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Determination of Probiotics Prescription Indications in Patients with Irritable Bowel Syndrome (Materials of the Expert Council and Literature Review)

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Aim. To review the main indications for probiotics prescription in patients with irritable bowel syndrome and to present the materials of an Expert Council, which was held on 18 March 2022 in Moscow.
Key points. Gut microbiota disturbance is an integral part of irritable bowel syndrome (IBS) pathogenesis. Changes of colonic microbiota composition are associated with its functional potential modification, which leads to an increasing of the pro-inflammatory immune response, as well as to an exacerbation of the disease symptoms and quality of life decreasing in patients with IBS. The novel coronavirus infection (COVID-19) is an independent risk factor for both exacerbation and onset of IBS, which predispose to increase IBS incidence. Correction of gut microbiota composition with probiotics seems to be a promising therapeutic target for IBS treatment optimizing. The optimal probiotic should be effective, safe, strain-specific, and its dose and duration of administration should be confirmed by the results of clinical studies. Some of the probiotics with proven efficacy in IBS are Alflorex® and Enterol®.
Conclusion. Prescription of certain probiotics in IBS is advisable to normalize the frequency and consistency of stools, relieve abdominal pain and bloating, as well as improve patients' quality of life.
Keywords: irritable bowel syndrome, novel coronavirus infection, COVID-19, probiotics, *Bifidobacterium longum* 35624, Alflorex®, *Saccharomyces boulardii* CNCM I-745, Enterol®
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Определение показаний к назначению пробиотиков у пациентов с синдромом раздраженного кишечника (обзор литературы и резолюция Совета экспертов)

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Цель публикации: рассмотреть основные показания к назначению пробиотиков у пациентов с синдромом раздраженного кишечника и представить материалы Совета экспертов, который состоялся 18 марта 2022 г. в Москве.

Основные положения. Нарушение состава кишечной микробиоты — неотъемлемая часть патогенеза синдрома раздраженного кишечника (СРК). Изменение состава толстокишечной микробиоты сопряжено с изменением ее функционального потенциала, что приводит к повышению провоспалительного иммунного ответа, а также к обострению симптомов заболевания и снижению качества жизни пациентов с СРК. Новая коронавирусная инфекция (COVID-19) является независимым фактором риска как обострения, так и дебюта СРК, что создает предпосылки к росту заболеваемости СРК. Коррекция состава кишечной микробиоты с помощью пробиотиков представляется перспективной терапевтической мишенью для оптимизации терапии больных с СРК. Оптимальный пробиотик должен характеризоваться эффективностью, безопасностью, штаммоспецифичностью, а его эффективная доза и продолжительность курса лечения должны подтверждаться результатами клинических исследований. Одними из пробиотиков с доказанной эффективностью при СРК являются Альфлорекс® и Энтерол®.

Вывод. Назначение определенных пробиотиков при СРК целесообразно для нормализации частоты и консистенции стула, купирования абдоминальной боли и вздутия живота, а также улучшения качества жизни больных.

Ключевые слова: синдром раздраженного кишечника, новая коронавирусная инфекция, COVID-19, пробиотики, *Bifidobacterium longum* 35624, Альфлорекс®, *Saccharomyces boulardii* CNCM I-745, Энтерол®

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On March 18, 2022, a meeting of the Expert Council was held in Moscow under the chairmanship of V.T. Ivashkin, Chief Expert in Gastroenterology of the Ministry of Health of Russia, President of the Scientific community for human microbiome research (CHMR), Academician of the Russian Academy of Sciences (RAS). The purpose of the meeting was to discuss the prospects of the use of probiotics in patients with irritable bowel syndrome. Opinion exchange was conducted both in person and remotely (with live broadcast), which allowed involving experts from different subjects of the Russian Federation (Central, Far-Eastern, Privolzhsky, North-Western, Siberian, Ural, and Southern Federal Districts of Russia).

In his welcoming speech, V.T. Ivashkin drew attention to the relevance and key aspects of optimizing the treatment of patients with IBS, i.e. accumulation of evidence about the role of the gut microbiota in the pathogenesis of the disease, growing interest in probiotics in the global clinical practice, understanding of therapeutic targets for probiotic strains and publications of practical guidelines for a reasonable selection of probiotics approved in the Russian Federation.

The agenda of the Expert Council meeting included reports on potential opportunities of the use of probiotic strains in IBS management including in patients who have developed the disease after COVID-19.

