33 mg of fructooligosaccharide, for 28 days	3	[168]	Reduced crying and/or fussing time in breastfed infants
	<i>L. paracasei</i> DSM 24733, <i>L. plantarum</i> DSM 24730, <i>L. acidophilus</i> DSM 24735, <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> DSM 24734),	5 billion cfu, for 21 days	3	[169]	Reduced crying in exclusively breastfed infants

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
	<i>B. longum</i> DSM 24736, <i>B. breve</i> DSM 24732, and <i>B. infantis</i> DSM 24737, and <i>S. thermophilus</i> DSM 24731				
Infantile colic – prevention	<i>L. reuteri</i> DSM 17938	10 ⁸ cfu/day, to newborns each day for 90 days	1	[157,170]	Reduced crying time in both breast-fed and formula fed infants
Functional abdominal pain disorders		N/A	1	[171–173]	No firm evidence for the use of probiotics (as a group) in children with FAPD
Functional abdominal pain / IBS	<i>L. reuteri</i> DSM 17938	10 ⁸ cfu to 2 x 10 ⁸ cfu/day	1	[171,173,174]	ESPGHAN 2022 [124]
	<i>L. rhamnosus</i> GG	10 ⁹ cfu to 3×10 ⁹ cfu twice daily	1	[173,175]	ESPGHAN 2022 [124]
Ulcerative colitis	Probiotics as a group	N/A	1	[15]	May induce clinical remission in patients with active ulcerative colitis
	A mixture of 8 strains (<i>L. paracasei</i> DSM 24733, <i>L. plantarum</i> DSM 24730, <i>L. acidophilus</i> DSM 24735, <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> DSM 24734, <i>B. longum</i> DSM 24736, <i>B. infantis</i> DSM 24737, <i>B. breve</i> DSM 24732, and <i>S. thermophilus</i> 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	[176]	For induction and maintenance of remission. ESPGHAN & ECCO 2018 [177]
	<i>Escherichia coli</i> 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	[117,118,178]	For induction and maintenance of remission. ESPGHAN & ECCO 2018 [177]

Disorder, action	Probiotic strain / prebiotic / synbiotic	Recommended dose	Evidence level	References	Comments
Pouchitis	A mixture of 8 strains (<i>L. paracasei</i> DSM 24733, <i>L. plantarum</i> DSM 24730, <i>L. acidophilus</i> DSM 24735, <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> DSM 24734, <i>B. longum</i> DSM 24736, <i>B. infantis</i> DSM 24737, <i>B. breve</i> DSM 24732, and <i>S. thermophilus</i> 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	[179,180]	Maintaining remission (but in adult patients) with chronic pouchitis ESPGHAN & ECCO 2018 [177] and AGA 2020 [14]
Nonalcoholic fatty liver disease	<i>Lactobacillus acidophilus</i> in combination with other strains of <i>Bifidobacterium</i> or <i>Lactobacillus</i> 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	[181]	

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

AAD, 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.

Table 10 Abbreviations used in this guideline

AAD	antibiotic-associated diarrhea
AGA	American Gastroenterological Association
ALT	alanine aminotransferase
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
ATCC	American Type Culture Collection
cfu	colony-forming unit
CNCM	<i>Collection Nationale de Cultures de Microorganismes</i>
CRP	C-reactive protein
ECCO	European Crohn's and Colitis Organization
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
FAO	Food and Agriculture Organization
FAPD	functional abdominal pain disorder
FOS	fructooligosaccharide
GOS	galactooligosaccharide
HMO	human milk oligosaccharide
HOMA	homeostasis model assessment
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
ISAPP	International Scientific Association for Probiotics and Prebiotics
LAB	lactic acid bacteria
LGG	<i>Lactocaseibacillus rhamnosus</i> GG
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NCIMB	National Collection of Industrial, Food and Marine Bacteria
NEC	necrotizing enterocolitis
NSAID	nonsteroidal anti-inflammatory drug
OCEBM	Oxford Centre for Evidence-Based Medicine
PICO	population, intervention, comparison, and outcome
QoL	quality of life
RCT	randomized controlled trial
TNF- α	tumor necrosis factor-alpha

UC ulcerative colitis

WHO World Health Organization

References

- Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol*. 2014 Aug;11(8):506–14.
- Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *J Nutr*. 1995 Jun;125(6):1401–12.
- Swanson KS, Gibson GR, Hutkins R, Reimer RA, Reid G, Verbeke K, et al. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. *Nat Rev Gastroenterol Hepatol*. 2020 Nov;17(11):687–701.
- Li J, Jia H, Cai X, Zhong H, Feng Q, Sunagawa S, et al. An integrated catalog of reference genes in the human gut microbiome. *Nat Biotechnol*. 2014 Aug;32(8):834–41.
- Sanders ME, Merenstein DJ, Ouwehand AC, Reid G, Salminen S, Cabana MD, et al. Probiotic use in at-risk populations. *J Am Pharm Assoc*. 2016;56(6):680–6.
- Collinson S, Deans A, Padua-Zamora A, Gregorio GV, Li C, Dans LF, et al. Probiotics for treating acute infectious diarrhoea. *Cochrane Database Syst Rev*. 2020 Dec 8;12(12):CD003048.
- Guo Q, Goldenberg JZ, Humphrey C, El Dib R, Johnston BC. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Cochrane Database Syst Rev*. 2019 Apr 30;4(4):CD004827.
- Goodman C, Keating G, Georgousopoulou E, Hespe C, Levett K. Probiotics for the prevention of antibiotic-associated diarrhoea: a systematic review and meta-analysis. *BMJ Open*. 2021 Aug 12;11(8):e043054.
- Zhang L, Zeng X, Guo D, Zou Y, Gan H, Huang X. Early use of probiotics might prevent antibiotic-associated diarrhea in elderly (>65 years): a systematic review and meta-analysis. *BMC Geriatr*. 2022 Jul 6;22(1):562.
- Goldenberg JZ, Yap C, Lytvyn L, Lo CKF, Beardsley J, Mertz D, et al. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children. *Cochrane Database Syst Rev*. 2017 Dec 19;12(12):CD006095.
- Hamad A, Fragkos KC, Forbes A. A systematic review and meta-analysis of probiotics for the management of radiation induced bowel disease. *Clin Nutr*. 2013 Jun;32(3):353–60.
- Malfërtheiner P, Megraud F, Rokkas T, Gisbert JP, Liou JM, Schulz C, et al. Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report. *Gut*. 2022 Aug 8;gutjnl-2022-327745.
- Dalal R, McGee RG, Riordan SM, Webster AC. Probiotics for people with hepatic encephalopathy. *Cochrane Database Syst Rev*. 2017 Feb 23;2(2):CD008716.
- Su GL, Ko CW, Bercik P, Falck-Ytter Y, Sultan S, Weizman AV, et al. AGA Clinical practice guidelines on the role of probiotics in the management of gastrointestinal disorders. *Gastroenterology*. 2020 Aug;159(2):697–705.

