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Methodological Guidelines of the Scientific Community for Human Microbiome Research (CHMR) and the Russian Gastroenterology Association (RGA) on the Use of Probiotics, Prebiotics, Synbiotics, Metabiotics and Functional Foods Enriched with Them for the Treatment and Prevention of Gastrointestinal Diseases in Adults and Children

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Aim: to optimize outcomes of the treatment and prevention of gastrointestinal diseases in adults and children.
Key points. The Methodological Guidelines contain sections on the terminology, classification, mechanisms of action, requirements for sale in the Russian Federation, requirements for proving the efficacy and safety of probiotics, prebiotics, synbiotics and metabiotics, as well as functional foods enriched with them. An overview of relevant data allowing to include these drugs and products in the treatment and prevention of gastrointestinal diseases in adults and children is presented.
Conclusion. The clinical efficacy of probiotics, prebiotics, synbiotics and metabiotics depends on the specificity and quantity of their components, the dosage form, the regimen and duration of treatment. Products and functional foods with proven efficacy and safety are recommended for the treatment and prevention of gastrointestinal diseases in adults and children.
Keywords: probiotic, prebiotic, synbiotic, metabiotic, functional food, diarrhea, *C. difficile*, *H. pylori*, IBS, SIBO, constipation, dyspepsia, MAFLD, liver cirrhosis, acute gastroenteritis, AGI, atopic dermatitis, food allergy, infection
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Методические рекомендации Научного сообщества по содействию клиническому изучению микробиома человека (НСОИМ) и Российской гастроэнтерологической ассоциации (РГА) по применению пробиотиков, пребиотиков, синбиотиков, метабиотиков и обогащенных ими функциональных пищевых продуктов для лечения и профилактики заболеваний гастроэнтерологического профиля у взрослых и детей

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Цель: оптимизировать результаты лечения и профилактики заболеваний гастроэнтерологического профиля у взрослых и детей.

Основное содержание. В методических рекомендациях представлены разделы, посвященные терминологии, классификации, механизмам действия, требованиям к реализации на территории Российской Федерации, требованиям к доказательству эффективности и безопасности пробиотиков, пребиотиков, синбиотиков и метабиотиков, а также обогащенных ими функциональных пищевых продуктов. Представлен обзор актуальных данных, позволяющих включать данные препараты и продукты в схемы лечения и профилактики заболеваний гастроэнтерологического профиля у взрослых и детей.

Заключение. Клиническая эффективность пробиотиков, пребиотиков, синбиотиков и метабиотиков зависит от специфичности и количества входящих в их состав компонентов, формы выпуска, режима и длительности приема. Доказавшие свою эффективность и безопасность препараты и функциональные пищевые продукты рекомендованы к применению для лечения и профилактики заболеваний гастроэнтерологического профиля у взрослых и детей.

Ключевые слова: пробиотик, пребиотик, синбиотик, метабиотик, функциональный пищевой продукт, диарея, *C. difficile*, *H. pylori*, СРК, СИБР, запор, диспепсия, МАЖБП, цирроз печени, острый гастроэнтерит, ОКИ, атопический дерматит, пищевая аллергия, инфекция

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1. Definitions

Probiotics — live microorganisms that benefit the health of the host when administered in adequate quantities [1].

Prebiotics — substances that are not digested by human digestive enzymes but are fermented by the intestinal microbiota, leading to specific changes in the composition and/or activity of the gastrointestinal microbiota, thus benefiting the health of the host [2].

Synbiotics — products containing probiotic strains and prebiotic substances with both probiotic and prebiotic properties [3].

Metabiotics — structural components of probiotic microorganisms, in combination with their metabolites and/or signaling molecules, that can optimize the host's physiological functions, metabolism, and behavioral responses associated with the symbiotic microbiota [4, 5].

2. Classification

Probiotic microorganisms are identified at the genus, species, and strain level, which has an alphabetic, numeric, or alphanumeric designation (e.g., *Lactobacillus casei Actimunis*, *Bifidobacterium longum* 35624, *Saccharomyces boulardii* CNCM I-745). In systematic reviews, probiotics are often divided into single-strain (containing only one microbial strain) and multistrain (containing two or more strains) products. However, this classification lacks clinical significance, because the claimed effects of a particular probiotic product must be confirmed by appropriate clinical trials, regardless of the number of strains. The classification of probiotics by their scope is also conditional. For example, probiotic compounds that have a positive effect on the psychoemotional status are conventionally referred to as "psychobiotics", and those that can increase life expectancy are referred to as "gerobiotics".

The most important groups of prebiotics include fructans (inulin and fructooligosaccharides), oligosaccharides (e.g., starch monomers), and galactooligosaccharides. Food fibers have similar properties to prebiotics; however, they are traditionally classified as a separate subgroup [2].

Synbiotics are divided into synergistic and complementary products, depending on the properties of their prebiotic component. Synergistic synbiotics contain a prebiotic substrate, which stimulates the reproduction and activity of the predominantly probiotic microorganisms included in its composition. Complementary synbiotics contain probiotic and prebiotic components that benefit the human body independently [3].

The classification of metabiotics is conditional and based on their structural properties. Metabiotics include inactivated microbial cells, components of the bacterial cell wall (including lipopolysaccharides, peptidoglycans and their derivatives), and microbial metabolites: short-chain fatty acids (acetate, propionate, butyrate), bacteriocins, enzymes, branched-chain amino acids, carbohydrates (e.g., teichoic acids), organic acids, vitamins, and other molecules. The most commonly used metabiotics are inactivated microbial cells of probiotic strains [6, 7].

3. Mechanism of action

3.1. Mechanisms of action of probiotics

Despite the significant diversity and widespread use of probiotic strains, their mechanisms of action are not fully understood. The functions of probiotics are much similar to those of normal human intestinal microbiota, but their effect may vary depending on the genus, species and strain. The main mechanisms of action and functions of probiotics are presented below.

Maintenance of colonization resistance

Colonization resistance is due to the ability of probiotic strains to prevent colonization of the gastrointestinal (GI) tract by opportunistic and pathogenic microorganisms through inhibition of their activity and ability to reproduce due to competition for nutrients, as well as through the synthesis of a number of antibacterial metabolites active against pathogenic bacteria (organic acids, bacteriocins, amines, etc.) [8].

Metabolism of nutrients, endogenous and exogenous molecules

In the intestinal lumen, probiotics metabolize nutrients (e.g., plant fibers) and some other substances (e.g., primary bile acids and lactate) due to the presence of specific enzymes not found in humans. Examples of such enzymes are β-galactosidase (hydrolyzes β-galactosides into

monosaccharides) and bile salt hydrolase (involved in the deconjugation of bile acids and their salts) [9].