The report presented by by RAS Academician, Professor **V.T. Ivashkin and A.I. Ulyanin** (Moscow) discussed the key points of the practical guidelines developed by the CHMR and the Russian Gastroenterology Association (RGA) for the use of probiotics in adult patients with gastrointestinal disorders. Recent interest in the use of probiotics is due to a number of factors such as the search for safe medicinal products, growing interest to natural products and substances, the availability of a substrate for the drug development and potential beneficial properties of probiotic microorganisms [1]. For a long time, the definition of probiotics has remained unchanged: these are living microorganisms that benefit the health of the host body when administered in adequate quantities [2].

In the Russian Federation and the countries of the Eurasian Economic Union probiotics may be authorized as either a dietary supplement (DS) or a medicinal product (MP). Probiotic cultures are usually bacteria, e.g. *Lactobacillus, Bifidobacterium*, *Streptococcus* and *Bacillus*, as well as yeasts *Saccharomyces* [3]. The microorganisms that are components of probiotics are conventionally classified by their genus, species and strain. Knowing a specific probiotic strain is important as it allows predicting the development of the expected clinical response [4]. However, not all probiotics approved in the Russian Federation, regarding of their registration status as a DS or an MP, specify the name of the specific strain in their composition, which does not guarantee the expected clinical effect. Some probiotics are an exception as they contain certain probiotic microorganisms with no information about their strains (with a trade name) that have proven to be effective for the treatment of some disorders in appropriate clinical studies.

The effectiveness of probiotics also depends on the number of colony-forming units (CFUs) in a certain dosage form that provides for the safety and viability of the strains while they advance to the distal regions of the gastrointestinal tract. The authors emphasized that the optimal dose of CFUs should be selected based on the results of clinical studies that demonstrate the achievement of beneficial effects of a particular probiotic strain at the specified dose and dosage form (capsules, powders for preparation of solutions etc.) [5].

According to the guidelines developed by the CHMR and RGA, probiotics can be prescribed to adult patients for the treatment of acute diarrhea, prevention of antibiotic-associated diarrhea (AAD) and *C. difficile*-associated diarrhea; they can be used as a component of eradication therapy for *H. pylori*, and to eliminate the symptoms of IBS and functional constipation [6]. With the exception of the latter, the *CNCM I-745 strain of Saccharomyces boulardii* is indicated for the treatment of all disorders specified above, suggesting its multitarget effect in therapy of some gastrointestinal disorders [7–11].

The probiotic formulations recommended by the CHMR and RGA can produce various clinical effects, e.g. improved quality of life, reduced severity of abdominal pain and flatulence, as well as normalization of bowel movements, which is the main indication for the use of probiotics in such patients.

RAS Academician, Professor I.V. Mayev (Moscow) dedicated his presentation to the approaches to the diagnosis and treatment of IBS described in the international and Russian clinical guidelines. The authors noted that the diagnostic criteria for IBS and treatment strategies have undergone significant changes, ranging from the Manning criteria (1978) to the Rome IV Diagnostic Criteria (2016) [12] as well as clinical guidelines developed by the RGA and the Russian Association of Coloproctology (RAC) (2021) [13]. Improvement of clinical guidelines appears to be

a necessary measure due to the availability of new data on the pathogenesis of the disease, and its high prevalence that clearly tends to increase, especially in developing countries. According to a meta-analysis that included 57 epidemiological studies involving more than 400,000 subjects, the global incidence of IBS in adult population (Rome IV Diagnostic Criteria) is 3.8 % (95 % CI: 3.1–4.5) [14]. However, some studies report higher incidence rates. The results of a global online survey with participation of 73,076 respondents indicate a higher incidence of 4.1 % (according to the Rome IV Diagnostic Criteria). Among 2000 respondents from Russia, the symptoms of IBS were reported by 5.9 % of participants (95 % CI: 4.8–6.9) [15]. The difference in the obtained data is assumed to be related to the epidemiological "iceberg phenomenon", which means that the actual IBS prevalence is significantly higher than the above mentioned [16].

The concept that IBS is the "diagnosis of exception" is still relevant. According to the guidelines developed by the RGA and the RAC, the diagnosis of IBS is made if the patient's complaints meet the Rome IV Diagnostic Criteria, there are no «anxiety symptoms» and there are no signs of laboratory abnormalities or abnormal investigation findings [13].