15. Kaur L, Gordon M, Baines PA, Ihezor-Ejiofor Z, Sinopoulou V, Akobeng AK. Probiotics for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev.* 2020 Mar 4;3(3):CD005573.
16. Savaiano DA, Hutkins RW. Yogurt, cultured fermented milk, and health: a systematic review. *Nutr Rev.* 2021 Apr 7;79(5):599–614.
17. van den Akker CHP, van Goudoever JB, Shamir R, Domellöf M, Embleton ND, Hojsak I, et al. Probiotics and preterm infants: a position paper by the European Society for Paediatric Gastroenterology Hepatology and Nutrition Committee on Nutrition and the European Society for Paediatric Gastroenterology Hepatology and Nutrition Working Group for Probiotics and Prebiotics. *J Pediatr Gastroenterol Nutr.* 2020 May;70(5):664–80.
18. Sharif S, Meader N, Oddie SJ, Rojas-Reyes MX, McGuire W. Probiotics to prevent necrotising enterocolitis in very preterm or very low birth weight infants. *Cochrane Database Syst Rev.* 2020 Oct 15;10(10):CD005496.
19. Zhang GQ, Hu HJ, Liu CY, Zhang Q, Shakya S, Li ZY. Probiotics for prevention of atopy and food hypersensitivity in early childhood: a PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore).* 2016 Feb;95(8):e2562.
20. Hatakka K, Ahola AJ, Yli-Knuuttila H, Richardson M, Poussa T, Meurman JH, et al. Probiotics reduce the prevalence of oral candida in the elderly—a randomized controlled trial. *J Dent Res.* 2007 Feb;86(2):125–30.
21. Kraft-Bodi E, Jørgensen MR, Keller MK, Kragelund C, Twetman S. Effect of probiotic bacteria on oral candida in frail elderly. *J Dent Res.* 2015 Sep;94(9 Suppl):181S–6S.
22. Ishikawa KH, Mayer MPA, Miyazima TY, Matsubara VH, Silva EG, Paula CR, et al. A Multispecies probiotic reduces oral *Candida* colonization in denture wearers: reduction of *Candida* by probiotics. *J Prosthodont.* 2015 Apr;24(3):194–9.
23. Grossi E, Buresta R, Abbiati R, Cerutti R. Clinical trial on the efficacy of a new symbiotic formulation, Flortec, in patients with acute diarrhea: a multicenter, randomized study in primary care. *J Clin Gastroenterol.* 2010 Sep;44(Supplement 1):S35–41.
24. McFarland LV. Systematic review and meta-analysis of *Saccharomyces boulardii* in adult patients. *World J Gastroenterol.* 2010 May 14;16(18):2202–22.
25. Greuter T, Michel MC, Thomann D, Weigmann H, Vavricka SR. Randomized, placebo-controlled, double-blind and open-label studies in the treatment and prevention of acute diarrhea with *Enterococcus faecium* SF68. *Front Med.* 2020;7:276.
26. Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JNV, Shanman R, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *JAMA.* 2012 May 9;307(18):1959–69.
27. Liao W, Chen C, Wen T, Zhao Q. Probiotics for the prevention of antibiotic-associated diarrhea in adults: a meta-analysis of randomized placebo-controlled trials. *J Clin Gastroenterol.* 2021 Jul 1;55(6):469–80.
28. Cai J, Zhao C, Du Y, Zhang Y, Zhao M, Zhao Q. Comparative efficacy and tolerability of probiotics for antibiotic-associated diarrhea: Systematic review with network meta-analysis. *United Eur Gastroenterol J.* 2018 Mar;6(2):169–80.
29. Szajewska H, Kołodziej M. Systematic review with meta-analysis: *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea. *Aliment Pharmacol Ther.* 2015 Oct;42(7):793–801.

30. Cimperman L, Bayless G, Best K, Diligente A, Mordarski B, Oster M, et al. A randomized, double-blind, placebo-controlled pilot study of *Lactobacillus reuteri* ATCC 55730 for the prevention of antibiotic-associated diarrhea in hospitalized adults. *J Clin Gastroenterol*. 2011 Oct;45(9):785–9.
31. Ouwehand AC, DongLian C, Weijian X, Stewart M, Ni J, Stewart T, et al. Probiotics reduce symptoms of antibiotic use in a hospital setting: a randomized dose response study. *Vaccine*. 2014 Jan 16;32(4):458–63.
32. Koning CJM, Jonkers DMAE, Stobberingh EE, Mulder L, Rombouts FM, Stockbrügger RW. The effect of a multispecies probiotic on the intestinal microbiota and bowel movements in healthy volunteers taking the antibiotic amoxicillin. *Am J Gastroenterol*. 2008 Jan;103(1):178–89.
33. Wenus C, Goll R, Loken EB, Biong AS, Halvorsen DS, Florholmen J. Prevention of antibiotic-associated diarrhoea by a fermented probiotic milk drink. *Eur J Clin Nutr*. 2008 Feb;62(2):299–301.
34. Selinger CP, Bell A, Cairns A, Lockett M, Sebastian S, Haslam N. Probiotic VSL#3 prevents antibiotic-associated diarrhoea in a double-blind, randomized, placebo-controlled clinical trial. *J Hosp Infect*. 2013 Jun;84(2):159–65.
35. Johnson S, Maziade PJ, McFarland LV, Trick W, Donskey C, Currie B, et al. Is primary prevention of *Clostridium difficile* infection possible with specific probiotics? *Int J Infect Dis*. 2012 Nov;16(11):e786–792.
36. Shen NT, Maw A, Tmanova LL, Pino A, Ancy K, Crawford CV, et al. Timely use of probiotics in hospitalized adults prevents *Clostridium difficile* infection: a systematic review with meta-regression analysis. *Gastroenterology*. 2017 Jun;152(8):1889–1900.e9.
37. Plummer S, Weaver MA, Harris JC, Dee P, Hunter J. *Clostridium difficile* pilot study: effects of probiotic supplementation on the incidence of *C. difficile* diarrhoea. *Int Microbiol*. 2004 Mar;7(1):59–62.
38. Lewis S, Burmeister S, Brazier J. Effect of the prebiotic oligofructose on relapse of *Clostridium difficile*-associated diarrhea: a randomized, controlled study. *Clin Gastroenterol Hepatol*. 2005 May;3(5):442–8.
39. Yu M, Zhang R, Ni P, Chen S, Duan G. Efficacy of *Lactobacillus*-supplemented triple therapy for *H. pylori* eradication: a meta-analysis of randomized controlled trials. *PLoS One*. 2019;14(10):e0223309.
40. Hauser G, Salkic N, Vukelic K, Jajacknez A, Stimac D. Probiotics for standard triple *Helicobacter pylori* eradication: a randomized, double-blind, placebo-controlled trial. *Medicine (Baltimore)*. 2015 May;94(17):e685.
41. Seddik H, Boutallaka H, Elkoti I, Nejari F, Berraida R, Berrag S, et al. *Saccharomyces boulardii* CNCM I-745 plus sequential therapy for *Helicobacter pylori* infections: a randomized, open-label trial. *Eur J Clin Pharmacol*. 2019 May;75(5):639–45.
42. Nista EC, Candelli M, Cremonini F, Cazzato IA, Zocco MA, Franceschi F, et al. *Bacillus clausii* therapy to reduce side-effects of anti-*Helicobacter pylori* treatment: randomized, double-blind, placebo controlled trial. *Aliment Pharmacol Ther*. 2004 Nov 15;20(10):1181–8.
43. Plomer M, III Perez M, Greifenberg DM. Effect of *Bacillus clausii* capsules in reducing adverse effects associated with *Helicobacter pylori* eradication therapy: a randomized, double-blind, controlled trial. *Infect Dis Ther*. 2020 Dec;9(4):867–78.
44. Bekar O, Yilmaz Y, Gulden M. Kefir improves the efficacy and tolerability of triple therapy in eradicating *Helicobacter pylori*. *J Med Food*. 2011 Apr;14(4):344–7.