Some probiotic strains are able to metabolize xenobiotics, exogenous chemicals that are foreign to the human body and not part of its metabolism. These include pesticides, synthetic dyes, medicinal products, and other chemical agents [10].

Production of metabolites necessary for the host organism

During their life, probiotic strains synthesize metabolites that enter the systemic circulation and participate in the host's homeostasis. Most importantly, these metabolites include short-chain fatty acids (SCFAs) (acetate, propionate and butyrate), which support the regulation of energy homeostasis (especially in colonocytes) and serve as signaling molecules for the cells of the immune system, determining their differentiation and anti-inflammatory activity [11]. Living probiotic microorganisms also produce various mediators: dopamine (involved in motivation and behavioral reactions, a precursor of norepinephrine and epinephrine), norepinephrine (regulates the processes in the central nervous system (CNS) responsible for waking, memory, learning and attention), serotonin (regulates gastrointestinal secretion and peristalsis, vasoconstriction and psychoemotional status), gamma-aminobutyric acid (the main inhibitory neurotransmitter in the CNS), acetylcholine (the main mediator in the cholinergic nervous pathways), and histamine (a mediator of histamine receptors in the cells of the CNS, GI organs, cardiovascular, respiratory, and immune systems) [12].

In addition, probiotics synthesize metabolites essential for the host, such as tryptophan (essential amino acid, a precursor of serotonin) [12] and B vitamins, which serve as co-enzymes of many biochemical processes in the human body: riboflavin (vitamin B_2), cobalamin (vitamin B_{12}) and folic acid [13].

Regulation of local and adaptive immune response

The interaction of the components of probiotic bacteria with immunocompetent host cells directly or indirectly activates local and systemic anti-inflammatory immune response by stimulating the synthesis of anti-inflammatory cytokines (mainly interleukin-4 and interleukin-10). Adequate levels of anti-inflammatory cytokines determine the direction of differentiation of regulatory immune cells (primarily regulatory T lymphocytes), which is manifested by inhibition of pro-inflammatory reactions and maintenance of the anti-inflammatory immune response [14].

Due to the above mechanisms, probiotics can have an effect on almost all human organs and systems. However, probiotic microorganisms are not able to colonize the human GI tract sustainably, so the development of these effects is largely determined by the time of exposure to probiotics and their activity in the colon [15].

3.2. Mechanisms of action of prebiotics

Prebiotics can change the composition and functions of the intestinal microbiota by selectively stimulating the growth and reproduction of certain species of bacteria, acting as food substrates for them [16]. For example, fructooligosaccharides and galactooligosaccharides are metabolized mainly by organisms of the genera *Actinobacteria, Bacteroidetes* and *Firmicutes*, and starch and fructans are fermented by bacteria of the genera *Bifidobacterium* and *Ruminococcus*. Bacterial metabolism in the colon results in the production of SCFAs, low molecular weight compounds (e.g., methane, hydrogen sulfide, sulfides), and other metabolites serving as food substrates for other microorganisms [17]. Prebiotic components of synergistic synbiotics selectively stimulate the growth and reproduction of the probiotic strains included in the composition [3].

Fermentation of prebiotics by commensal bacteria also results in the production of acids that reduce the colonic pH thus affecting the composition and function of the intestinal microbiota (for example, the amount of *Bacteroides* organisms and butyrate production are stimulated by *Firmicutes* bacteria) [2, 3].

3.3. Mechanism of action of metabiotics

The total number of potential metabiotics and their mechanisms of action are not fully understood. Acting as effector molecules, metabiotics exert local and systemic effects due to mechanisms similar to those of probiotics. For example, SCFAs and bacterial cell components influence colonic immune cells and regulate local and systemic immune responses, and bacteriocins maintain colonization resistance and inhibit intercellular communication of pathogens. Metabiotics containing bacterial enzymes also have a metabolic function similar to that of probiotics. Bacterial metabolites included in metabiotics (e.g., branched-chain polysaccharides, organic acids, peptides, folates) can act as food substrates for some commensal microorganisms and affect their reproduction and activity, which is typical for prebiotics [4, 5].

Some metabiotics can act as metabolic and signaling molecules, precursors or co-factors of

bioactive compounds that directly affect physiological processes in the human body (e.g., neurotransmitters of microbial origin) [6].

4. Requirements for probiotics, prebiotics, synbiotics and metabiotics

4.1. Legal requirements for circulation in the Russian Federation

Probiotics and metabiotics can be authorized in the Russian Federation as dietary supplements (DSs) and medicinal products (MPs) in accordance with the legislation of the Russian Federation. The only prebiotic that can be authorized as a medicinal product is lactulose. Synbiotics and other prebiotics, in accordance with the legislation, can be authorized in the Russian Federation only as a dietary supplement. All synbiotic components declared to be biologically active substances are subject to proper marketing authorization.

The safety of probiotics, prebiotics, synbiotics and metabiotics should meet the strict microbiological standards of the "Uniform sanitary epidemiological and hygienic requirements for goods subject to sanitary epidemiological surveillance" controlled by Rospotrebnadzor.

Dietary supplements (DSs) are natural and/or identical (to natural) biologically active substances, as well as probiotic microorganisms, intended for administration with food or addition to foods.

Marketing authorization of probiotics, prebiotics, synbiotics and metabiotics as dietary supplements includes three main stages:

- sample testing;
- expert examination of documentation;
- preparation of a state marketing authorization certificate.

These substances must be studied to confirm their safety and the presence of the declared components. Sale of probiotics, prebiotics, synbiotics and metabiotics in the Russian Federation and the Eurasian Economic Union (EAEU) as dietary supplements is allowed if they conform to the hygienic food safety requirements established in Appendices 1–3 of the Technical Regulations of the Customs Union "On food safety" (TR CU 021/2011 with 2019 addenda). In accordance with Appendix 7 of these regulations, the manufacture (production) of DSs must not use microorganisms that cause diseases or can transmit or mediate the transmission of antibiotic resistance genes, including:

– spore-forming aerobic and anaerobic microorganisms (including representatives of the genera *Bacillus and Clostridium*);
– microorganisms of the genera *Escherichia, Enterococcus* and *Corynebacterium*;
– microorganisms with hemolytic activity;
– non-spore-forming microorganisms isolated from animals and birds and not typical for normal human microbiota;
– viable yeast and yeast-like fungi (including representatives of the genus *Candida*, actinomycetes, streptomycetes, all genera and species of microscopic mold fungi).

In addition, the hygienic requirements for food safety and nutritional value specified in the Sanitary Epidemiological Rules and Regulations 2.3.2.2340-08 must be met.

After testing samples, a decision on the state marketing authorization of the DS is made and recorded in the Unified Register of State Marketing Authorization Certificates, which is controlled by the Federal Service for Surveillance on Consumer Rights Protection and Human Well-being (Rospotrebnadzor).

