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Modern Approaches to the Diagnosis and Treatment of *Clostridioides difficile (C. difficile)*-associated Disease in Adults (literature Review and Expert Council Resolution)

Vladimir T. Ivashkin[1], Igor V. Maev[2], Dmitry N. Andreev[2], Oleg V. Goloshchapov[3], Aleksandr A. Derinov[1], Oksana Yu. Zolnikova[1], Konstantin V. Ivashkin[1], Olga Yu. Kiseleva[1], Andrey P. Kiryukhin[1], Olga S. Lyashenko[1,*], Elena A. Poluektova[1], Aleksandr S. Tertychnyy[1], Aleksander. S. Trukhmanov[1], Anatoly I. Ulyanin[1], Arkadiy A. Sheptulin[1], Oleg S. Shifrin[1]

[1] *I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation*
[2] *A.I. Yevdokimov Moscow State University of Medicine and Dentistry, Moscow, Russian Federation*
[3] *I.P. Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russian Federation*

Aim: to review the modern approaches to the diagnosis and treatment of *C. difficile*-associated disease in adults and present the resolution of the Expert Council held on March 25, 2023 in Moscow.
General provisions. *C. difficile* is the most important nosocomial pathogen which spores are also commonly found in the environment. Microbiota impairment, primarily due to the use of antibacterial drugs, is a key stage in the development of *C. difficile*-associated disease. A search for an infection should be carried out only in patients with diarrhea, and it is advisable to use at least 2 laboratory methods. The drug of choice for first-line treatment is vancomycin. If drug treatment is ineffective or the patient has recurrent clostridial infection, fecal microbiota transplantation should be considered. The probiotic strain *Saccharomyces boulardii CNCM I-745* has a direct inhibitory effect on *C. difficile* toxin A, promotes normalization of the intestinal microbiota composition, and decreases the inflammatory reaction in colonic mucosa colonized with a toxigenic strain of *C. difficile*.
Conclusions. Addition of the probiotic strain *Saccharomyces boulardii CNCM I-745* to antibacterial therapy promotes both primary and secondary prevention of *C. difficile*-associated disease.
Keywords: intestinal microbiota, antibiotics, diarrhea, *C. difficile*, pseudomembranous colitis, video colonoscopy, fecal transplantation, probiotics, *Saccharomyces boulardii CNCM I-745*
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Современные подходы к диагностике и лечению *Clostridioides difficile (C. difficile)*-ассоциированной болезни у взрослых (Обзор литературы и резолюция Экспертного совета)

В.Т. Ивашкин[1], И.В. Маев[2], Д.Н. Андреев[2], О.В. Голощапов[3], А.А. Деринов[1], О.Ю. Зольникова[1], К.В. Ивашкин[1], О.Ю. Киселёва[1], А.П. Кирюхин[1], О.С. Ляшенко[1,*], Е.А. Полуэктова[1], А.С. Тертычный[1], А.С. Трухманов[1], А.И. Ульянин[1], А.А. Шептулин[1], О.С. Шифрин[1]

[1] *ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» (Сеченовский Университет) Министерства здравоохранения Российской Федерации», Москва, Российская Федерация*

[2] *ФГБОУ ВО «Московский государственный медико-стоматологический университет им. А.И. Евдокимова» Министерства здравоохранения Российской Федерации, Москва, Российская Федерация*

[3] *ФГБОУ ВО «Первый Санкт-Петербургский государственный медицинский университет им. академика И.П. Павлова», Санкт-Петербург, Российская Федерация*

Цель публикации. Рассмотреть современные подходы к диагностике и лечению *C. difficile*-ассоциированной болезни у взрослых и представить материалы Экспертного совета, который состоялся 25 марта 2023 г. в Москве.

Основные положения. *C. difficile* является наиболее значимой нозокомиальной инфекцией, споры которой также широко представлены в окружающей среде. Нарушение состава микробиоты, в первую очередь при приеме антибактериальных препаратов, является ключевым этапом в развитии *C. difficile*-ассоциированной болезни. Диагностика инфекции должна проводиться только у пациентов с диареей, при этом целесообразно использовать не менее двух лабораторных методов. Препаратом выбора для первой линии лечения служит ванкомицин. В случае неэффективности консервативного лечения, а также у пациентов с рецидивирующей клостридиальной инфекцией целесообразно рассмотреть вопрос о проведении трансплантации фекальной микробиоты. Пробиотический штамм *Saccharomyces boulardii CNCM I-745* оказывает прямое ингибирующее действие на токсин А *C. difficile*, способствует нормализации состава кишечной микробиоты, а также уменьшению воспалительной реакции в слизистой оболочке толстой кишки при колонизации токсигенным штаммом *C. difficile*.

Выводы. Добавление пробиотического штамма *Saccharomyces boulardii CNCM I-745* на фоне антибактериальной терапии способствует как первичной, так и вторичной профилактике *C. difficile*-ассоциированной болезни.

Ключевые слова: кишечная микробиота, антибиотики, диарея, *C. difficile*, псевдомембранозный колит, видеоколоноскопия, фекальная трансплантация, пробиотики, *Saccharomyces boulardii CNCM I-745*

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A meeting of the Expert Council discussing modern approaches to the diagnosis and treatment of *Clostridioides difficile (C. difficile)*-associated disease in adults was held in Moscow on March 25, 2023 under the chairmanship of Professor V.T. Ivashkin, Academician of the Russian Academy of Sciences (RAS). The experts were present at the Council in person or participated remotely via live broadcast from various regions of the Russian Federation (Central, Siberian, Volga, Far Eastern, Southern, North-Western and Ural Federal Districts of the Russian Federation).

In his opening remarks, RAS Academician V.T. Ivashkin highlighted the high significance of clostridial infection for clinicians, including timely diagnosis of the disease, appropriate patient management and rational use of antibacterial therapy, which was especially important during the COVID-19 pandemic.

Reports made at the Expert Council on the main items of the agenda were focused on the current views on the risk factors, pathogenesis, methods of diagnosis, treatment and prevention of *C. difficile*-associated disease.