45. Delia P, Sansotta G, Donato V, Frosina P, Messina G, De Renzis C, et al. Use of probiotics for prevention of radiation-induced diarrhea. *World J Gastroenterol*. 2007 Feb 14;13(6):912–5.
46. Liu MM, Li ST, Shu Y, Zhan HQ. Probiotics for prevention of radiation-induced diarrhea: a meta-analysis of randomized controlled trials. *PloS One*. 2017;12(6):e0178870.
47. Wei D, Heus P, van de Wetering FT, van Tienhoven G, Verleye L, Scholten RJ. Probiotics for the prevention or treatment of chemotherapy- or radiotherapy-related diarrhoea in people with cancer. *Cochrane Database Syst Rev*. 2018 Aug 31;8(8):CD008831.
48. Chitapanarux I, Chitapanarux T, Traisathit P, Kudumpee S, Tharavichitkul E, Lorvidhaya V. Randomized controlled trial of live *Lactobacillus acidophilus* plus *Bifidobacterium bifidum* in prophylaxis of diarrhea during radiotherapy in cervical cancer patients. *Radiat Oncol*. 2010 May 5;5:31.
49. Demers M, Dagnault A, Desjardins J. A randomized double-blind controlled trial: impact of probiotics on diarrhea in patients treated with pelvic radiation. *Clin Nutr*. 2014 Oct;33(5):761–7.
50. Linn YH, Thu KK, Win NHH. Effect of probiotics for the prevention of acute radiation-induced diarrhoea among cervical cancer patients: a randomized double-blind placebo-controlled study. *Probiotics Antimicrob Proteins*. 2019 Jun;11(2):638–47.
51. Zhao R, Wang Y, Huang Y, Cui Y, Xia L, Rao Z, et al. Effects of fiber and probiotics on diarrhea associated with enteral nutrition in gastric cancer patients: a prospective randomized and controlled trial. *Medicine (Baltimore)*. 2017 Oct;96(43):e8418.
52. de Castro Soares GG, Marinho CH, Pitol R, Andretta C, Oliveira E, Martins C, et al. Sporulated *Bacillus* as alternative treatment for diarrhea of hospitalized adult patients under enteral nutrition: a pilot randomized controlled study. *Clin Nutr ESPEN*. 2017 Dec;22:13–8.
53. Frohmader TJ, Chaboyer WP, Robertson IK, Gowardman J. Decrease in frequency of liquid stool in enterally fed critically ill patients given the multispecies probiotic VSL#3: a pilot trial. *Am J Crit Care*. 2010 May 1;19(3):e1–11.
54. Gluud LL, Vilstrup H, Morgan MY. Non-absorbable disaccharides versus placebo/no intervention and lactulose versus lactitol for the prevention and treatment of hepatic encephalopathy in people with cirrhosis. *Cochrane Database Syst Rev*. 2016 May 6;2016(5):CD003044.
55. Lunia MK, Sharma BC, Sharma P, Sachdeva S, Srivastava S. Probiotics prevent hepatic encephalopathy in patients with cirrhosis: a randomized controlled trial. *Clin Gastroenterol Hepatol*. 2014 Jun;12(6):1003-1008.e1.
56. Dhiman RK, Thumburu KK, Verma N, Chopra M, Rathi S, Dutta U, et al. Comparative efficacy of treatment options for minimal hepatic encephalopathy: a systematic review and network meta-analysis. *Clin Gastroenterol Hepatol*. 2020 Apr;18(4):800-812.e25.
57. Mittal VV, Sharma BC, Sharma P, Sarin SK. A randomized controlled trial comparing lactulose, probiotics, and L-ornithine L-aspartate in treatment of minimal hepatic encephalopathy. *Eur J Gastroenterol Hepatol*. 2011 Aug;23(8):725–32.
58. Bajaj JS, Saeian K, Christensen KM, Hafeezullah M, Varma RR, Franco J, et al. Probiotic yogurt for the treatment of minimal hepatic encephalopathy. *Am J Gastroenterol*. 2008 Jul;103(7):1707–15.
59. Ziada DH, Soliman HH, El Yamany SA, Hamisa MF, Hasan AM. Can *Lactobacillus acidophilus* improve minimal hepatic encephalopathy? A neurometabolite study using magnetic resonance spectroscopy. *Arab J Gastroenterol*. 2013 Sep;14(3):116–22.
60. Vlachogiannakos J, Vasianopoulou P, Viazis N, Chroni M, Voulgaris T, Ladas S, et al. The role of probiotics in the treatment of minimal hepatic encephalopathy. A prospective, randomized, placebo-controlled, double-blind study [abstract]. *Hepatology*. 2014;60((4 Suppl)):376A.