To prevent actions that mislead consumers, Rospotrebnadzor has approved a "System of voluntary certification of dietary supplements, food additives, and food products obtained from genetically modified sources" and entered it into the Unified Register of Voluntary Certification Systems (VCSs). This system serves to confirm the quality of products in accordance with Sanitary Epidemiological Rules and Regulations 2.3.2.1290-03 "Hygienic requirements for the organization of manufacture and circulation of dietary supplements (DSs)". The VCS for probiotics, prebiotics and metabiotics authorized as dietary supplements confirms the efficacy and conformity of the substance properties declared by the manufacturer or importer. Application on the label of the dietary supplement (and/or the consumer (secondary) packaging of the dietary supplement, instruction for use, package insert, etc.) of information on the efficacy of the probiotic or prebiotic as a dietary supplement is possible only after the voluntary certification of the dietary supplement and the issue of such certificate of conformity.

When probiotics, prebiotics, synbiotics and metabiotics are authorized as dietary supplements in the Russian Federation, the information on the label must include:

– *inscription "dietary supplement";*
– *name: DS;*
– *inscription "not a medicinal product";*
– *composition (with excipients);*
– *information on the presentation and packaging;*

– scope of use, specifying which dietary biologically active substances are provided by the DS;
– percentage of the adequate intake;
– dosage;
– recommendations for use;
– contraindications;
– storage conditions, shelf life;
– information about the possibility of sale in pharmacies and specialized stores or food store departments selling dietary products;
– production specification number (for domestic dietary supplements);
– name of the manufacturing organization and its legal address (for products imported into the Russian Federation, the country of origin and the name of the manufacturing company);
– number and date of the certificate of state marketing authorization;
– details and contact phone number of the organization authorized to accept complaints from consumers.

According to Decree No. 886 of the Government of the Russian Federation dated May 31, 2023 "On approval of the rules for labeling dietary supplements with means of identification and specifics of the implementation of the State Information System for monitoring the circulation of goods subject to mandatory labeling with means of identification with respect to dietary supplements", all dietary supplements are subject to additional registration in the national labeling system "Chestny ZNAK"("Honest SIGN") to prevent the distribution of substandard and counterfeit products. This measure is strictly mandatory for all dietary supplements from September 1, 2025, and its implementation is monitored by Rospotrebnadzor.

Marketing authorization of probiotics and metabiotics as medicinal products is carried out in accordance with the requirements of Federal Law of the Russian Federation No. 61-ФЗ "On the circulation of medicinal products". The rules for the circulation of medicinal products defined by Order No. 403н of the Ministry of Health of the Russian Federation dated July 11, 2017 "On approval of the rules for the dispensing of medicinal products for human use, including immunobiological medicinal products, by pharmacies and individual entrepreneurs licensed for pharmaceutical activities" are applicable to probiotics and metabiotics authorized as medicinal products.

In the State Pharmacopoeia of the Russian Federation, probiotics and metabiotics are defined as a single class of products: metabiotics are regarded as a type of probiotics. These products are identified as immunobiological medicinal products that contain live or inactivated non-pathogenic microorganisms (eubiotics), which antagonize pathogenic and opportunistic bacteria, as well as their metabolic products or growth factors for normal microbiota (prebiotics) and their rational combinations with each other (synbiotics). The above products must meet the pharmacopoeial requirements for obtaining a production strain and its seed material for the formation of production biomass, as well as the product quality requirements for the specific dosage form.

A probiotic or metabiotic authorized as a medicinal product must be classified into a certain pharmacotherapeutic group (e.g., a probiotic, eubiotic, anti-diarrheal agent, probiotic or eubiotic from the group of medical immunobiological products (MIBP probiotic or MIBP eubiotic), other immunomodulators, etc.) and according to the Anatomical Therapeutic Chemical (ATC) Classification System. Probiotics authorized as medicinal products in the Russian Federation have the following ATC codes: *Saccharomyces Boulardii* – A07FA02; Antidiarrheal microorganisms – A07FA; *Lactobacillus* – G01AX14; Lactic acid producing organisms – A07FA01; Lactic acid producing organisms, combinations – A07FA51; Other immunomodulators – L03A. Metabiotics authorized as medicinal products belong to the following ATC categories: Antidiarrheal microorganisms (A07FA), Immunostimulants based on bacterial lysates (R07AX), Leukopoietic stimulator (V03AF) and Other immunomodulators (L03, L03A). Some of the products authorized as medicinal products may have the same composition, but different ATC codes and pharmacotherapeutic groups.

4.2. Legal requirements for the circulation of functional foods enriched with probiotics, prebiotics or synbiotics

A functional food (FF) is a food product intended for regular use in diets by all age groups of the healthy population, reducing the risk of nutrition-related diseases, preserving and improving health due to the presence of physiologically functional food ingredients in its composition.

A physiologically functional food ingredient (PFFI) is a biologically active and/or physiologically valuable ingredient that is safe for health and has well-known physicochemical characteristics, properties that have been identified and scientifically justified, and recommended dietary daily allowances that can maintain and improve

health: dietary fibers, vitamins, minerals, polyunsaturated fatty acids, probiotics, prebiotics or synbiotics.

The above terms are defined in GOST R 52349-2005 dated July 01, 2006 "Food products. Functional food products. Terms and definitions (with Amendment No. 1)" (GOST — Russian National Standard). It should be noted that in this document, metabiotics are not included in the list of PFFIs as a separate nomenclature.

The proper quality and safety of FFs for children and adults is ensured by the general requirements for food products specified in Federal Law No. 29-ФЗ "On the quality and safety of food products" dated January 2, 2000, and Federal Law No. 47-ФЗ "On amendments to the Federal Law "On the quality and safety of food products"" dated March 1, 2020.

However, in the Russian Federation, the status of FFs is not strictly regulated, despite the adopted state standards GOST R 55577-2013 and GOST R 54059-2010, which define functional products. GOST R 55577-2013 contains requirements for confirming that the efficacy of FFs has been "demonstrated using approved methods of evidence-based medicine", but without references to approving regulations. Appendices A and B to the above GOST contain acceptable phrases for describing the effects of an FF in the product information (in the composition section), but do not specify requirements for confirming these effects.

GOST R 54059-2010 approves the classification of PFFIs based on their effects on the human body. According to the proposed classification, a PFFI can be classified into multiple effect classes (for example, maintenance of the immune system and maintenance of gastrointestinal function). Citing this GOST, the manufacturer can describe these properties in the product information on the consumer packaging of the FF.

Thus, the legal regulation of the FF market requires improvement in view of the absence of a comprehensive regulation of the circulation and control of the therapeutic efficacy of FFs and PFFIs.