IBS treatment is associated with a number of difficulties including frequent combinations of functional disorders ("overlap" syndrome), low effectiveness of conventional drug therapy options (high NNT in meta-analyses), as well as low adherence to treatment with psychotropic drugs, which creates the need for a search for new therapeutic options [17]. In addition to dietary and lifestyle modifications, IBS treatment also includes the use of various classes of drug products. These include antispasmodics, loperamide, dioctahedral smectite, rifaximin, laxatives (osmotic, contact ones; those increasing the volume of intestinal contents), prucalopride, trimebutine, a fixed combination of herbal components STW5, a drug containing antibodies to the brain-specific protein S-100 and antibodies to the human tumor necrosis factor alpha, antidepressants, neuroleptics, and probiotics. As was shown in a meta-analysis that included 43 randomized controlled trials (RCTs) (see the clinical guidelines developed by the RGA and RAC), the latter demonstrated superior effectiveness in terms of elimination of IBS symptoms (HR 0.79; 95 % CI: 0.70–0.89) [18] with a high level of evidence (2) and a class of recommendations (A) compared to placebo. Considering the above, probiotic strains were included in the relevant clinical guidelines for the IBS treatment developed by the RGA and the RAC. However, to ensure a higher range of therapeutic options, the list of recommended probiotics should be updated with strains that have a well studied mechanism of action and have proven to be effective.

Dr. Sci. (Med.), I.B. Khlynov (Ekaterinburg) presented a report on an important and relevant issue of IBS course during the COVID-19 pandemic and development in COVID-19 survivors. The COVID-19 pandemic is a factor that reduces the quality of life of patients with IBS. An online survey conducted during the COVID-19 pandemic based on the Hospital Anxiety and Depression Scale (HADS) and the assessment of the severity of functional disorders (IBS and functional dyspepsia) that involved 5,157 participants showed that 12.6 % of respondents with IBS had more severe psychoemotional disorders (7.5 ± 4.8 and 8.7 ± 3.7, respectively) compared to healthy subjects (6.3 ± 4.3 and 8.1 ± 3.9, respectively, $p < 0.001$). At the same time, 31.9 % of patients with IBS reported significant worsening of their condition during the survey [19].

It is noteworthy that patients with IBS and COVID-19 survivors demonstrate similar changes in their gut microbiota, i.e. reduced alpha diversity, increased levels of opportunistic pathogens and decreased levels of beneficial commensal bacteria [20–22].

Gut microbiota disturbances are associated with changes in the cytokine profile of COVID-19 patients as a result of an increased pool of pro-inflammatory cytokines [23]. Gut microbiota disturbances, cytokine shift, anxiety and depression are the main factors that lead to the development of visceral hypersensitivity, and therefore, IBS [24].

New coronavirus infection (COVID-19) produces an ambivalent effect on IBS: on the one hand, there is a decrease in the quality of life (due to increased severity of anxiety and depression) and worsening of current symptoms, and on the other hand, the prerequisites are created for the development of a disease in a healthy subject as a result of increased pro-inflammatory immune response [19]. Among COVID-19 survivors, 31.9 % of patients with IBS start feeling worse, while 5.3 % of previously healthy individuals develop IBS for the first time (among the latter, 60 % of subjects develop diarrhea-predominant IBS, 20 % — constipation-predominant IBS, and 20 % — undifferentiated IBS [25]. Given this trend and the total number of COVID-19 cases in Russia during the pandemic, more than 850,000 new cases of IBS might be expected.

One of the approaches to IBS prevention is the use of probiotics that effectively regulate the immune response [26]. An example is a probiotic drug that contains *Bifidobacterium longum 35624* (*Symbiosis Alflorex®*), which contributes to decreased concentrations of inflammatory markers (C-reactive protein, pro-inflammatory cytokines IL-6 and tumor necrosis factor alpha) and increased levels of IL-10. The observed changes in the cytokine pool are closely associated with reduced severity of clinical manifestations of IBS: abdominal pain, flatulence and changes in bowel habits [26]. The use of this probiotic in patients with IBS is reasonable as this drug affects the immune-mediated mechanisms of the development of symptoms including those in the presence of coronavirus infection. However, the potential of probiotics use in COVID-19 patients needs to be evaluated in further studies.

Possible effects of the use of probiotics on the course of COVID-19 were discussed by **Dr. Sci. (Med.) E.A. Poluektova and Cand. Sci. (Med.) R.V. Maslennikov** (Moscow). In addition to lung involvement, COVID-19 is quite often accompanied by gastrointestinal disorders, and almost 10 % of patients develop viral diarrhea [27]. Frequent use of massive antimicrobial therapy for COVID-19 worsens the course of viral diarrhea due to the development of AAD and *C. difficile* infection [28]. Given the clinical potential of the use of probiotics for elimination of viral diarrhea and the prevention of AAD, it appears crucial to study their effects on the course of COVID-19.