61. Nabavi S, Rafrat M, Somi MH, Homayouni-Rad A, Asghari-Jafarabadi M. Effects of probiotic yogurt consumption on metabolic factors in individuals with nonalcoholic fatty liver disease. *J Dairy Sci.* 2014 Dec;97(12):7386–93.
62. Eslamparast T, Poustchi H, Zamani F, Sharafkhah M, Malekzadeh R, Hekmatdoost A. Synbiotic supplementation in nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled pilot study. *Am J Clin Nutr.* 2014 Mar;99(3):535–42.
63. Mofidi F, Poustchi H, Yari Z, Nourinayyer B, Merat S, Sharafkhah M, et al. Synbiotic supplementation in lean patients with non-alcoholic fatty liver disease: a pilot, randomised, double-blind, placebo-controlled, clinical trial. *Br J Nutr.* 2017 Mar;117(5):662–8.
64. Malaguarnera M, Vacante M, Antic T, Giordano M, Chisari G, Acquaviva R, et al. *Bifidobacterium longum* with fructo-oligosaccharides in patients with non alcoholic steatohepatitis. *Dig Dis Sci.* 2012 Feb;57(2):545–53.
65. Duseja A, Acharya SK, Mehta M, Chhabra S, Shalimar, Rana S, et al. High potency multistrain probiotic improves liver histology in non-alcoholic fatty liver disease (NAFLD): a randomised, double-blind, proof of concept study. *BMJ Open Gastroenterol.* 2019 Aug;6(1):e000315.
66. Bakhshimoghaddam F, Shateri K, Sina M, Hashemian M, Alizadeh M. Daily consumption of synbiotic yogurt decreases liver steatosis in patients with nonalcoholic fatty liver disease: a randomized controlled clinical trial. *J Nutr.* 2018 Aug 1;148(8):1276–84.
67. Guglielmetti S, Mora D, Gschwender M, Popp K. Randomised clinical trial: *Bifidobacterium bifidum* MIMBb75 significantly alleviates irritable bowel syndrome and improves quality of life—a double-blind, placebo-controlled study. *Aliment Pharmacol Ther.* 2011 May;33(10):1123–32.
68. Andresen V, Gschossmann J, Layer P. Heat-inactivated *Bifidobacterium bifidum* MIMBb75 (SYN-HI-001) in the treatment of irritable bowel syndrome: a multicentre, randomised, double-blind, placebo-controlled clinical trial. *Lancet Gastroenterol Hepatol.* 2020 Jul;5(7):658–66.
69. Ducrotté P. Clinical trial: *Lactobacillus plantarum* 299v (DSM 9843) improves symptoms of irritable bowel syndrome. *World J Gastroenterol.* 2012;18(30):4012.
70. Ford AC, Harris LA, Lacy BE, Quigley EMM, Moayyedi P. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. *Aliment Pharmacol Ther.* 2018 Nov;48(10):1044–60.
71. Enck P, Zimmermann K, Menke G, Klosterhalfen S. Randomized controlled treatment trial of irritable bowel syndrome with a probiotic *E.-coli* preparation (DSM17252) compared to placebo. *Z Gastroenterol.* 2009 Feb;47(2):209–14.
72. Sisson G, Ayis S, Sherwood RA, Bjarnason I. Randomised clinical trial: A liquid multi-strain probiotic vs. placebo in the irritable bowel syndrome--a 12 week double-blind study. *Aliment Pharmacol Ther.* 2014 Jul;40(1):51–62.
73. Jafari E, Vahedi H, Merat S, Momtahan S, Riahi A. Therapeutic effects, tolerability and safety of a multi-strain probiotic in Iranian adults with irritable bowel syndrome and bloating. *Arch Iran Med.* 2014 Jul;17(7):466–70.
74. Choi CH, Jo SY, Park HJ, Chang SK, Byeon JS, Myung SJ. A randomized, double-blind, placebo-controlled multicenter trial of *Saccharomyces boulardii* in irritable bowel syndrome: effect on quality of life. *J Clin Gastroenterol.* 2011 Sep;45(8):679–83.
75. Paineau D, Payen F, Panserieu S, Coulombier G, Sobaszek A, Lartigau I, et al. The effects of regular consumption of short-chain fructo-oligosaccharides on digestive comfort of subjects with minor functional bowel disorders. *Br J Nutr.* 2008 Feb;99(2):311–8.

76. Silk DBA, Davis A, Vulevic J, Tzortzis G, Gibson GR. Clinical trial: the effects of a trans-galactooligosaccharide prebiotic on faecal microbiota and symptoms in irritable bowel syndrome. *Aliment Pharmacol Ther.* 2009 Mar;29(5):508–18.
77. Vulevic J, Tzortzis G, Juric A, Gibson GR. Effect of a prebiotic galactooligosaccharide mixture (B-GOS®) on gastrointestinal symptoms in adults selected from a general population who suffer with bloating, abdominal pain, or flatulence. *Neurogastroenterol Motil.* 2018 Nov;30(11):e13440.
78. Huaman JW, Mego M, Manichanh C, Cañellas N, Cañueto D, Segurola H, et al. Effects of prebiotics vs a diet low in FODMAPs in patients with functional gut disorders. *Gastroenterology.* 2018 Oct;155(4):1004–7.
79. Lorenzo-Zúñiga V, Llop E, Suárez C, Alvarez B, Abreu L, Espadaler J, et al. I.31, a new combination of probiotics, improves irritable bowel syndrome-related quality of life. *World J Gastroenterol.* 2014 Jul 14;20(26):8709–16.
80. Wong RK, Yang C, Song GH, Wong J, Ho KY. Melatonin regulation as a possible mechanism for probiotic (VSL#3) in irritable bowel syndrome: a randomized double-blinded placebo study. *Dig Dis Sci.* 2015 Jan;60(1):186–94.
81. Pinto-Sanchez MI, Hall GB, Ghajar K, Nardelli A, Bolino C, Lau JT, et al. Probiotic *Bifidobacterium longum* NCC3001 reduces depression scores and alters brain activity: a pilot study in patients with irritable bowel syndrome. *Gastroenterology.* 2017 Aug;153(2):448–459.e8.
82. Majeed M, Nagabhushanam K, Natarajan S, Sivakumar A, Ali F, Pande A, et al. *Bacillus coagulans* MTCC 5856 supplementation in the management of diarrhea predominant irritable bowel syndrome: a double blind randomized placebo controlled pilot clinical study. *Nutr J.* 2015 Dec;15(1):21.
83. Mezzasalma V, Manfrini E, Ferri E, Sandionigi A, La Ferla B, Schiano I, et al. A randomized, double-blind, placebo-controlled trial: the efficacy of multispecies probiotic supplementation in alleviating symptoms of irritable bowel syndrome associated with constipation. *BioMed Res Int.* 2016;2016:4740907.
84. Cayzeele-Decherf A, Pélerin F, Leuillet S, Douillard B, Housez B, Cazaubiel M, et al. *Saccharomyces cerevisiae* CNCM I-3856 in irritable bowel syndrome: an individual subject meta-analysis. *World J Gastroenterol.* 2017;23(2):336.
85. Ishaque SM, Khosruzzaman SM, Ahmed DS, Sah MP. A randomized placebo-controlled clinical trial of a multi-strain probiotic formulation (Bio-Kult®) in the management of diarrhea-predominant irritable bowel syndrome. *BMC Gastroenterol.* 2018 May 25;18(1):71.
86. Martoni CJ, Srivastava S, Leyer GJ. *Lactobacillus acidophilus* DDS-1 and *Bifidobacterium lactis* UABla-12 improve abdominal pain severity and symptomology in irritable bowel syndrome: randomized controlled trial. *Nutrients.* 2020 Jan 30;12(2):363.
87. Sadrin S, Sennoune S, Gout B, Marque S, Moreau J, Zinoune K, et al. A 2-strain mixture of *Lactobacillus acidophilus* in the treatment of irritable bowel syndrome: a placebo-controlled randomized clinical trial. *Dig Liver Dis.* 2020 May;52(5):534–40.
88. Francavilla R, Piccolo M, Francavilla A, Polimeno L, Semeraro F, Cristofori F, et al. Clinical and microbiological effect of a multispecies probiotic supplementation in celiac patients with persistent IBS-type symptoms: a randomized, double-blind, placebo-controlled, multicenter trial. *J Clin Gastroenterol.* 2019 Mar;53(3):e117–25.
89. Smecuol E, Constante M, Temprano MP, Costa AF, Moreno ML, Pinto-Sanchez MI, et al. Effect of *Bifidobacterium infantis* NLS super strain in symptomatic coeliac disease patients on long-term gluten-free diet—an exploratory study. *Benef Microbes.* 2020 Oct 12;11(6):527–34.