4.3. Clinical efficacy and safety assessment requirements

Microbial strains are not specified for some probiotics, synbiotics and metabiotics (DSs, MPs, and FFs), therefore the expected efficacy and safety of such products are not guaranteed. The name of the strains in some formulations may be hidden at the discretion of the manufacturer, however, such products must have their efficacy and safety confirmed in clinical studies (the trade name must be specified).

At the discretion of the manufacturer, auxiliary active substances (e.g., vitamins, minerals, nutraceutical components) may be included in the composition of probiotics, prebiotics, synbiotics and metabiotics. In this case, the efficacy and safety of such formulations should be proven in separate clinical studies.

4.3.1. Efficacy and safety of probiotics

The clinical efficacy of a probiotic is determined by its strain specificity, the number of microorganisms in the single and daily dose, as well as the dosage form and duration of use.

Strain specificity is the most important characteristic of probiotics, determining their functional potential resulting from the presence of probiotic microorganisms.

The optimal dose of a probiotic is determined by the survival of a sufficient number of microbial colony-forming units (CFUs) for a clinical effect to develop after the product passes through the aggressive environment of the upper GI tract [18]. A screening tool for determining the survival of probiotic strains is testing *in vitro* with simulation of the proximal GI tract environment with its high acidity, activity of digestive enzymes and bile acid salts, partial pressure of oxygen, and temperature. Various dosage forms are used to ensure preservation and achievement of predominant release of probiotic strains in the colon, with the most effective being capsules and microcapsules made of synthetic, semisynthetic or natural polymers. Also, the efficacy of probiotics depends on the sustained viability of the strains in the specified amount until the expiry date of the product. In the latest generation of probiotics, probiotic strains can be found inside the capsule in the form of biofilms — this form increases the shelf life of the product and ensures the release of a sufficient amount of CFUs directly in the colon [19]. Nevertheless, the appropriate dose of a probiotic is determined by clinical studies demonstrating the expected favorable effects of the specified probiotic strains with the specified dose and dosage form [20].

Probiotics are characterized by high safety: a benefit is significantly more frequent than adverse events (AEs). Cases of cholangitis, bacteremia, fungal infection, sepsis, or endocarditis have been reported in patients with immunodeficiency, but the risk of these adverse effects is low and similar to the risk of infection with strains of commensal bacteria [21].

4.3.2. Efficacy and safety of prebiotics

As with probiotics, the choice of a prebiotic should be based on the results of clinical studies demonstrating the expected beneficial effects of its use with the specified dose, dosage form (e.g., powder, syrup or component of a functional food), and duration of use.

It is assumed that no life-threatening or serious AEs can occur with prebiotics. However, the use of prebiotics can be associated with osmotic diarrhea and flatulence due to their osmotic properties and the production of gases (methane, hydrogen sulfide, carbon dioxide) as a result of fermentation by commensal colonic microorganisms. The main characteristics determining the development of these AEs are the dose of the prebiotic and the chain length of the prebiotic substance. Shorter molecules (e.g., inulin) are metabolized rapidly and predominantly in the proximal colon, whereas longer chains (e.g., food fibers and polysaccharides), on the contrary, are fermented more slowly and predominantly in the distal colon, which increases the risk of these AEs. It is assumed that the above AEs can develop even with therapeutic doses of prebiotics [2].

4.3.3. Efficacy and safety of synbiotics

Synbiotics are assessed using the same efficacy and safety criteria as for probiotics and prebiotics. The clinical effect of a synbiotic formulation should be confirmed in clinical studies, regardless of the evidence of benefits of its constituent components from individual studies.

For synergistic synbiotics, the selectivity of the prebiotic substrate towards the probiotic strains must be demonstrated. The recommended approach is to conduct clinical studies demonstrating the superiority of the effects of the synergistic synbiotic over those of its individual components. To date, there is no consensus on the need to apply this approach to complementary synbiotics [3].

4.3.4. Efficacy and safety of metabiotics

The main characteristics of the efficacy of metabiotics are the specificity of the components (including the strain specificity of inactivated microorganisms), the amount of active substances, the dosage form, and the duration of use. The efficacy and safety of metabiotics are confirmed by clinical study results (the dose and dosage form must be specified).

Inactivation of live microbial cells for the production of metabiotics is achieved by chemical or physical exposure (for example, heat treatment, ultraviolet irradiation, electric current, high pressure, organic solvents, and other approaches). To assess the safety of such metabiotics, a preliminary analysis of the genome of candidate bacteria is carried out to screen for potentially undesirable genes (which emphasizes the importance of microbial strain specificity), with subsequent confirmation of their non-viability after inactivation [6].

Metabiotics containing inactivated microorganisms are characterized by a longer shelf life and good preservation in the human GI tract, as compared with probiotic microorganisms. It is assumed that metabiotics, unlike probiotics, do not induce sepsis and infectious complications and do not promote the transfer of antibiotic resistance genes [22]. Single AEs have been reported with inactivated microorganisms in children (abdominal distension, dehydration and vomiting), and their frequency did not differ significantly from the control group of subjects who received placebo. Despite the safety of other types of metabiotics (e.g., bacterial metabolites) demonstrated in clinical studies, their potential risks have not been properly studied [4].

5. Therapeutic indications

5.1. Assessment criteria

The criteria for assessing the strength of recommendations (SoR) and the level of evidence (LoE) for the use of probiotics, prebiotics, synbiotics and metabiotics are given in accordance with Order No. 103н of the Ministry of Health of the Russian Federation dated February 28, 2019 "On approval of the procedure and terms of the development of clinical guidelines, their revision, the standard form of clinical guidelines and requirements for their structure, the composition and scientific validity of the information included in clinical guidelines" (Table 1, Table 2).

5.2. Clinical use

Below are the indications for use and treatment regimens for probiotics, prebiotics, synbiotics and metabiotics authorized with the appropriate doses and dosage forms, including FFs, with the marketing authorization valid in the Russian Federation at the time of preparation of these Guidelines. For the ease of prescription in clinical practice, these drugs and products are listed under non-commercial and trade names.