At the beginning of the meeting, **RAS Academician Professor V.T. Ivashkin, Professor E.A. Poluektova and A.I. Ulyanin** presented a clinical task that clearly demonstrated the difficulties of preventing recurrent C. difficile infection and the need to optimize measures to prevent it.

It was a case report of a 72-year-old female patient. She had a history of repeated antibacterial therapy over the preceding 2 years. The last hospitalization that involved antibacterial therapy, 3 months previously, was complicated by the development of a mild C. difficile infection that was successfully treated with fidaxomicin. Physical examination: body temperature 38.4 °C; no significant respiratory, cardiovascular or gastrointestinal abnormalities. Blood tests revealed neutrophilic leukocytosis and a moderately elevated creatinine level; a urinalysis demonstrated leukocyturia and bacteriuria; results of a urine culture test are pending. Based on the task conditions, it was decided to start intravenous ceftriaxone for the treatment of the urinary tract infection. Discussion was focused on whether prevention with vancomycin was needed to reduce the risk of recurrent clostridial infection [1].

On the one hand, the patient had risk factors for recurrent clostridial infection (female sex, age over 65 years, chronic kidney disease, hospitalization and antibiotic therapy in the preceding 3 months, a previous episode of *C. difficile*-associated disease) [1, 2]. The risk of recurrence is

known to be as high as 65 % after each episode [3, 4]. According to foreign clinical guidelines, vancomycin prevention is needed in patients with a history of clostridial infection and a high risk of recurrence if systemic antibiotic therapy is necessary [5]. A significant reduction in the risk of clostridial infection achieved with the addition of a prophylactic dose of vancomycin to the main course of antibacterial therapy was demonstrated both by results of clinical studies [6, 7] and a meta-analysis of 8 retrospective studies and one prospective study (2174 patients) (HR = 0.263; 95 % CI 0.13–0.52) [8]. Efficacy was higher when vancomycin was used for ≥ 50 % of the antibiotic therapy time (HR = 0.41; 95 % CI 0.27–0.63; P < 0.0001) [7]. However, differences in the designs of the analyzed studies do not allow an unambiguous interpretation of the obtained results, and there is no consensus on the dose and duration of use of vancomycin.

On the other hand, the adverse effect of antibiotics on the intestinal microbiome should be borne in mind, as recovery after a course of treatment takes up to 6 months, and there is a risk of irretrievable loss of normal microbiota and decreased colonization resistance [9]. Resistance to *C. difficile* colonization is due to the diversity of microbial communities, and *Bacteroidetes* and *Firmicutes* organisms make a significant contribution to the development of this resistance [10]. In *C. difficile*-associated disease, intestinal microbiota contains fewer representatives of the *Firmicutes*, *Bacteroidetes* and *Actinobacteria* phyla [11]. Experiments on mice revealed that in the long term, vancomycin treatment (including low doses) promotes the development of *C. difficile*-associated disease due to changes in *Bacteroidetes* and *Firmicutes* levels, also leading to the accumulation of a pool of vancomycin-resistant enterococci [12]. It can be assumed that the discussed patient could be expected to develop an intestinal microbiota imbalance due to both ceftriaxone (for the treatment of the underlying disease) and vancomycin (for the empirical prevention of *C. difficile* infection) and has an increased risk of *C. difficile*-associated disease both in the short and long term.

Professor E.A. Poluektova dedicated her report to a modern view of the pathogenesis of *C. difficile*-associated disease.

C. difficile spores are widespread in the environment thanks to the multi-layer protective membrane that helps the microorganism survive in unfavorable conditions for up to 6 months [13]. It is found on many objects in the environment, as well as foods [14–16]. However, there are currently no confirmed cases of food-borne infection. Sources of toxigenic strains include domestic (dogs and cats) and farm animals, as well as patients discharged from hospital after treatment for *C. difficile* infection [14, 17, 18]. Generally, the risk of *C. difficile* infection in healthy adults is about 15 % for non-toxigenic strains and about 10 % for toxigenic strains. About 15 % of hospitalized patients are infected with toxigenic strains [19].

The infection is transmitted by the fecal-oral route. Along with symptomatic disease, transient detection of toxigenic strains without clinical manifestations or persistent colonization are also possible. Clinical symptoms occur when the *C. difficile* cell density is more than 108 colony-forming units per mL (CFU/mL). Clinical manifestations are due to the production by a toxigenic strain of toxin A (TcdA), toxin B (TcdB) and binary toxin (CDTa), which impair permeability at the level of epithelial cells and intercellular contacts, thus leading to the production of cytokines and chemokines, involvement of macrophages and neutrophils, and destruction of the epithelial layer with the formation of pseudomembranes [14, 20]. The type of infection depends on the composition of the intestinal microbiota, the composition of the metabolome, and the strength of the adaptive immune response.

Spore maturation to the vegetative form occurs in the distal part of the small intestine due to the combined action of primary bile acid salts (taurocholate, glycocholate) and glycine. Secondary bile acids, in particular deoxycholic acid, inhibit this process. Enzymes produced only by the intestinal microbiota play an important role in the biotransformation of bile acids. Under the influence of bile acid hydrolases synthesized by *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, primary bile acid salts are converted back to primary bile acids. *Clostridium clusters* XIVa and XI produce the enzyme 7a-dehydroxylase converting primary bile acids into secondary ones. Therefore, microbiota imbalance increases the risk of clostridial infection [21].

In the large intestine, vegetative forms of C.difficile are found in the outer layer of mucus covering the epithelial cells, where they multiply and change the microbial composition [22]. Patients with *C. difficile*-associated disease have a reduced diversity of intestinal microbiota and decreased numbers of 7-alpha-dehydroxylase and

short-chain bile acid producers. In asymptomatic carriers, such changes are less pronounced. It is assumed that a microbiota with a lower level of Proteobacteria and higher levels of *Firmicutes*, *Bacteroidetes*, as well as *Lachnospiracae* and *Clostridium scindens*, inhibits growth of *C. difficile*, which is related to the production of short-chain fatty acids [14]. Acetate helps increase the expression of antimicrobial peptides and reduce the effect of C. difficile toxin A on colonocytes due to activation of innate immune system cells. Butyrate increases the expression of proteins that form tight contacts (claudin-1, occludin), and also stabilizes the enzyme hypoxia-inducible factor (HIF-1), which helps preserve the function of epithelial cells in inflammation. Valerate inhibits the conversion of spores into vegetative cells and can reduce the number of *C. difficile* CFUs by 95 %. At the same time, an increase in the content of succinate produced by *Bacteroidetes thetaiotaomicron*, which is associated with antibiotic therapy, induces an increase in *C. difficile* CFUs [23].