90. Yeun Y, Lee J. Effect of a double-coated probiotic formulation on functional constipation in the elderly: a randomized, double blind, controlled study. *Arch Pharm Res.* 2015 Jul;38(7):1345–50.
91. Ojetti V, Ianiro G, Tortora A, D'Angelo G, Di Rienzo TA, Bibbò S, et al. The effect of *Lactobacillus reuteri* supplementation in adults with chronic functional constipation: a randomized, double-blind, placebo-controlled trial. *J Gastrointestin Liver Dis.* 2014 Dec 1;23(4):387–91.
92. Riezzo G, Orlando A, D'Attoma B, Linsalata M, Martulli M, Russo F. Randomised double blind placebo controlled trial on *Lactobacillus reuteri* DSM 17938: improvement in symptoms and bowel habit in functional constipation. *Benef Microbes.* 2018 Jan 29;9(1):51–60.
93. Schumann C. Medical, nutritional and technological properties of lactulose. An update. *Eur J Nutr.* 2002;41(Suppl 1):117-25.
94. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific opinion on the substantiation of a health claim related to “native chicory inulin” and maintenance of normal defecation by increasing stool frequency pursuant to Article 13(5) of Regulation (EC) No 1924/2006. *EFSA J.* 2015;13(1):3951.
95. Waitzberg DL, Logullo LC, Bittencourt AF, Torrinhas RS, Shiroma GM, Paulino NP, et al. Effect of synbiotic in constipated adult women – a randomized, double-blind, placebo-controlled study of clinical response. *Clin Nutr.* 2013 Feb;32(1):27–33.
96. Ding C, Ge X, Zhang X, Tian H, Wang H, Gu L, et al. Efficacy of synbiotics in patients with slow transit constipation: a prospective randomized trial. *Nutrients.* 2016 Sep 28;8(10):605.
97. Toda T, Nanba F, Arai K, Takamizawa N, Shioya N, Suzuki S. Effect of supplement containing *Lactococcus lactis* subsp. *cremoris* FC on defecation in healthy humans: a randomized, placebo-controlled, double-blind crossover trial. *Jpn Pharmacol Ther.* 2017;45(6):989–97.
98. Ibarra A, Latreille-Barbier M, Donazzolo Y, Pelletier X, Ouwehand AC. Effects of 28-day *Bifidobacterium animalis* subsp. *lactis* HN019 supplementation on colonic transit time and gastrointestinal symptoms in adults with functional constipation: a double-blind, randomized, placebo-controlled, and dose-ranging trial. *Gut Microbes.* 2018 May 4;9(3):236–51.
99. Venkataraman R, Shenoy R, Ahire JJ, Neelamraju J, Madempudi RS. Effect of *Bacillus coagulans* unique IS2 with lactulose on functional constipation in adults: a double-blind placebo controlled study. *Probiotics Antimicrob Proteins* [Internet]. 2021 Oct 2 [cited 2023 Feb 22]; Available from: <https://link.springer.com/10.1007/s12602-021-09855-8>
100. Ibrahim A, Ali RAR, Manaf MRA, Ahmad N, Tajjruddin FW, Qin WZ, et al. Multi-strain probiotics (Hexbio) containing MCP BCMC strains improved constipation and gut motility in Parkinson's disease: a randomised controlled trial. *Plos One.* 2020 Dec 31;15(12):e0244680.
101. Sakai T, Makino H, Ishikawa E, Oishi K, Kushiro A. Fermented milk containing *Lactobacillus casei* strain Shirota reduces incidence of hard or lumpy stools in healthy population. *Int J Food Sci Nutr.* 2011 Jun;62(4):423–30.
102. Tursi A, Brandimarte G, Elisei W, Picchio M, Forti G, Pianese G, et al. Randomised clinical trial: mesalazine and/or probiotics in maintaining remission of symptomatic uncomplicated diverticular disease—a double-blind, randomised, placebo-controlled study. *Aliment Pharmacol Ther.* 2013 Oct;38(7):741–51.
103. Lahner E, Esposito G, Zullo A, Hassan C, Cannaviello C, Paolo MCD, et al. High-fibre diet and *Lactobacillus paracasei* B21060 in symptomatic uncomplicated diverticular disease. *World J Gastroenterol.* 2012 Nov 7;18(41):5918–24.