5.2.1. Indications for use in adults

Indications for the use of the above products and FFs in adults include the prevention of antibiotic-associated diarrhea (AAD), *C. difficile*-associated disease, improvement of *H. pylori*

Table 1. Scale for assessing the level of credibility of recommendations for methods of prevention, diagnosis, treatment, medical rehabilitation, including those based on the use of natural therapeutic factors (preventive, diagnostic, curative, rehabilitative interventions)

Level	Decoding
A	Strong recommendation (all efficacy measures (outcomes) considered are important, all studies are of high or fair methodological quality, and their conclusions on the outcomes of interest are consistent)
B	Conditional recommendation (not all efficacy measures (outcomes) considered are important, not all studies are of high or fair methodological quality, and/or their conclusions on the outcomes of interest are not consistent)
C	Weak recommendation (lack of adequate quality evidence (all efficacy measures (outcomes) considered are not important, all studies are of low methodological quality and their conclusions on the outcomes of interest are not consistent)

Table 2. Scale of levels of evidence for methods of prevention, treatment, medical rehabilitation, including those based on the use of natural therapeutic factors (preventive, curative, rehabilitative interventions)

Level	Decoding
1	Systematic review of randomized clinical trials using a meta-analysis
2	Separate randomized clinical trials and systematic reviews of studies of any design, with the exception of randomized clinical trials, using a meta-analysis
3	Non-randomized comparative studies, including cohort studies
4	Non-comparative studies, case report or case series report, case-control studies
5	There is only a rationale for a mechanism of action of an intervention (preclinical studies) or expert opinion

eradication outcomes, treatment of irritable bowel syndrome, treatment of functional (chronic) constipation, prevention of infectious diarrhea and functional gastrointestinal disorders in healthy adults (including after COVID-19), treatment of liver diseases (liver cirrhosis and metabolic-associated liver disease), as well as improvement of eradication outcomes in small intestinal bacterial overgrowth (SIBO) [23–52]. Summary data for specific indications are presented in Tables 3–11.

Table 3. Drugs and functional food products recommended for the prevention of antibiotic-associated diarrhea in adults

Composition	PhF	Dosage regimen	Comment	LoC, LoE
Saccharomyces boulardii CNCM I-745	C	5×10^9 CFU (**Enterol**, 1 capsule) 2–4 times a day, not less than the duration of taking AB	Reducing the risk of AAD in outpatients and hospitalized patients [23]	A2
Lactobacillus casei CNCM I-1518 (DN-11400), Actimunis	FF	$\geq 1 \times 10^{10}$ CFU (**Actimuno**, ≥ 100 g) 2 times a day, while taking AB + 7 days after	Reducing the risk of AAD in hospitalized patients [24]	A2
Bifidobacterium longum CBT BG7, *B. lactis* CBT BL3, *B. bifidum* CBT BF3, *Lactobacillus acidophilus* CBT LA1, *L. rhamnosus* CBT LR5, *Streptococcus thermophilus* CBT ST3 + FOS 175 mg + vitamin C 12 mg	C	5×10^9 CFU (**Neobiotic Lactobalance**, 1 capsule) 1 per day, 21 days	Reducing the severity of diarrhea, dyspepsia and abdominal pain symptoms (GSRS) in patients with AAD [25]	B4
Lactobacillus acidophilus LA-5, *Bifidumbacterium animalis* ssp. *lactis* BB-12	C	2×10^9 CFU (**Probiologist** or **Linex Forte**, 1 capsule) 2 times a day, while taking AB + 7 days after	Reducing the duration of AAD [26]	C2

Note: LoC — level of credibility; LoE — level of evidence; PhF — pharmaceutical form; C — capsules; FF — functional food; AB — antibiotics; FOS — fructooligosaccharides; AAD — antibiotic-associated diarrhea; GSRS — Gastrointestinal Symptom Rating Scale questionnaire.

Table 4. Drugs and functional foods recommended for the prevention of C. difficile-associated disease in adults

Composition	PhF	Dosage regimen	Comment	LoC, LoE
Saccharomyces boulardii CNCM I-745	C	10×10^9 CFU (**Enterol**, 2 capsules) 2 times a day, 28 days	Prevention of relapse when included in the relapse treatment regimen [27]	A2
			Prevention of first episode in hospitalized patients [28]	B4
Lactobacillus casei CNCM I-1518 (DN-11400), Actimunis	FF	1×10^{10} CFU (**Actimuno**, 100 g) 2 times a day, while taking AB + 7 days after	Prevention of the first episode in hospitalized patients taking AB [24]	A2
Oligofructose	P	4 g 3 times a day, 30 days after treatment	Prevention of recurrence of infection after treatment [29]	C3

Note: LoC — level of credibility; LoE — level of evidence; PhF — pharmaceutical form; C — capsules; FF — functional food; P — powder; AB — antibiotics.

Table 5. Products recommended for improvement of *H. pylori* eradication outcomes in adults

Composition	PhF	Dosage regimen	Comment	LoC, LoE
L. reuteri DSM 17648	C	1×10^{10} CFU (**Helinorm**, 1 capsule) 2 times per day, for 14 days	Improving treatment efficacy, reducing the risk of nausea, diarrhea, constipation and taste disturbance during triple eradication therapy [30]	A2
Saccharomyces boulardii CNCM I-745	C	5×10^9 CFU (**Enterol**, 1 capsule) 2 times per day, for 10 days	Reducing the frequency of AEs, improving the efficacy of eradication and patient adherence to the sequential treatment regimen [31]	A2
		5×10^9 CFU (**Enterol**, 1 capsule) 2 times per day, for 14 days	Reducing the frequency of AEs, improving the efficacy of eradication and patient adherence to treatment [32]	C5
Enterococcus faecium ENCfa-68, *Bifidobacterium longum* BB-46	C	4×10^7 CFU (**Bifiform**, 2 capsules) 2 times per day, for 14 days	Improving the efficacy of eradication and adherence to treatment, reducing the risk of diarrhea, abdominal pain, flatulence and vomiting during bismuth triple therapy [33]	A2

Note: LoC — level of credibility; LoE — level of evidence; PhF — pharmaceutical form; C — capsules; AE — adverse event.

Table 6. Products and functional foods recommended for the treatment of irritable bowel syndrome in adults

Composition	PhF	Dosage regimen	Comment	LoC, LoE
Bifidobacterium longum (infantis) 35624	C	1×10^9 CFU (**Symbiosys Alflorex**, 1 capsule) Once a day, for ≥ 28 days, monotherapy	Reducing symptom severity (IBS-SSS) in IBS patients (ROME IV) [34]	A1
Bifidobacterium animalis subsp. *lactis* CNCM I-2494 (DN-173 010), Bioregularis	FF	≥ $1{,}25 \times 10^{10}$ CFU (**Actibio**, ≥ 125 g) 2 times per day, for 42 days, monotherapy	Reducing abdominal distension and improving quality of life (HRQoL), increasing the frequency of bowel movements in IBS-C patients (ROME II) [35]	B2
		≥ $1{,}25 \times 10^{10}$ CFU (**Actibio**, ≥ 125 g) 2 times per day, for 28 days, monotherapy	Reducing abdominal pain in IBS-C patients (ROME III) [35]	B2
Lactobacillus plantarum CECT 7484, *Lactobacillus plantarum* CECT 7485, *Pediococcus acidilactici* CECT 7483	C	3×10^9 CFU (**ProbioLog IBS**, 1 capsule) Once daily, for 42 days, monotherapy	Improving quality of life (IBS-QoL) in IBS patients (ROME III) [36]	B2
Gingerol + menthol + D-limonene	C	7 mg / 80 mg / 5 mg (**Paleka**, 1 capsule) Once a day, for 30 days, together with treatment	Reducing symptom severity (7 × 7) in IBS and IBS/FD patients (ROME IV) [37]	B2
Bifidobacterium longum CBT BG7, *B. lactis* CBT BL3, *B. bifidum* CBT BF3, *Lactobacillus acidophilus* CBT LA1, *L. rhamnosus* CBT LR5, *Streptococcus thermophilus* CBT ST3 + FOS 175 mg + vitamin C 12 mg	C	5×10^9 CFU (**Neobiotic Lactobalance**, 1 capsule) Once a day, 21 days, monotherapy	Reducing the severity of diarrhea, dyspepsia symptoms and abdominal pain (GSRS) in patients with IBS-D (CG MoH RF) [24]	B4