An abnormal pool of follicular T helper cells in the mesenteric lymph nodes contributes to an abnormal development of humoral immunity. Decreased production of memory B cells responsible for a rapid immune response and production of immunoglobulins upon repeated administration of the same agent, as well as possible immunodeficiency related to the content of IgA, IgM, IgG, increases the probability of recurrent clostridial infection [24].

A joint report by **O.S. Lyashenko** and **A.P. Kiryukhin** was dedicated to methods of diagnosis of *C. difficile*-associated disease.

According to the report, the main diagnostic criteria are the typical clinical manifestations, medical history data, and results of laboratory fecal tests. The key points in assessing the medical history are the exclusion of other causes of diarrhea (the main clinical symptom) and the identification of risk factors of the development or recurrence of infection (most importantly, antibiotic therapy) [25, 26].

In order to prevent overdiagnosis and unjustified treatment, stool samples should be used in laboratory diagnosis only in persons with new-onset diarrhea of unknown etiology within 24 hours [5, 26–28]. Molecular genetic (based on the polymerase chain reaction) and serological (based on enzyme-linked immunosorbent assay and immunochemical analysis) laboratory methods are used in daily practice. None of them can be used as the only diagnostic tool due to differences in the determined markers of infection (toxins, the enzyme glutamate dehydrogenase or toxin-encoding genes) and, accordingly, sensitivity and specificity. The main purpose of the laboratory study is to differentiate active infection from colonization in order to decide whether treatment is required. In this regard, it is recommended to use at least 2 methods [5, 25–29].

Complete blood count and blood chemistry tests are performed to assess the severity of the clostridial infection episode [5, 26, 28]. Abdominal imaging methods (ultrasound, plain abdominal X-ray, MSCT with intravenous and oral contrast enhancement) are supplementary and allow timely detection of complications [25–27].

Video colonoscopy with biopsy is also not the main diagnostic method. It was noted that the endoscopic findings do not always correlate with the clinical picture, especially in refractory, recurrent disease. The “classic” variant of pseudomembranous colitis (PMC) includes the presence of pseudomembranes (multiple, of different colors from cream to yellowish, movable, with hyperemic, edematous underlying mucous membrane). Ulcers, if present, are usually linear and superficial. The formation of pseudomembranes is associated not only with toxigenic *C. difficile*, but also with *Salmonella enterica*, *Esherichia coli O157:H7*, *Campylobacter*, cytomegalovirus, as well as the presence of ischemic colitis, but no endoscopic classification has yet been developed [27, 30–32].

The “non-classic” variant is characterized by focal hyperemia, mucosal edema, erosions with a perifocal halo of hyperemia, which is also observed when the exacerbation of the disease improves.

In a combination of *C. difficile* infection and inflammatory bowel disease (IBD) or diversion colitis, the endoscopic picture of the main disease comes to the fore, posing a particularly difficult diagnostic challenge. In this case, possible signs of infection include the presence of viscous, non-specific yellowish mucus on the walls of the intestine and, in the case of diversion colitis, the “frost sign” in the mucous membrane and the absence of a capillary pattern.

In general, video colonoscopy with biopsy is indicated when clostridial infection is highly probable or the patient with diarrhea has negative laboratory tests. This eliminates other causes of diarrhea, but many experts believe that a

video proctosigmoidoscopy will be sufficient to make a diagnosis [5].

Professor A.S. Tertychnyy discussed in detail the morphological diagnosis of *C. difficile* infection and pseudomembranous colitis.

The main macroscopic manifestation of PMC is the formation of focal or diffuse deposits of fibrinous exudate with a diameter of several millimeters to 1–2 cm on the surface of the mucous membrane. Lesions are mainly found in the distal part of the colon, but one third of patients have them only in the proximal part of the colon. The small intestine can also be involved in the pathological process. As the disease progresses, deposits merge and completely cover the surface of the mucosa, which becomes necrotic and ulcerated when the exudate is discharged; in such cases, a differential diagnosis with ischemic colitis becomes difficult [33].

According to opinion of a number of authors, a diagnosis of PMC can be reliably made by morphological examination of biopsies, not even requiring confirmation by a history of antibiotic therapy and/or detection of *C. difficile* and its toxins [34]. This is true for stage 2 PMC, but not always for stages 1 and 3. Three histological types of PMC lesions are distinguished; one can follow another, which, however, does not always mean more severe clinical manifestations of the disease [35].

Type 1 is small surface erosions between two adjacent crypts. Accumulations of nuclear dust, white blood cells and mucus are usually observed on the surface. Edema, dilated capillaries, and small accumulations of white blood cells are observed in the lamina propria, right in the erosion area. Some crypts may contain white blood cells and subepithelial accumulations of eosinophilic masses. Intact cells of the integumentary epithelium often begin to form clusters protruding above the surface and appearing like budding outgrowths of irregular shape. Such minimal changes may be the first evidence of PMC, but incorrect interpretation of them leads to a diagnosis of PMC in the presence of adenomas and even changes in the urinary bladder. In the differential diagnosis with IBD, attention should be paid to regenerative rearrangement of the crypts and a high density of inflammatory infiltrate, which is not typical for PMC.

Type 2 is the classic morphological manifestation of PMC consistent with endoscopic findings. The mucosa between deposits remains virtually unchanged. Groups (usually 2–3) of abnormal crypts are observed, each consisting of 2–6 crypts in an individual biopsy. Crypts have a markedly dilated lumen, desquamated epithelium in the upper parts and exudate on the surface that blocks the mouth of the crypt. The exudate contains fibrin, mucus and white blood cells [36]. In some cases, small clots and leukostasis in the capillaries can be seen. In the differential diagnosis with ischemic colitis, attention should be paid to the absence of such changes in intact mucosa. Changes in the crypts do not extend beyond the basement membrane.