104. Petruzziello C, Marannino M, Migneco A, Brigida M, Saviano A, Piccioni A, et al. The efficacy of a mix of three probiotic strains in reducing abdominal pain and inflammatory biomarkers in acute uncomplicated diverticulitis. *Eur Rev Med Pharmacol Sci*. 2019 Oct;23(20):9126–33.
105. Petruzziello C, Migneco A, Cardone S, Covino M, Saviano A, Franceschi F, et al. Supplementation with *Lactobacillus reuteri* ATCC PTA 4659 in patients affected by acute uncomplicated diverticulitis: a randomized double-blind placebo controlled trial. *Int J Colorectal Dis*. 2019 Jun;34(6):1087–94.
106. Liu Z, Li C, Huang M, Tong C, Zhang X, Wang L, et al. Positive regulatory effects of perioperative probiotic treatment on postoperative liver complications after colorectal liver metastases surgery: a double-center and double-blind randomized clinical trial. *BMC Gastroenterol*. 2015 Mar 20;15:34.
107. Chowdhury AH, Adiamah A, Kushairi A, Varadhan KK, Krznaric Z, Kulkarni AD, et al. Perioperative probiotics or synbiotics in adults undergoing elective abdominal surgery: a systematic review and meta-analysis of randomized controlled trials. *Ann Surg*. 2020 Jun;271(6):1036–47.
108. Flesch AT, Tonial ST, Contu PDC, Damin DC. Perioperative synbiotics administration decreases postoperative infections in patients with colorectal cancer: a randomized, double-blind clinical trial. *Rev Col Bras Cir*. 2017;44(6):567–73.
109. Endo H, Higurashi T, Hosono K, Sakai E, Sekino Y, Iida H, et al. Efficacy of *Lactobacillus casei* treatment on small bowel injury in chronic low-dose aspirin users: a pilot randomized controlled study. *J Gastroenterol*. 2011 Jul;46(7):894–905.
110. Suzuki T, Masui A, Nakamura J, Shiozawa H, Aoki J, Nakae H, et al. Yogurt containing *Lactobacillus gasseri* mitigates aspirin-induced small bowel injuries: a prospective, randomized, double-blind, placebo-controlled trial. *Digestion*. 2017;95(1):49–54.
111. Mortensen B, Murphy C, O’Grady J, Lucey M, Elsafi G, Barry L, et al. *Bifidobacterium breve* Bif195 protects against small-intestinal damage caused by acetylsalicylic acid in healthy volunteers. *Gastroenterology*. 2019 Sep;157(3):637–646.e4.
112. Gionchetti P, Rizzello F, Morselli C, Poggioli G, Tambasco R, Calabrese C, et al. High-dose probiotics for the treatment of active pouchitis. *Dis Colon Rectum*. 2007 Dec;50(12):2075–82; discussion 2082–4.
113. Nguyen N, Zhang B, Holubar SD, Pardi DS, Singh S. Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. *Cochrane Database Syst Rev*. 2019 Nov 30;11(11):CD001176.
114. Gionchetti P, Rizzello F, Helwig U, Venturi A, Lammers KM, Brigidi P, et al. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. *Gastroenterology*. 2003 May;124(5):1202–9.
115. Yasueda A, Mizushima T, Nezu R, Sumi R, Tanaka M, Nishimura J, et al. The effect of *Clostridium butyricum* Miyairi on the prevention of pouchitis and alteration of the microbiota profile in patients with ulcerative colitis. *Surg Today*. 2016 Aug;46(8):939–49.
116. Bibiloni R, Fedorak RN, Tannock GW, Madsen KL, Gionchetti P, Campieri M, et al. VSL#3 probiotic-mixture induces remission in patients with active ulcerative colitis. *Am J Gastroenterol*. 2005 Jul;100(7):1539–46.
117. Kruis W, Fric P, Pokrotnieks J, Lukás M, Fixa B, Kascák M, et al. Maintaining remission of ulcerative colitis with the probiotic *Escherichia coli* Nissle 1917 is as effective as with standard mesalazine. *Gut*. 2004 Nov;53(11):1617–23.

118. Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon AT. Non-pathogenic *Escherichia coli* versus mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet*. 1999 Aug 21;354(9179):635–9.
119. Chen MY, Qiu ZW, Tang HM, Zhuang KH, Cai QQ, Chen XL, et al. Efficacy and safety of bifid triple viable plus aminosalicyclic acid for the treatment of ulcerative colitis: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2019 Nov;98(47):e17955.
120. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific opinion on the substantiation of health claims related to live yoghurt cultures and improved lactose digestion (ID 1143, 2976) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA J*. 2010;8(10):1763.
121. Pakdaman MN, Udani JK, Molina JP, Shahani M. The effects of the DDS-1 strain of lactobacillus on symptomatic relief for lactose intolerance—a randomized, double-blind, placebo-controlled, crossover clinical trial. *Nutr J*. 2016 May 20;15(1):56.
122. Vitellio P, Celano G, Bonfrate L, Gobetti M, Portincasa P, De Angelis M. Effects of *Bifidobacterium longum* and *Lactobacillus rhamnosus* on gut microbiota in patients with lactose intolerance and persisting functional gastrointestinal symptoms: a randomised, double-blind, cross-over study. *Nutrients*. 2019 Apr 19;11(4):886.
123. Cano-Contreras AD, Minero Alfaro IJ, Medina López VM, Amieva Balmori M, Remes Troche JM, Espadaler Mazo J, et al. Efficacy of i3.1 probiotic on improvement of lactose intolerance symptoms: a randomized, placebo-controlled clinical trial. *J Clin Gastroenterol*. 2022 Feb 1;56(2):141–7.
124. Szajewska H, Berni Canani R, Domellöf M, Guarino A, Hojsak I, Indrio F, et al. Probiotics for the management of pediatric gastrointestinal disorders: position paper of the ESPGHAN Special Interest Group on Gut Microbiota and Modifications. *J Pediatr Gastroenterol Nutr*. 2023 Feb 1;76(2):232–47.
125. Szajewska H, Kołodziej M, Gieruszczak-Białek D, Skórka A, Ruszczyński M, Shamir R. Systematic review with meta-analysis: *Lactobacillus rhamnosus* GG for treating acute gastroenteritis in children—a 2019 update. *Aliment Pharmacol Ther*. 2019 Jun;49(11):1376–84.
126. Szajewska H, Kołodziej M, Zalewski BM. Systematic review with meta-analysis: *Saccharomyces boulardii* for treating acute gastroenteritis in children—a 2020 update. *Aliment Pharmacol Ther*. 2020 Apr;51(7):678–88.
127. Patro-Gołąb B, Szajewska H. Systematic review with meta-analysis: *Lactobacillus reuteri* DSM 17938 for treating acute gastroenteritis in children. An update. *Nutrients*. 2019 Nov 14;11(11):2762.
128. Rosenfeldt V, Michaelsen KF, Jakobsen M, Larsen CN, Møller PL, Tvede M, et al. Effect of probiotic *Lactobacillus* strains on acute diarrhea in a cohort of nonhospitalized children attending day-care centers. *Pediatr Infect Dis J*. 2002 May;21(5):417–9.
129. Rosenfeldt V, Michaelsen KF, Jakobsen M, Larsen CN, Møller PL, Pedersen P, et al. Effect of probiotic *Lactobacillus* strains in young children hospitalized with acute diarrhea. *Pediatr Infect Dis J*. 2002 May;21(5):411–6.
130. İşlek A, Sayar E, Yılmaz A, Baysan BÖ, Mutlu D, Artan R. The role of *Bifidobacterium lactis* B94 plus inulin in the treatment of acute infectious diarrhea in children. *Turk J Gastroenterol*. 2014 Dec;25(6):628–33.
131. Passariello A, Terrin G, Cecere G, Micillo M, De Marco G, Di Costanzo M, et al. Randomised clinical trial: efficacy of a new synbiotic formulation containing *Lactobacillus paracasei* B21060 plus arabinogalactan and xilooligosaccharides in children with acute diarrhoea. *Aliment Pharmacol Ther*. 2012 Apr;35(7):782–8.