End of the table 6. Products and functional foods recommended for the treatment of irritable bowel syndrome in adults

Composition	PhF	Dosage regimen	Comment	LoC, LoE
Lactobacillus paracasei CNCM I-1572 (DG) + FOS 5.2 g	SV	5×10^9 CFU (**Enterolactis Fibra**, 1 vial) Once a day, for 28 days, together with treatment	Reducing symptom severity (GSRS) in IBS-C (ROME IV) patients receiving mebeverine [38]	C4
Enterococcus faecium ENCfa-68, *Bifidobacterium longum* BB-46	C	2×10^7 CFU (**Bifiform**, 1 capsule) 3 times per day, for 14 days, together with treatment	Improving well-being (IBS-SSS and IBS-QOL) in patients with PI-IBS (CG MoH RF) [39]	C4
Saccharomyces boulardii CNCM I-745	C	5×10^9 CFU (**Enterol**, 1 capsule) 2 times per day, for 28 days, monotherapy	Reducing the severity of abdominal pain and bloating, improving the quality of life in IBS patients [40]	C5

Note: LoC — level of credibility; LoE — level of evidence; PhF — pharmaceutical form; C — capsules; SV — syrup in vials; FF — functional food; FOS — fructooligosaccharide; IBS-C — IBS with constipation; IBS-D — IBS with diarrhea; PI-IBS — post-infectious IBS; IBS/FD — IBS in combination with functional dyspepsia; CG MoH RF — Clinical Guidelines of the Ministry of Health of the Russian Federation; ROME — Rome Diagnostic Criteria for Functional Gastrointestinal Disorders; 7 × 7 — "7 × 7" questionnaire; GSRS — Gastrointestinal Symptom Rating Scale; IBS-SSS — Irritable Bowel Syndrome Severity Scoring System; IBS-QoL — Irritable Bowel Syndrome Quality of Life; HRQoL — Health-related quality of life.

Table 7. Products and functional foods for the treatment of functional (chronic) constipation in adults

Composition	PhF	Dosage regimen	Comment	LoC, LoE
Bifidobacterium animalis subsp. *lactis* CNCM I-2494 (DN-173 010), Bioregularis	FF	$\geq 1{,}2\ 5\times 10^{10}$ CFU (**Actibio**, ≥ 125 g) Once a day, for 14 days	Improving the frequency and consistency of stools in women [41]	B2
Lactulose	S	10–60 mL 1–2 times per day, for 3–12 weeks	Improving the frequency and consistency of stools [42]	B2
Inulin	SDL	4 g 3 times per day, for 28 days	Improving stool frequency [43]	B2

Note: LoC — level of credibility; LoE — level of evidence; PhF — pharmaceutical form; FF — functional food; S — syrup; SDL — sachets (for dilution in liquid).

Table 8. Products recommended for the prevention of infectious diarrhea in adults

Composition	PhF	Dosage regimen	Comment	LoC, LoE
Saccharomyces boulardii CNCM I-745	C	5×10^9 CFU (**Enterol**, 1 capsule) 1–2 times per day, for 5 days prior to + the entire period of travel	Reducing the risk of travelers' diarrhea [44]	A1

Note: LoC — level of credibility; LoE — level of evidence; PhF — pharmaceutical form; C — capsules.

5.2.2 Indications for use in children

Indications for the use of the above products and FFs in children include the treatment of acute diarrhea (including acute gastroenteritis and acute intestinal infections), prevention of antibiotic-associated diarrhea (including C. difficile infection), improving outcomes of H. pylori eradication, prevention of infectious diseases and functional gastrointestinal disorders in healthy children, as well as in children with food allergies and atopic dermatitis [53–68]. Summary data for specific indications are presented in Tables 12–16.

Table 9. Products and functional foods recommended for the prevention of functional gastrointestinal disorders in healthy adults

Composition	PhF	Dosage regimen	Comment	LoC, LoE
Bifidobacterium animalis subsp. *lactis* CNCM I-2494 (DN-173 010), Bioregularis	FF	≥ 1,25 × 10^{10} CFU (**Actibio**, 125 g) 2 times per day, for 28 days	Improving the quality of life (HRQoL), reducing the severity of abdominal distension, normalizing the frequency of stools in healthy women [45]	B2
		3,4 × 10^{7} CFU* (**Actibio**, 125 g) 2 times per day, for 28 days	Reducing the severity of flatulence in healthy people consuming foods rich in plant fiber [46]	B4
Metabolites *B. subtilis* SA44 + polyfructosans	C	5/400 mg (**Bactimunal**, 1 capsule) 2 times per day, for 28 days	Reducing the severity of dyspepsia, abdominal pain and diarrhea (GSRS) and asthenia severity (AS) in patients with mild to moderate COVID-19 [47]	B4

Note: LoC — level of credibility; LoE — level of evidence; PhF — pharmaceutical form; FF — functional food; S — syrup; SDL — sachet (for dilution in liquid); HRQoL — Health-related quality of life; GSRS — Gastrointestinal Symptom Rating Scale; AS — asthenia scale; * — the different CFU numbers of the FF are due to different calculation methods.

Table 10. Products recommended for the treatment of liver diseases in adults

Composition	PhF	Dosage regimen	Comment	LoC, LoE
Lactulose	S	15–30 mL 2 times per day, then individually	Reducing the severity of hepatic encephalopathy in patients with liver cirrhosis [48]	B1
Saccharomyces boulardii CNCM I-745	C	5 × 10^{9} CFU (**Enterol**, 1 capsule) 2 times per day, for 3 months	Improving hemodynamic and laboratory parameters (CRP, serum albumin, ALP, GGT, sodium and platelet count), decreasing the Child — Pugh score, reducing the severity of ascites and hepatic encephalopathy in patients with liver cirrhosis (Child — Pugh Class B or C) [49]	B2
Metabolites *B. subtilis* SA44 + polyfructosans	C	5/400 mg (**Bactimunal**, 1 capsule) 2 times per day, for 6 weeks	Reducing the severity of heaviness in the right hypochondrium, reducing ALT activity and fasting blood glucose, improving the lipid profile in patients with MAFLD [50]	B3

Note: LoC — level of credibility; LoE — level of evidence; PhF — pharmaceutical form; S — syrup; C — capsule; MAFLD — metabolic-associated fatty liver disease; CRP — C-reactive protein; ALP — alkaline phosphatase, GGT — gamma-glutamyltransferase; ALT — alanine aminotransferase.