The authors presented the results of their single-center RCT evaluating the course of COVID-19 after the addition of a multi-strain probiotic containing *Lacticaseibacillus rhamnosus PDV 1705*, *Bifidobacterium bifidum PDV 0903*, *Bifidobacterium longum subsp. infantis PDV 1911* and *Bifidobacterium longum subsp. longum PDV 2301* (10^9 CFUs of each strain) into the treatment regimen [29]. The study included 200 patients with a PCR-confirmed diagnosis of COVID-19, who were subsequently randomized into two groups — the main group to receive a probiotic TID for 14 days as adjunctive therapy to the main treatment and the control group to receive standard therapy. In 11.5 % of patients, COVID-19 was accompanied by the development of viral diarrhea; however, in the main group, its duration was significantly lower than in the control group (2 [1–4] versus 4 [3–6]; days $p = 0.049$). 9.1 % of hospitalized patients developed AAD; however, among COVID-19 patients treated with only one antibiotic, the use of a probiotic prevented the development of AAD compared to those patients who did not receive probiotics (0 % versus 12.5 %; $p = 0.023$). Thus, the study demonstrated a potential role of probiotics in elimination of viral diarrhea and AAD in COVID-19 patients.

Professor N.V. Korochanskaya (Krasnodar) elaborated the gut microbiota disturbances in patients with IBS. The most detailed data on the gut microbiota functions were obtained after the end of phase 2 international study called Human Microbiome Project (HMP) [30]. According to current concepts, the gut microbiota is an integral organ with its secretory, digestive and protective functions that are closely related [31]. Colonic microbiota produces both local and systemic effects due to the synthesis of regulatory metabolites and interactions with the human immune system [32]. These effects underlie complex functional interactions between the body systems (including digestive, nervous, genitourinary, respiratory and cardiovascular systems) and the gut microbiota, the stability of which contributes to the maintenance of homeostasis in the whole body [33]. Changes in the bacterial composition of the colon are known to impair the functional axis of the gut–microbiota–brain axis, which results not only in the development of symptomatic IBS but also manifestations of concomitant psychoemotional disorders (anxiety, depression, somatic symptoms) that worsen the patient health and reduce their quality of life [34]. In this regard, the correction of the gut microbiota composition is a potential therapeutic target for the treatment of IBS, which explains the interest to the use of probiotics [6, 31].

The results of a meta-analysis that included 28 randomized controlled clinical trials (RCCTs) involving 3,606 patients demonstrated that the use of probiotics resulted in a significant decrease in the severity of symptoms of IBS; however, this effect was strain-specific [35]. Another important factor (apart from the strain specificity and the doses of a probiotic) is the duration of treatment, which should also be confirmed in clinical studies.

The potential role of probiotics in terms of their effects on the symptoms of IBS and the patients' quality of life was evaluated in a prospective study FLORAVIE that includes 233 patients with various forms of the disease [36]. The IBS severity was assessed using the Irritable Bowel Syndrome Severity Scoring System (IBS-SSS), the responses to the questions of which are converted to points with their subsequent counting. According to the IBS-SSS, the IBS is considered mild if the total score is 75–174, moderate if it is 175–299, and severe if it is 300–500. The quality of life was assessed using the Irritable Bowel Syndrome Quality of Life (IBS-QoL) questionnaire that consists of 34 5-point questions. Total

score is converted to a 0 to 100 % scale, in which the higher the score, the better the quality of life [36].

The analysis of the results of IBS-SSS assessment showed that most patients had moderate to severe disease (48.1 % and 46.4 %, respectively), and the disease severity correlated with low quality of life assessed by IBS-QoL (r = -0.66; $p < 0.0001$). The use of a probiotic strain *Bifidobacterium longum 35624 (Symbiosis Alflorex®)* 10^9 CFU per day for 30 days resulted in reduced severity of IBS symptoms and improved the patients' quality of life. Patients with more severe IBS demonstrated more significant changes; thus, improvement was reported in 9.1 % of patients with mild disease, 28.6 % and 49.1 % of patients with moderate and severe disease, respectively. In the whole study population, the severity of symptoms decreased from 303 ± 81 (severe) to 208 ± 104 (moderate) according to the IBS-SSS ($p < 0.0001$). The quality of life of these patients improved from 60.2 ± 20.5 % to 68.8 ± 20.9 % ($p < 0.0001$), according to the IBS-QoL questionnaire. 68.3 % of all patients reported their satisfaction with treatment, which was well tolerated. The obtained data make it reasonable to include a probiotic to the IBS treatment regimens.