132. Szymański H, Pejcz J, Jawień M, Chmielarczyk A, Strus M, Heczko PB. Treatment of acute infectious diarrhoea in infants and children with a mixture of three *Lactobacillus rhamnosus* strains—a randomized, double-blind, placebo-controlled trial. *Aliment Pharmacol Ther.* 2006 Jan 15;23(2):247–53.
133. Canani RB, Cirillo P, Terrin G, Cesarano L, Spagnuolo MI, De Vincenzo A, et al. Probiotics for treatment of acute diarrhoea in children: randomised clinical trial of five different preparations. *BMJ.* 2007 Aug 18;335(7615):340.
134. Chen K, Xin J, Zhang G, Xie H, Luo L, Yuan S, et al. A combination of three probiotic strains for treatment of acute diarrhoea in hospitalised children: an open label, randomised controlled trial. *Benef Microbes.* 2020 Aug 12;11(4):339–46.
135. Szajewska H, Canani RB, Guarino A, Hojsak I, Indrio F, Kolacek S, et al. Probiotics for the prevention of antibiotic-associated diarrhea in children. *J Pediatr Gastroenterol Nutr.* 2016 Mar;62(3):495–506.
136. Szajewska H, Kolodziej M. Systematic review with meta-analysis: *Lactobacillus rhamnosus* GG in the prevention of antibiotic-associated diarrhoea in children and adults. *Aliment Pharmacol Ther.* 2015 Nov;42(10):1149–57.
137. Lukasiak J, Dierikx T, Besseling-van der Vaart I, de Meij T, Szajewska H, Multispecies Probiotic in AAD Study Group. Multispecies probiotic for the prevention of antibiotic-associated diarrhea in children: a randomized clinical trial. *JAMA Pediatr.* 2022 Sep 1;176(9):860–6.
138. Ruzczyński M, Radzikowski A, Szajewska H. Clinical trial: effectiveness of *Lactobacillus rhamnosus* (strains E/N, Oxy and Pen) in the prevention of antibiotic-associated diarrhoea in children. *Aliment Pharmacol Ther.* 2008 Jul;28(1):154–61.
139. Szajewska H, Wanke M, Patro B. Meta-analysis: the effects of *Lactobacillus rhamnosus* GG supplementation for the prevention of healthcare-associated diarrhoea in children. *Aliment Pharmacol Ther.* 2011 Nov;34(9):1079–87.
140. Hojsak I, Szajewska H, Canani RB, Guarino A, Indrio F, Kolacek S, et al. Probiotics for the prevention of nosocomial diarrhea in children. *J Pediatr Gastroenterol Nutr.* 2018 Jan;66(1):3–9.
141. Beghetti I, Panizza D, Lenzi J, Gori D, Martini S, Corvaglia L, et al. Probiotics for preventing necrotizing enterocolitis in preterm infants: a network meta-analysis. *Nutrients.* 2021 Jan 9;13(1):192.
142. Chi C, Li C, Buys N, Wang W, Yin C, Sun J. Effects of probiotics in preterm infants: a network meta-analysis. *Pediatrics.* 2021 Jan;147(1):e20200706.
143. Gao X, Wang Y, Shi L, Feng W, Yi K. Effect and safety of *Saccharomyces boulardii* for neonatal necrotizing enterocolitis in pre-term infants: a systematic review and meta-analysis. *J Trop Pediatr.* 2021 Jul 2;67(3):fmaa022.
144. van den Akker CHP, van Goudoever JB, Szajewska H, Embleton ND, Hojsak I, Reid D, et al. Probiotics for preterm infants: a strain-specific systematic review and network meta-analysis. *J Pediatr Gastroenterol Nutr.* 2018 Jul;67(1):103–22.
145. Athalye-Jape G, Rao S, Patole S. *Lactobacillus reuteri* DSM 17938 as a probiotic for preterm neonates: a strain-specific systematic review. *JPEN J Parenter Enteral Nutr.* 2016 Aug;40(6):783–94.
146. Lin HC, Su BH, Chen AC, Lin TW, Tsai CH, Yeh TF, et al. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. *Pediatrics.* 2005 Jan;115(1):1–4.

147. Feng JR, Wang F, Qiu X, McFarland LV, Chen PF, Zhou R, et al. Efficacy and safety of probiotic-supplemented triple therapy for eradication of *Helicobacter pylori* in children: a systematic review and network meta-analysis. *Eur J Clin Pharmacol*. 2017 Oct;73(10):1199–208.
148. Wen J, Peng P, Chen P, Zeng L, Pan Q, Wei W, et al. Probiotics in 14-day triple therapy for Asian pediatric patients with *Helicobacter pylori* infection: a network meta-analysis. *Oncotarget*. 2017 Nov 10;8(56):96409–18.
149. Zhou BG, Chen LX, Li B, Wan LY, Ai YW. *Saccharomyces boulardii* as an adjuvant therapy for *Helicobacter pylori* eradication: a systematic review and meta-analysis with trial sequential analysis. *Helicobacter*. 2019 Oct;24(5):e12651.
150. Szajewska H, Horvath A, Kołodziej M. Systematic review with meta-analysis: *Saccharomyces boulardii* supplementation and eradication of *Helicobacter pylori* infection. *Aliment Pharmacol Ther*. 2015 Jun;41(12):1237–45.
151. Fang HR, Zhang GQ, Cheng JY, Li ZY. Efficacy of *Lactobacillus*-supplemented triple therapy for *Helicobacter pylori* infection in children: a meta-analysis of randomized controlled trials. *Eur J Pediatr*. 2019 Jan;178(1):7–16.
152. Hurduc V, Plesca D, Dragomir D, Sajin M, Vandenplas Y. A randomized, open trial evaluating the effect of *Saccharomyces boulardii* on the eradication rate of *Helicobacter pylori* infection in children. *Acta Paediatr*. 2009 Jan;98(1):127–31.
153. Bin Z, Ya-Zheng X, Zhao-Hui D, Bo C, Li-Rong J, Vandenplas Y. The efficacy of *Saccharomyces boulardii* CNCM I-745 in addition to standard *Helicobacter pylori* eradication treatment in children. *Pediatr Gastroenterol Hepatol Nutr*. 2015 Mar;18(1):17–22.
154. Viazis N, Argyriou K, Kotzampassi K, Christodoulou DK, Apostolopoulos P, Georgopoulos SD, et al. A four-probiotics regimen combined with a standard *Helicobacter pylori*-eradication treatment reduces side effects and increases eradication rates. *Nutrients*. 2022 Feb 1;14(3):632.
155. Sung V, D'Amico F, Cabana MD, Chau K, Koren G, Savino F, et al. *Lactobacillus reuteri* to treat infant colic: a meta-analysis. *Pediatrics*. 2018 Jan;141(1):e20171811.
156. Skonieczna-Żydecka K, Janda K, Kaczmarczyk M, Marlicz W, Łoniewski I, Łoniewska B. The Effect of probiotics on symptoms, gut microbiota and inflammatory markers in infantile colic: a systematic review, meta-analysis and meta-regression of randomized controlled trials. *J Clin Med*. 2020 Apr 2;9(4):999.
157. Ong TG, Gordon M, Banks SS, Thomas MR, Akobeng AK. Probiotics to prevent infantile colic. *Cochrane Database Syst Rev*. 2019 Mar 13;3(3):CD012473.
158. Dryl R, Szajewska H. Probiotics for management of infantile colic: a systematic review of randomized controlled trials. *Arch Med Sci*. 2018 Aug;14(5):1137–43.
159. Gutiérrez-Castrellón P, Indrio F, Bolio-Galvis A, Jiménez-Gutiérrez C, Jimenez-Escobar I, López-Velázquez G. Efficacy of *Lactobacillus reuteri* DSM 17938 for infantile colic: systematic review with network meta-analysis. *Medicine (Baltimore)*. 2017 Dec;96(51):e9375.
160. Schreck Bird A, Gregory PJ, Jalloh MA, Risoldi Cochrane Z, Hein DJ. Probiotics for the treatment of infantile colic: a systematic review. *J Pharm Pract*. 2017 Jun;30(3):366–74.
161. Harb T, Matsuyama M, David M, Hill RJ. Infant Colic—what works: a systematic review of interventions for breast-fed infants. *J Pediatr Gastroenterol Nutr*. 2016 May;62(5):668–86.
162. Xu M, Wang J, Wang N, Sun F, Wang L, Liu XH. The efficacy and safety of the probiotic bacterium *Lactobacillus reuteri* DSM 17938 for infantile colic: a meta-analysis of randomized controlled trials. *PloS One*. 2015;10(10):e0141445.