Table 11. Products recommended for improving eradication outcomes in small intestinal bacterial overgrowth in adults

Composition	PhF	Dosage regimen	Comment	LoC, LoE
Saccharomyces boulardii CNCM I-745	C	5×10^{9} CFU (**Enterol**, 1 capsule) 2 times per day, for 3 months, monotherapy	Eradication of SIBO (hydrogen breath test with lactulose) in 80 % of patients with liver cirrhosis (Child — Pugh Class B and C) [51]	B2
		5×10^{9} CFU (**Enterol**, 1 capsule) 2 times per day, for the treatment period	Reducing the risk of AEs and improving outcomes of antibiotic therapy [52]	C5

Note: LoC — level of credibility; LoE — level of evidence; PhF — pharmaceutical form; C — capsule; SIBO — small intestinal bacterial overgrowth; AE — adverse event.

Table 12. Products effective in the treatment of acute gastroenteritis and acute intestinal infections in children

Composition	PhF	Dosage regimen	Comment	LoC, LoE
Saccharomyces boulardii CNCM I-745	S	5×10^9 CFU (**Enterol**, 1 sachet) 2 times per day, 5 days, monotherapy	Reducing the duration of diarrhea and hospital stay in acute gastroenteritis [53]	A1
	C, S	5×10^9 CFU (**Enterol**, 1 capsule/sachet) 2 times per day, 5–10 days, monotherapy	Reducing the duration and severity of AII symptoms (including amebiasis and blastocytosis) [54, 55]	B2
Lactobacillus paracasei CNCM I-1572 (DG) + FOS 5.2 g	SV	5×10^9 CFU (**Enterolactis Fibra**, 1 vial) Once a day, 12 days, together with treatment	Reducing the duration of the disease and the need for antispasmodics in AIIs [56]	B2
Enterococcus faecium ENCfa-68, *Bifidobacterium longum* BB-46	C	2×10^7 CFU (**Bifiform**, 1 capsule) 4 times per day, for 3–7 days, together with treatment	Reducing the duration of intoxication, lethargy, decreased appetite, vomiting, flatulence, fever and diarrhea in AIIs [57]	B3
Lactobacillus acidophilus NK1, NK2, NK5, NK12 + kefiran	C	10^7 CFU /0,4 mg (**Acipol**, 1 capsule) 1–3 times per day, for 6–10 days, together with treatment	Reducing the duration of AII symptoms, mainly acute gastroenteritis [58]	C4

Note: LoC — level of credibility; LoE — level of evidence; PhF — pharmaceutical form; S — sachets; C — capsule; SV — syrup in vials; AII — acute intestinal infections.

Table 13. Products effective in the prevention of antibiotic-associated diarrhea in children

Composition	PhF	Dosage regimen	Comment	LoC, LoE
Saccharomyces boulardii CNCM I-745	C	5×10^9 CFU (**Enterol**, 1 capsule) 2 times per day, for the duration of AB therapy	Prevention of AAD and *C. difficile*-associated disease [59]	B2
Lactobacillus acidophilus (NK1, NK2, NK5, NK12) + kefiran	C	10^7 CFU / 0.4 mg (**Acipol**, 1 capsule) 2 times per day, for 14 days, together with treatment	Prevention of AAD in hospitalized children [60]	B2

Note: LoC — level of credibility; LoE — level of evidence; PhF — pharmaceutical form; C — capsule; AB — antibiotic; AAD — antibiotic-associated diarrhea.

Table 14. Products and functional foods effective in improving outcomes of *H. pylori* eradication in children

Composition	PhF	Dosage regimen	Comment	LoC, LoE
Saccharomyces boulardii CNCM I-745	S	5×10^9 CFU (**Enterol**, 1 sachet) 2 times per day, together with therapy	Reducing the risk of diarrhea and improving treatment adherence [61]	B1
Lactobacillus casei CNCM I-1518 (DN-11400), Actimunis	FF	1×10^{10} CFU (**Actimuno**, 100 mL) Once a day, for 14 days, together with therapy	Improving outcomes of triple therapy [62]	B2
Lactobacillus acidophilus (NK1, NK2, NK5, NK12) + kefiran	C	10^7 CFU / 0.4 mg (**Acipol**, 1 capsule) 2 times per day, for 14 days, after treatment	Reducing the severity of abdominal pain after triple therapy (in combination with magnesium and aluminum hydroxide) [63]	C2

Note: LoC — level of credibility; LoE — level of evidence; PhF — pharmaceutical form; S — sachets; FF — functional food; C — capsule.

Table 15. Products and functional foods effective in the prevention of gastrointestinal infections and the treatment of functional gastrointestinal disorders in children

Composition	PhF	Dosage regimen	Comment	LoC, LoE
Lactobacillus casei CNCM I-1518 (DN-11400), Actimunis	FF	1×10^{10} CFU (**Actimuno**, 100 mL) 1–2 times per day, for 28 days	Reducing the risk of diarrhea in healthy children [64]	A1
Bifidobacterium animalis subsp. lactis BB-12	DV	1×10^{9} CFU (**Complinex Bab**y, 6 drops / 0.25 g) Once a day, for 21 days	Reducing the duration of crying and increasing the duration of sleep in colic of newborns (ROME III) [65]	B2
Lactobacillus acidophilus LA-14, L. casei LC-11, L. paracasei Lpc-37, *L. plantarum* Lp-115, *L. rhamnosus* HN001, *L. salivarius* Ls-33, *Bifidobacterium lactis* BI-04, *B. bifidum* Bb-02/Lactis, *B. longum* Bi-05 + FOS 500 mg	S	**Maxilac Baby** 1 sachet, 2 times per day, for 28 days	Reducing the risk of recurrent nausea, vomiting and diarrhea, reducing the severity of abdominal pain in children after mild to moderate COVID-19 [66]	B3

Note: LoC — level of credibility; LoE — level of evidence; PhF — pharmaceutical form; FF — functional food; DV — drops in vials; S — sachets; FOS — fructooligosaccharide; ROME — Rome Diagnostic Criteria for Functional Gastrointestinal Disorders.