In stage 3, necrosis of the mucosa occurs and deposits observed on endoscopy can cover almost its entire surface. In case of total necrosis and mucosal ulceration, biopsy data may be uninformative, since any severe process may be associated with such changes. Shadows of crypts with shapes characteristic of PMC can sometimes be seen in necrotic mucosa. Crypts of similar shapes can be observed in ischemic colitis, which is also characterized by hyalinosis of the lamina propria, atrophic crypts, and hemorrhages. Necrosis due to ischemic colitis takes over the entire crypt. Numerous small clots not clearly connected to areas of ulceration are highly likely to be due to ischemic colitis. At the same time, microclots can be observed in PMC due to the effect of the exotoxin. This also explains the possible similarity between PMC and ischemic colitis, as well as the fact that PMC was long considered a variant of ischemic colitis.

Professor O.S. Shifrin discussed the clinical manifestations of *C. difficile*-associated disease.

Assessing the severity of clinical symptoms in patients with clostridial infection is of paramount importance in real-world clinical practice. In the presence of typical clinical manifestations and known causes of the disease, treatment can be started before obtaining laboratory test results, and sometimes despite them [11, 27, 28].

Asymptomatic carriers have no diarrhea, but carry a toxigenic strain of *C. difficile*; they are common in the population (up to 3 % of the healthy population) and very common among inpatients (up to 30 %), especially those with long hospital stays (up to 50 %) [28]. Such carriers do not require treatment, but screening for this infection is advisable for inpatients in transplant departments or patients with severe comorbidities. This approach may decrease the need for antibacterial therapy to prevent *C. difficile*-associated disease [5].

Mild *C. difficile*-associated disease is characterized by diarrhea (not more than

3 semi-formed stools a day). In moderate disease, diarrhea is more severe (Bristol scale type 6–7 loose stools at least 3 times a day) and other clinical symptoms are present, including abdominal pain and moderate fever. Nausea, decreased appetite, and moderate tenderness on abdominal palpation may also occur. In severe disease, severe diarrhea with numerous stools is combined with hectic fever. Other clinical signs include abdominal pain, general weakness, nausea, dry mucous membranes, decreased skin turgor. Complicated disease with organ failure can be life-threatening. Patients develop hypotension, respiratory failure, renal failure, and sometimes shock. Toxic dilatation of the colon is also typical. Patients should stay in an intensive care unit [25, 27, 28, 37, 38].

Clostridial infection often complicates IBD. Such cases are difficult to diagnose due to similar clinical manifestations of the diseases.

Recurrent clostridial infection is common because of possible spore formation. The recurrence rate is 10–35 % after the first attack and 40–65 % after the first recurrent episode [3, 4, 28]. Not every clinical situation associated with diarrhea in infected patients can be explained by *C. difficile*-associated disease; some may be related to another, pre-existing disease causing similar symptoms (irritable bowel syndrome, celiac disease, microscopic colitis, etc.). In such cases, the efficacy of treatment for clostridial infection should be evaluated, the patient's medical history thoroughly studied, and the course of the disease monitored without the use of etiological therapy.

It is also important to distinguish community-acquired and nosocomial *C. difficile*-associated disease. If the disease occurs in the hospital 4 days after the patient's hospitalization or within the first 4 weeks after discharge from the hospital, this is nosocomial infection, which may require special additional organizational measures to prevent it [25, 28].

O.Yu. Kiseleva presented a case report.

Patient F., male, had an examination within his monitoring program (esophagogastroscopy, colonoscopy), which revealed antral superficial gastritis associated with *H. pylori*, in late October 2022. Eradication treatment with amoxicillin and clarithromycin was complicated by the development of diarrhea (up to 7 stools daily) on day 3 of treatment. After discontinuation of the antibiotics, the frequency of bowel movements decreased, but the stool volume did not. General weakness increased, and the patient had low-grade fever. An additional examination revealed *C. difficile* toxins A and B in the stool, and the patient was admitted to a hospital, where his condition continued to deteriorate despite the use of vancomycin at a dose of up to 2 g per day and fidaxomicin, as well as fecal transplantation. The disease progressed with the development of grade 3 dehydration, systemic inflammatory response syndrome, protein-energy malnutrition, heart failure, polyserositis (hydrothorax, ascites, peripheral edema), acute liver failure, deep vein thrombosis in the lower extremities, which required intensive care and additional antibacterial and anticoagulant therapy.

Taking into account the rapid development of pseudomembranous colitis revealed by incomplete colonoscopy, a physician council decided to perform an ileostomy in order to reduce the mechanical load on the intestine and decrease the risk of perforation of the hollow organ, after which the patient received triple antibacterial therapy (two antibacterials and an antifungal), targeted delivery of vancomycin into the colon, treatment for albumin and electrolyte abnormalities, and a special diet. A stable improvement was achieved with the treatment, including improvement of the edema and abdominal distension, normalization of stools, and better laboratory test results.

After discharge, however, the patient still had severe general weakness, shortness of breath with minimal physical activity, pieces of undigested food discharged from the stoma, and a pronounced weight loss. In January 2023, he visited the Vasilenko Clinic of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology for a consultation and was hospitalized. The severity of the patient's condition was due to a severe intestinal bacterial overgrowth syndrome, malnutrition, malabsorption, water and electrolyte disorders, vitamin deficiency, and hypoxemia symptoms. Nutritional support, infusions, treatment with B vitamins, enzyme therapy, anticoagulant therapy, anti-inflammatory therapy with mesalazine, and dioctahedral smectite were used. Oral vancomycin (2 g/day) was added after toxin A, toxin B, and binary toxin of C. difficile were revealed in two tests of ileostomy discharge.

During this treatment, the patient's condition significantly improved. Two fecal samples were negative for C. dificille toxins. On February 09, 2023, a reconstructive surgery was performed to

close the ileostomy and form a side-to-side ileoileal anastomosis.