163. Anabrees J, Indrio F, Paes B, AlFaleh K. Probiotics for infantile colic: a systematic review. *BMC Pediatr.* 2013 Nov 15;13:186.
164. Simonson J, Haglund K, Weber E, Fial A, Hanson L. Probiotics for the management of infantile colic: a systematic review. *MCN Am J Matern Child Nurs.* 2021 Apr 1;46(2):88–96.
165. Szajewska H, Gyrczuk E, Horvath A. *Lactobacillus reuteri* DSM 17938 for the management of infantile colic in breastfed infants: a randomized, double-blind, placebo-controlled trial. *J Pediatr.* 2013 Feb;162(2):257–62.
166. Nocerino R, De Filippis F, Cecere G, Marino A, Micillo M, Di Scala C, et al. The therapeutic efficacy of *Bifidobacterium animalis* subsp. *lactis* BB-12[®] in infant colic: a randomised, double blind, placebo-controlled trial. *Aliment Pharmacol Ther.* 2020 Jan;51(1):110–20.
167. Chen K, Zhang G, Xie H, You L, Li H, Zhang Y, et al. Efficacy of *Bifidobacterium animalis* subsp. *lactis*, BB-12[®] on infant colic—a randomised, double-blinded, placebo-controlled study. *Benef Microbes.* 2021 Nov 16;12(6):531–40.
168. Gerasimov S, Gantzel J, Dementieva N, Schevchenko O, Tsitsura O, Guta N, et al. Role of *Lactobacillus rhamnosus* (FloraActive™) 19070-2 and *Lactobacillus reuteri* (FloraActive™) 12246 in infant colic: a randomized dietary study. *Nutrients.* 2018 Dec 13;10(12):1975.
169. Baldassarre ME, Di Mauro A, Tafuri S, Rizzo V, Gallone MS, Mastromarino P, et al. Effectiveness and safety of a probiotic-mixture for the treatment of infantile colic: a double-blind, randomized, placebo-controlled clinical trial with fecal real-time PCR and NMR-based metabolomics analysis. *Nutrients.* 2018 Feb 10;10(2):195.
170. Indrio F, Di Mauro A, Riezzo G. Prophylactic use of a probiotic in the prevention of colic, regurgitation, and functional constipation—reply. *JAMA Pediatr.* 2014 Aug;168(8):778.
171. Wegh CAM, Benninga MA, Tabbers MM. Effectiveness of probiotics in children with functional abdominal pain disorders and functional constipation: a systematic review. *J Clin Gastroenterol.* 2018;52 Suppl 1, Proceedings from the 9th Probiotics, Prebiotics and New Foods, Nutraceuticals and Botanicals for Nutrition&Human and Microbiota Health Meeting, held in Rome, Italy from September 10 to 12, 2017:S10–26.
172. Xu HL, Zou LL, Chen MB, Wang H, Shen WM, Zheng QH, et al. Efficacy of probiotic adjuvant therapy for irritable bowel syndrome in children: a systematic review and meta-analysis. *PloS One.* 2021;16(8):e0255160.
173. Trivić I, Niseteo T, Jadrešin O, Hojsak I. Use of probiotics in the treatment of functional abdominal pain in children—systematic review and meta-analysis. *Eur J Pediatr.* 2021 Feb;180(2):339–51.
174. Weizman Z, Abu-Abed J, Binsztok M. *Lactobacillus reuteri* DSM 17938 for the management of functional abdominal pain in childhood: a randomized, double-blind, placebo-controlled trial. *J Pediatr.* 2016 Jul;174:160-164.e1.
175. Gawrońska A, Dziechciarz P, Horvath A, Szajewska H. A randomized double-blind placebo-controlled trial of *Lactobacillus* GG for abdominal pain disorders in children. *Aliment Pharmacol Ther.* 2007 Jan 15;25(2):177–84.
176. Miele E, Pascarella F, Giannetti E, Quaglietta L, Baldassano RN, Staiano A. Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with ulcerative colitis. *Am J Gastroenterol.* 2009 Feb;104(2):437–43.
177. Turner D, Ruemmele FM, Orlanski-Meyer E, Griffiths AM, de Carpi JM, Bronsky J, et al. Management of paediatric ulcerative colitis, part 1: ambulatory care—an evidence-based guideline from European Crohn’s and Colitis Organization and European Society of Paediatric

- Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr.* 2018 Aug;67(2):257–91.
178. Henker J, Müller S, Laass MW, Schreiner A, Schulze J. Probiotic *Escherichia coli* Nissle 1917 (EcN) for successful remission maintenance of ulcerative colitis in children and adolescents: an open-label pilot study. *Z Gastroenterol.* 2008 Sep;46(9):874–5.
 179. Mimura T, Rizzello F, Helwig U, Poggioli G, Schreiber S, Talbot IC, et al. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut.* 2004 Jan;53(1):108–14.
 180. Gionchetti P, Rizzello F, Venturi A, Brigidi P, Matteuzzi D, Bazzocchi G, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology.* 2000 Aug;119(2):305–9.
 181. Gkiourtzis N, Kalopitas G, Vadarlis A, Bakaloudi DR, Dionysopoulos G, Karanika E, et al. The benefit of probiotics in pediatric nonalcoholic fatty liver disease: a meta-analysis of randomized control trials. *J Pediatr Gastroenterol Nutr.* 2022 Sep 1;75(3):e31–7.