Table 16. Products and functional foods effective in the prevention of gastrointestinal infections and the treatment of functional gastrointestinal disorders in children

Composition	PhF	Dosage regimen	Comment	LoC, LoE
Lactobacillus rhamnosus LGG, *Bifidobacterium animalis* subsp. *lactis* BB-12 + vitamin B_1 + vitamin B_6	CT	4×10^{9} CFU / 0.4 mg / 0.5 mg (**Bifiform Kids**, 2 tablets) 2 times per day, for 21 days	Improving skin symptoms (SCORAD), reducing abdominal pain, eructation, abdominal distension, frequency of bowel movements and unformed stools in children with gastrointestinal and skin manifestations of FA [67]	B2
Bifidobacterium longum Bl-05, *B. breve* Bb-03, *B. bifidum* Bb-06, *Lactobacillus acidophilus* La-14, *L. rhamnosus* Lr-32, *L. casei* Lc-11, *L. plantarum* Lp-115, *Lactococcus lactis* Ll-23, *Streptococcus thermophilus* St-21 + FOS 63 mg	C	**Maxilac,** 1 capsule Once a day, for 30 days, together with treatment	Improving stool consistency, the frequency of bowel movements and quality of life (FLIP) in children with AD [68]	B3
Lactobacillus acidophilus LA-14, *L. casei* LC-11, *L. paracasei* Lpc-37, *L. plantarum* Lp-115, *L. rhamnosus* HN001, *L. salivarius* Ls-33, *Bifidobacterium lactis* BI-04, *B. bifidum* Bb-02/Lactis, *B. longum* Bi-05 + FOS 500 mg	S	**Maxilac Baby,** 1 sachet Once a day, for 30 days, together with treatment		

Note: LoC — level of credibility; LoE — level of evidence; PhF — pharmaceutical form; CT — chewable tablets; C — capsules; S — sachets; SCORAD — Scoring of Atopic Dermatitis; FLIP — Flow, latch, injury, and post-feed behavior scale; FA — food allergy; AD — atopic dermatitis.

Table 17. Summary data on the use of products and functional foods containing probiotics, prebiotics, synbiotics and metabiotics in the treatment and prevention of gastrointestinal diseases in adults

	AAD	CDI	HP	IBS	FC	ID	DFN	MAFLD	LC	SIBO
Actibio				≥ 125 g twice dailyfor 28–42 d.	≥125 g twice daily for 14 d.		≥125 g twice daily for 28 d.*			
Actimuno	≥ 100 g twice daily together with AB + 7 d.	100 g twice daily together with AB + 7 d.								
Bactimunal							1 C twice daily for 28 d.**	1 C twice daily for 6 weeks		
Bifiform			2 C twice daily for 14 d.	1 C 3 times/day, for 14 d.						
Neobiotic Lactobalance	1 C once daily, for 21 d.			1 C once daily, for 21 d.						
Linex Forte	1 C twice daily, together with AB + 7 d.									
Paleka				1 C once daily, for 30 d.						
Probiolog	1 C twice daily, together with AB + 7 d.									
Probiolog-IBS				1 C once daily, for 42 d.						
Symbiosys Alflorex				1 C once daily, for ≥ 28 d.						
Helinorm			1 C twice daily for 14 d.							
Enterol	1 C 2–4 times/day, together with AB	1 C twice daily, for 28 d.	1 C twice daily for 10–14 d.	1 C twice daily, for 28 d.		1 C 1–2 times/ day, for ≥ 5 d.***			1 C twice daily, for 3 months	1 C twice daily, together with AB or for 3 months
Enterolactis Fibra				1 V once daily, for 28 d.						
Inulin					4 g 3 times/ day for 28 d.					
Lactulose					10–60 mL 1–2 times/day, for 3–12 weeks				15–30 mL twice daily, for ≥ 1 d.	
Oligofructose		4 g 3 times/ day, for 30 d.								

Note: AAD — prevention of antibiotic-associated diarrhea; CDI — prevention of *C. difficile*-associated disease; HP — improvement of outcomes of *H. pylori* eradication; IBS — treatment of irritable bowel syndrome; FC — treatment of functional constipation; ID — prevention of infectious diarrhea; DFN — prevention of gastrointestinal dysfunction; MAFLD — treatment of metabolic-associated fatty liver disease; LC — treatment of liver cirrhosis and its complications; SIBO — improvement of small intestinal bacterial overgrowth eradication outcomes; C — capsules; V — vial; d. — day; * — reducing dyspeptic events in healthy adults, improving the tolerability of plant-fiber-rich foods; ** — decreasing the severity of dyspeptic events after COVID-19; *** — prevention of travelers' diarrhea.

Table 18. Summary data on the use of products and functional foods containing probiotics, prebiotics, and synbiotics in the treatment and prevention of gastrointestinal diseases in children

	AGE	AII	AAD	HP	DFN	ID	FA	BP
Actimuno				100 g twice daily, for 14 d.		100 g 1–2 times/ day, for 28 d.*		
Acipol	1 C 3 times/ day, for 6–10 d.	1 C 3 times/ day, for 6–10 d.	1 C twice daily, for 14 d.	1 C twice daily, for 14 d.				
Bifiform		1 C 4 times/ day, for 12 d.						
Bifiform Kids							2 T twice daily, for 21 d.	
Complinex Baby					6 drops (0.25 g) once daily, for 21 d.**			
Maxilac								1 C once daily, for 30 d.
Maxilac Baby					1 S twice daily, for 28 d.***			1 СП once daily, for 30 d.
Enterol	1 S twice daily, for 5 d.	1 C or 1 S twice daily, for 5–10 d.	1 C twice daily, for the duration of AB therapy	1 S twice daily, for the duration of AB therapy				
Enterolactis Fibra		1 V once daily, for 12 d.						

Note: AGE — treatment of acute gastroenteritis; AII, treatment of acute intestinal infections; AAD — prevention of antibiotic-associated diarrhea; HP — improvement of outcomes of *H. pylori* eradication; DFN — prevention of gastrointestinal dysfunction; ID — prevention of infectious diarrhea; FA — treatment of functional gastrointestinal disorders associated with food allergy; AD — treatment of functional gastrointestinal disorders associated with atopic dermatitis; C — capsules; S — sachets; T — tablet; V — vial; d. — day; * — reducing the risk of diarrhea in healthy children; ** — reducing the duration of crying and increasing the duration of sleep in colic of newborns; *** — reducing the severity of dyspeptic events after COVID-19.

Conclusion

Probiotics, prebiotics, synbiotics and metabiotics are commonly used as medicinal products, dietary supplements, and enriched functional foods for prevention and increasing the treatment efficacy in patients suffering from gastrointestinal diseases. Summary data on the efficacy of products and FFs containing these substances are presented in Tables 17 and 18.

These Methodological Guidelines have been developed to optimize patient management in order to prevent or achieve more rapid regression of symptoms of gastrointestinal diseases in adults and children.

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