This case report clearly demonstrates the severity of *C. difficile*-associated disease and once again emphasizes the importance of rational antibacterial therapy, especially in the elderly.

RAS Academician Professor I.V. Maev and **D.N. Andreev** focused on the modern treatment of *C. difficile* infection: according to the most recent draft clinical guidelines for *C. difficile*-associated disease, the main objectives of treatment are clinical improvement, normal laboratory test results and abdominal imaging findings (if they were abnormal), endoscopic improvement (in PMC), and prevention of recurrence [39]. Generally, patients need to discontinue their antibacterial therapy (a risk factor) in order to improve clinical response and reduce the risk of recurrence [25, 28]. Mild-to-moderate *C. difficile*-associated disease in patients with the first attack should be treated with vancomycin at the standard dose for 10 days or metronidazole for 10-14 days. The latter should be administered if vancomycin cannot be used as a first-line treatment [5, 27, 28, 38]. A number of studies have shown the superiority of vancomycin over metronidazole [40, 41]. Vancomycin is also indicated for patients with the first episode of severe *C. difficile*-associated disease as a first-line treatment, whereas parenteral metronidazole should be considered as an alternative [25, 27, 28, 39]. Patients with the first recurrence of clostridial infection should be treated with vancomycin taper or pulse (125 mg four times daily for the first 10–14 days, then 125 mg twice daily for 7 days, then 125 mg once daily for 7 days, followed by 125 mg every 2 or 3 days for 2–8 weeks) if a standard course of vancomycin or metronidazole was used to treat the first episode [25, 28, 38, 39].

Data on the efficacy of fecal microbiota transplantation (FMT) were also presented. FMT is significantly more effective than drug therapy in the treatment of recurrent clostridial infection (HR 2.41; 95 % CI 1.20–4.83); however, the efficacies of FMT and drug therapy do not significantly differ in the treatment of a first episode (HR 1.0; 95 % CI 0.72–1.39) [3]. A meta-analysis of 23 RCTs (1357 patients) also demonstrated high efficacy rates of FMT in patients with recurrent clostridial infection: 93 % with repeated FMTs and 78.7 % with a single FMT ($p < 0.001$) [42]. According to a meta-analysis of 61 studies (5099 patients), the frequency of serious adverse events associated with FMT is less than 1 % [43].

It was stated that complicated disease, in which drug therapy is ineffective, requires a consultation with a surgeon to discuss the treatment plan [25, 28].

Professor A.S. Trukhmanov spoke about the role of probiotics in *C. difficile* infection.

The author emphasized that patients with *C. difficile* infection have an abnormal intestinal microbiota, especially in the presence of clinical symptoms, and it depends on the produced C. diffiicile toxin [46]. Antibacterial therapy plays an important role in microbiota imbalance, which emphasizes the importance of rational antibiotic therapy and the use of probiotics to reduce the risk of clostridial infection [47].

The efficacy of probiotics in the primary prevention of *C. difficile* infection has been shown in a number of clinical studies and meta-analyses. A meta-analysis of 31 RCTs (8762 patients) demonstrated the efficacy of the probiotic strains of *Saccharomyces boulardii* and *Lactobacillus acidiphilus* + *Lactobacillus casei* [48]. According to a meta-analysis and systematic review of 26 RCTs (7957 patients), the probiotic strains of *Lactobacillus*, Saccharomyces and a mixture of probiotic strains used with antibacterial therapy, especially in hospitalized patients, reduce the risk of *C. difficile* infection by 65 % [49]. A meta-analysis of 19 RCTs (6261 patients) showed a reduction in the incidence of clostridial infection by more than 50 % with *Saccharomyces boulardii, Lactobacillus* spp., *Bifidobacterium* spp., and *Streptococcus* spp. used simultaneously with antibiotics (the strain was not specified). The efficacy was higher when the probiotic was used around the first antibiotic dose [50].

A systematic review and meta-analysis of 11 RCTs (972 patients) showed that the prebiotic oligofructose, a probiotic strain of *Saccharomyces boulardii*, and a non-toxigenic strain of *C. difficile* (M3) were effective in preventing recurrent clostridial infection [51].

Saccharomyces boulardii was initially isolated from lychee and mangosteen fruit peel; it has versatile therapeutic properties and is not found in the normal intestinal microbiota. The probiotic strain *Saccharomyces boulardii CNCM I-745* is the first discovered yeast

probiotic, the first to be used in medicine. A number of studies have demonstrated its stability in a wide pH range, resistance to bile acid salts and gastrointestinal enzymes, as well as resistance to antibacterial drugs [52]. *Saccharomyces boulardii CNCM I-745* reduces adhesion to epithelial cells of toxin A due to the production of a protease that inactivates the receptor, and also stimulates the production of antibodies against toxin A and prevents the formation of *C. difficile* biofilm (in vitro). In addition, this probiotic helps normalize the composition of the intestinal microbiota, increase the production of SCFAs and the production of secondary bile acids that inhibit the growth of vegetative forms of *C. difficile*.[53, 54, 55, 56]. *Saccharomyces boulardii CNCM I-745* also significantly reduces cecum damage and histological scores (epithelial tissue damage, mucosal congestion and edema, neutrophil infiltration) in *C. difficile* infection (ribotypes 017, 027, 078). This is associated with a decrease in the expression of TNF-alpha, nuclear factor kappa-B. This probiotic strain can prevent disruption of the intracellular actin network caused by toxins A and B of *C. difficile* [57].

Studies have shown that *Saccharomyces boulardii CNCM I-745* is effective in the primary prevention of clostridial infection. There is strong evidence of its efficacy in the prevention of antibiotic-associated diarrhea in adults and children [44]. This probiotic strain is approved in the Russian Federation as a medicinal product (according to the State Register of Medicinal Products) and is recommended for the prevention of antibiotic-associated diarrhea and *C. difficile*-associated disease [58].