In his presentation, **Professor V.I. Simanenkov** (St. Petersburg) described the potential use of probiotic yeasts in the treatment of IBS. The human microbiota is known to include more than 1,000 bacterial species, and their four predominant phyla are *Firmicutes*, *Bacteroidetes*, *Proteobacteria* and *Actinobacteria* [37]. The fungal community (mycobiome) comprises about 0.1 % of all human microbiota. Their species diversity varies in different individuals, however, the most predominant species are *Candida* and *Saccharomyces,* and the latter are yeast-like fungi [38].

The targeted use of probiotics regardless of bacteria or yeasts in their composition should be based on the differential approach taking into account their properties. Different probiotic strains have different mechanisms of action: synthesis of bacteriocins, elimination of toxins, resistance to adhesion of opportunistic microorganisms, maintenance and restoration of the composition of the gut microbiota, as well as stimulation of a targeted immune response. The most well-studied yeast strain that has several mechanisms of action is *Saccharomyces boulardii CNCM I-745*, which is a component of a probiotic drug called Enterol®.

The key biological properties of this strain have been studied for almost 100 years since its discovery. These include [39]:

- rapid achievement of a high concentration in the colon with the impossibility of prolonged colonization;
- stability in the conditions of the highly aggressive environment of the upper gastrointestinal tract (including resistance to a wide range of pH, temperature, bile salts and digestive enzymes);
- resistance to antibiotics;
- virtually absolute impossibility to exchange resistance genes with bacteria;
- improvement of digestion due to the synthesis of digestive enzymes, as well as by the secretion of polyamines (e.g., spermin and spermidine), increasing the expression of intestinal enzymes and transporters of nutrient absorption [40];
- suppression of adhesion of opportunistic bacteria and elimination of their toxins;
- reduced severity of a local anti-inflammatory immune response [41];
- maintenance of the epithelial barrier integrity [42];
- elimination of secretory diarrhea due to inhibition of cAMP-dependent chloride secretion;
- indirect inhibition of pain and stress perception by stimulating the synthesis of indole-3-acetic acid by the commensal intestinal microbiota [43].

The clinical effectiveness of this strain in patients with IBS was clearly demonstrated in a meta-analysis of well-designed clinical studies (42 RCTs involving 3,856 patients). Treatment with a probiotic drug containing *Saccharomyces boulardii CNCM I-745* (95 % CI: 1.1–2.1; p = 0.009) resulted in significantly less severe abdominal pain (high level of evidence — 1) [44].

The author emphasized that this strain also has proven to be effective for the treatment of acute diarrhea, as well as prevention of AAD and a *C. difficile* infection. These effects are described in the practical guidelines developed by the CHMR and RGA as well as in the international clinical guidelines [6, 31].

In this closing speech, the Chairman of the Expert Council, Academician of the Russian Academy of Sciences V.T. Ivashkin pointed out the relevance of the data presented and the productivity of the discussion. After the discussion of the described report, the following resolution was adopted.

Expert Council Resolution

1. Changes in the composition and function of the gut microbiota are an integral part of the IBS pathogenesis. The use of probiotics that have proven to be effective and meet the modern requirements is a reasonable improvement of treatment strategy.

2. The clinical effectiveness of probiotics in patients with IBS should be ensured based on the specificity of strains included in their composition, proper number of microbial CFUs, optimal dosage form for their delivery to the colon, proper doses, and verified in adequate clinical studies.

3. Certain probiotic strains (including *Bifidobacterium longum 35624 and Saccharomyces boulardii CNCM I-745)* have proven to be effective in terms of normalization of bowel habits and stool consistency.

4. In addition to their antidiarrheal effects, the probiotic strains *Bifidobacterium longum 35624 and Saccharomyces boulardii CNCM I-745* have been shown to eliminate abdominal pain, flatulence and improve the quality of life of patients with IBS.

5. The probiotic formulation that includes *Lacticaseibacillus rhamnosus PDV 1705*, *Bifidobacterium bifidum PDV 0903*, *Bifidobacterium longum subsp. infantis PDV 1911* and *Bifidobacterium longum subsp. longum PDV 2301,* is effective not only in terms of elimination of abdominal pain, normalization of bowel habits and stool consistency, but also for the prevention of viral, *C. difficile*-associated and antibiotic-associated diarrhea in COVID-19 patients, which may allow reducing the risk of the IBS development in COVID-19 survivors.

6. The optimal duration of probiotic treatment in patients with IBS is at least 4 weeks, however, this period can be extended on an individual basis if it is necessary.

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