Based on the results of a systematic review and meta-analysis of 2 RCTs (92 patients), *Saccharomyces boulardii CNCM I-745* 250 mg 2 times daily for 4 weeks or during antibiotic therapy significantly reduces the risk of clostridial infection in patients with a history of clostridial infection who require systemic antibiotic therapy (OR 0.26; 95 % CI 0.11–0.63; $p = 0.003$) [45].

The above facts were analyzed and served as the basis for the inclusion of *Saccharomyces boulardii CNCM I-745* in the clinical guidelines of the Scientific Society for the Clinical Study of the Human Microbiome and the Russian Gastroenterology Association titled "*Clostridioides difficile* (C.difficile)-associated disease" as an agent for the primary and secondary prevention of clostridial infection.

O.V. Goloshchapov spoke about the role of fecal transplantation in the treatment of clostridial infection, the main techniques of the procedure and their comparison. This report was prepared by a research group consisting of O.V. Goloshchapov, O.B. Shchukin, A.V. Ishchenko.

Fecal microbiota transplantation (FMT) has been commonly used abroad in clinical practice for the treatment of *C. difficile* infection. Currently, studies on the use of FMT in other areas of medicine are being conducted. At the Pavlov University in Saint Petersburg, about 100 FMT procedures have been performed in immunocompromised patients after hematopoietic stem cell transplantation associated with intestinal graft versus host disease (IGVHD) and patients with IBD associated with C.difficile infection.

The efficacy of FMT depends on the donor's characteristics, which include the quantity and type of the graft (native/frozen), storage time, fecal transplant (FT) delivery route, transplant volume, as well as patient factors (the underlying disease, the degree of dysbiosis, the need to prepare the GI tract, the state of the recipient's immune system, the frequency of adverse events after FMT).

An evaluation of potential candidates for FT donation shows that only 28 % of volunteers successfully pass the final screening. Practically, material from allogenic donors is more cost-effective than material from related donors.

In their own study, the authors mostly used frozen transplants (74 %) after storage for 2 to 140 days at -80 °C. In 86 % of cases, capsules with frozen fecal microbiota were chosen. 73 % of patients received outpatient treatment. According to multicenter studies, the efficacy of FMT in delivering FT through the working channel of the colonoscope and transplantation via capsules is higher than that of enemas and a nasogastric (nasointestinal) tube. In addition, the efficacy of FMT depends not so much on the volume and dose of the FT, but more on the possibility of repeating the procedure [59]. The changes over time in the content of the main microbial groups should be monitored to confirm the microbiological efficacy of FMT, either with 16S sequencing or using PCR [60].

In total, 2092 patients with suspected *C. difficile* infection were evaluated at the Pavlov University from 2015 to 2021; of these,

35 % had their diagnosis confirmed. The first FMT at the University was performed on September 09, 2015 in a 10-year-old girl with IGVHD and *C. difficile* infection.

Foreign colleagues recommend to use FMT for refractory clostridial infection as an alternative to surgical treatment [5] and/or after more than two relapses and no effect of antibiotic therapy [38]. The efficacy rate of FMT in the treatment of clostridial infection is 92 %, which significantly exceeds the efficacy of fidaxomicin (42 %) and vancomycin (19 %) [61].

A group of investigators from Saint Petersburg presented the results of their own studies of the efficacy of FMT in the treatment of *C. difficile*-associated disease in patients with Crohn's disease. Indications for FMT were refractoriness upon repeated courses of vancomycin (n = 6) and its intolerance (n = 1). FMT was performed using capsules with frozen fecal microbiota. As early as on day 15 after FMT, all 7 patients had negative *C. difficile* toxin A and B tests (ELISA). With continued immunological, including biological, treatment, a complete clinical response in terms of the course of Crohn's disease was observed in 3 patients on day 3 after FMT and in 4 patients on day 120. Partial clinical response was observed in one patient, and one patient did not respond to therapy. The results of studies of the main groups of microorganisms by PCR indicated the changes in the microbiota composition before and after FMT. Patients with a complete clinical response after FMT had a significant increase in the total bacterial mass and *Bacteroides fragilis group, Bacteroides thetaiataomicron, Eubacterium rectale, Prevotella* spp, *Roseburia inulinivorans* levels. In the same group of patients, a decrease in *Lactobacillus* spp., *Escherichia coli*, *Acinetobacter* spp, *Streptococcus* spp., *Ruminococcus* spp. levels was observed.

A.P. Kiryukhin presented the results obtained by a group of authors (A.P. Kiryukhin, P.V. Pavlov, A.A. Fedorenko).

At present, the main indication is a recurrent and refractory *C. difficile*-associated disease. Based on current clinical evidence, there are no absolute contraindications to this procedure [62–64]. The safety of FMT was demonstrated in a systematic review involving 4241 patients over a 20-year follow-up period [65].

At the Vasilenko Clinic of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, Sechenov First Moscow State Medical University, FMT is most commonly performed with endoscopic delivery of intestinal microbiota using an extended gastroscope and colonoscope; its efficacy, according to the literature, is as high as 95 % [62].

In May 2019, the local ethics committee of the Clinic approved the protocol of a prospective, open-label, single-center, comparative clinical study for prospective assessment of the efficacy and safety of endoscopic fecal microbiota transplantation in patients with recurrent/refractory *Clostridium difficile*-associated disease.

Between June 2019 and March 2023, in Clinic there were performed 32 FMT procedures through the upper and lower gastrointestinal tract in 22 patients with a median age of 65 years. The ratio of women to men was 14:8. Indications were moderate refractory clostridial infection in 2 cases, mild recurrent *C. difficile*-associated disease in 10 patients, and moderate disease in 10 patients. Based on clinical improvements and the absence of *C. difficile* toxins A and B, 1 FMT procedure was effective in 13 patients with mild recurrent *C. difficile*-associated disease, 2 procedures were effective in 8 patients with moderate recurrent clostridial colitis, and 3 procedures were required in one patient with moderate-to-severe refractory clostridial colitis. No serious adverse events were reported; mild side effects were reported in 6 patients (27.3 %), these did not require additional drug therapy and resolved spontaneously within 1–2 days. Recurrent clostridial infection was observed in 2 patients (9 %), who were subsequently given a course of antibacterial therapy with subsequent improvement.

Analyzing the obtained results, the authors concluded that endoscopic FMT in patients with recurrent/refractory *C.difficile*-associated disease demonstrated its high clinical efficacy and relative safety.

In his final remarks, Expert Council Chairperson **RAS Academician V.T. Ivashkin** emphasized the relevance, scientific novelty and practical significance of the data and noted the fruitful nature of the discussion. After discussion of the reports, a resolution was adopted.

Expert Council resolution:

1. Spores and vegetative cells of *C. difficile* are commonly found in the environment, which increases the risk of colonization of a healthy person and severe *C. difficile*-associated disease.

2. The composition of the intestinal microbiota, the metabolome, and the strength of the adaptive immune response determine the risk of colonization by *C. difficile* and symptomatic disease.

3. Optimization of the diagnosis of *C. difficile* infection, including limited screening only in persons with diarrhea and performing at least 2 laboratory tests, allows to prevent overdiagnosis and unjustified treatment.

4. Video colonoscopy with biopsy is an additional diagnostic tool that should be used when indicated, as it allows to rule out other causes of diarrhea.

5. The choice of treatment depends on the severity of *C. difficile*-associated disease, but the first-line drug of choice is vancomycin.

6. In patients with severe disease in whom drug therapy is ineffective, fecal microbiota transplantation is useful, as repeatedly demonstrated in clinical studies.

7. Rational and justified use of antibacterial drugs is the main preventive measure in terms of *C. difficile*-associated disease.

8. The addition of the probiotic strain *Saccharomyces boulardii* CNCM I-745 250 mg 2 times a day to the antibacterial treatment course is important for both the primary and secondary prevention of *C. difficile* infection.

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Information about the authors

Vladimir T. Ivashkin — Dr. Sci. (Med.), RAS Academician, Prof., Departmental Head, Department of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, N.V. Chief of Vasilenko Clinic of Internal Disease Propaedeutics, Gastroenterology and Hepatology, Sechenov First Moscow State Medical University (Sechenov University).
Contact information: ivashkin_v_t@staff.sechenov.ru;
119435, Moscow, Pogodinskaya str., 1, bld. 1.
ORCID: https://orcid.org/0000-0002-6815-6015

Igor V. Maev — Dr. Sci. (Med.), RAS Academician, Prof., Departmental Head, Department of Propaedeutics of Internal Diseases and Gastroenterology, A.I. Yevdokimov Moscow State University of Medicine and Dentistry.
Contact information: igormaev@rambler.ru;
127473, Moscow, Delegatskaya str., 20, bld. 1.
ORCID: https://orcid.org/0000-0001-6114-564X

Сведения об авторах

Ивашкин Владимир Трофимович — доктор медицинских наук, академик РАН, профессор, заведующий кафедрой пропедевтики внутренних болезней, гастроэнтерологии и гепатологии ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: ivashkin_v_t@staff.sechenov.ru;
119435, г. Москва, ул. Погодинская, д. 1, стр. 1.
ORCID: https://orcid.org/0000-0002-6815-6015

Маев Игорь Вениаминович — доктор медицинских наук, академик РАН, профессор, заведующий кафедрой пропедевтики внутренних болезней и гастроэнтерологии ФГБОУ ВО «Московский государственный медико-стоматологический университет им. А.И. Евдокимова» Министерства здравоохранения Российской Федерации.
Контактная информация: igormaev@rambler.ru;
127473, г. Москва, ул. Делегатская, д. 20, стр. 1.
ORCID: https://orcid.org/0000-0001-6114-564X

Dmitry N. Andreev — Cand. Sci. (Med.), Assoc. Prof., Department of Internal Medicine Propaedeutics and Gastroenterology, Yevdokimov Moscow State University of Medicine and Dentistry.
Contact information: dna-mit8@mail.ru;
127473, Moscow, Delegatskaya str., 20, bld. 1.
ORCID: https://orcid.org/0000-0002-4007-7112

Oleg V. Goloshchapov — Cand. Sci. (Med.), Research Assistant, Department of anesthesiology and resuscitation, Pavlov University, St. Petersburg, Head of ICU No. 3, R.M. Gorbacheva Research Institute of Pediatric Oncology, Hematology and Transplantation.
Contact information: golocht@yandex.ru;
197022, Saint Petersburg, L'va Tolstogo str., 6–8.

Aleksandr A. Derinov — Cand. Sci. (Med.), Associate Professor; Department of Surgery, Institute of Clinical Medicine, Sechenov First Moscow State Medical University.
Contact information: alexandr.derinov@gmail.com;
119435, Moscow, Pogodinskaya str., 1, bld. 1.

Oksana Yu. Zolnikova — Dr. Sci. (Med.), Professor; Chair of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, Sechenov First Moscow State Medical University (Sechenov University); Chief External Gastroenterologist of the Central Federal District of the Russian Federation.
Contact information: zolnikova_o_yu@staff.sechenov.ru;
119435, Moscow, Pogodinskaya str., 1, bld. 1.
ORCID: https://orcid.org/0000-0002-6701-789X

Konstantin V. Ivashkin — Cand. Sci. (Med.), Associate Professor; Chair of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, Sechenov First Moscow State Medical University (Sechenov University).
Contact information: 2135833@mail.ru;
119435, Moscow, Pogodinskaya str., 1, bld. 1.
ORCID: https://orcid.org/0000-0002-5699-541X

Olga Yu. Kiseleva — Cand. Sci. (Med.); Head of the Department of Resuscitation and Intensive Care, Vasilenko Clinic of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology,
Sechenov First Moscow State Medical University (Sechenov University).
Contact information: oyukisa@mail.ru;
119435, Moscow, Pogodinskaya str., 1, bld. 1.
ORCID: https://orcid.org/0000-0001-8630-3616

Andrey P. Kiryukhin — Cand. Sci. (Med.); Endoscopist, Department of Diagnostic and Therapeutic Endoscopy, University Clinical Hospital No 2, Sechenov First Moscow State Medical University (Sechenov University).
Contact information: andresteam@mail.ru;
119435, Moscow, Pogodinskaya str., 1, bld. 1.
ORCID: https://orcid.org/0000-0001-5685-8784

Андреев Дмитрий Николаевич — кандидат медицинских наук, доцент кафедры пропедевтики внутренних болезней и гастроэнтерологии ФГБОУ ВО «Московский государственный медико-стоматологический университет им. А.И. Евдокимова» Министерства здравоохранения Российской Федерации.
Контактная информация: dna-mit8@mail.ru;
127473, г. Москва, ул. Делегатская, д. 20, стр. 1.
ORCID: https://orcid.org/0000-0002-4007-7112

Голощапов Олег Валерьевич — кандидат медицинских наук, ассистент кафедры анестезиологии и реаниматологии ФГБОУ ВО «Первый Санкт-Петербургский государственный медицинский университет им. академика И.П. Павлова» Министерства здравоохранения Российской Федерации; заведующий ОРиИТ № 3 Научно-исследовательского института детской онкологии, гематологии и трансплантологии им. Р.М. Горбачевой.
Контактная информация: golocht@yandex.ru;
197022, г. Санкт-Петербург, ул. Льва Толстого, д. 6–8.
ORCID: https://orcid.org/0000-0002-0736-1269

Деринов Александр Александрович — кандидат медицинских наук, доцент кафедры хирургии ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский университет).
Контактная информация: alexandr.derinov@gmail.com;
119435, г. Москва, ул. Погодинская, д. 1, стр. 1.

Зольникова Оксана Юрьевна — доктор медицинских наук, профессор кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: zolnikova_o_yu@staff.sechenov.ru;
119435, г. Москва, ул. Погодинская, д. 1, стр. 1.
ORCID: https://orcid.org/0000-0002-6701-789X

Ивашкин Константин Владимирович — доктор медицинских наук, доцент кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: 2135833@mail.ru;
119435, г. Москва, ул. Погодинская, д. 1, стр. 1.
ORCID: https://orcid.org/0000-0002-5699-541X

Киселева Ольга Юрьевна — кандидат медицинских наук, заведующая отделением реанимации и интенсивной терапии Клиники пропедевтики внутренних болезней, гастроэнтерологии, гепатологии им. В.Х. Василенко ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: oyukisa@mail.ru;
119435, г. Москва, ул. Погодинская, д. 1, стр. 1.
ORCID: https://orcid.org/0000-0001-8630-3616

Кирюхин Андрей Павлович — кандидат медицинских наук, врач-эндоскопист отделения диагностической и лечебной эндоскопии Университетской клинической больницы № 2 ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский университет).
Контактная информация: andresteam@mail.ru;
119435, г. Москва, ул. Погодинская, д. 1, стр. 1.
ORCID: https://orcid.org/0000-0001-5685-8784

Olga S. Lyashenko* — Gastroenterologist, Department of Gastroenterology, Vasilenko Clinic of Internal Disease Propaedeutics, Gastroenterology and Hepatology, Sechenov First Moscow State Medical University (Sechenov University).
Contact information: olga-ljashenko@rambler.ru;
119435, Moscow, Pogodinskaya str., 1, bld. 1.
ORCID: https://orcid.org/0000-0002-7330-6268

Ляшенко Ольга Сергеевна* — врач-гастроэнтеролог гастроэнтерологического отделения клиники пропедевтики внутренних болезней, гастроэнтерологии и гепатологии им. В.Х. Василенко ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: olga-ljashenko@rambler.ru;
119435, г. Москва, ул. Погодинская, д. 1, стр. 1.
ORCID: https://orcid.org/0000-0002-7330-6268

Elena A. Poluektova — Dr. Sci. (Med.), Prof., Chair of Internal Disease Propaedeutics, Gastroenterology and Hepatology; Gastroenterologist, Department of Chronic Intestinal and Pancreatic Diseases, Vasilenko Clinic of Internal Disease Propaedeutics, Gastroenterology and Hepatology, Sechenov First Moscow State Medical University (Sechenov University).
Contact information: poluektova_e_a@staff.sechenov.ru;
119435, Moscow, Pogodinskaya str., 1, bld. 1.
ORCID: https://orcid.org/0000-0003-1312-120X

Полуэктова Елена Александровна — доктор медицинских наук, профессор кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: poluektova_e_a@staff.sechenov.ru;
119435, г. Москва, ул. Погодинская, д. 1, стр. 1.
ORCID: https://orcid.org/0000-0003-1312-120X

Aleksandr S. Tertychnyy — Dr. Sci. (Med.), Professor; Strukov Department of Anatomical Pathology, Sechenov First Moscow State Medical University (Sechenov University).
Contact information: tertychnyy_a_s@staff.sechenov.ru;
119048, Moscow, Trubetskaya str., 8, bld. 2.
ORCID: https://orcid.org/0000-0001-5635-6100

Тертычный Александр Семёнович — доктор медицинских наук, профессор кафедры патологической анатомии имени академика А.И. Струкова ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: tertychnyy_a_s@staff.sechenov.ru;
119048, г. Москва, ул. Трубецкая, д. 8, стр. 2.
ORCID: https://orcid.org/0000-0001-5635-6100

Alexander S. Trukhmanov — Dr. Sci. (Med.), Professor; Chair of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, Sechenov First Moscow State Medical University (Sechenov University).
Contact information: alexander.trukhmanov@gmail.com;
119435, Moscow, Pogodinskaya str., 1, bld. 1.
ORCID: https://orcid.org/0000-0003-3362-2968

Трухманов Александр Сергеевич — доктор медицинских наук, профессор кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии Института клинической медицины им. Н.В. Склифосовского ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: trukhmanov_a_s@staff.sechenov.ru;
119435, г. Москва, ул. Погодинская, д. 1, стр. 1.
ORCID: https://orcid.org/0000-0003-3362-2968

Anatoly I. Ulyanin — Gastroenterologist, Department of Chronic Intestinal and Pancreatic Diseases, Vasilenko Clinic of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, Sechenov First Moscow State Medical University (Sechenov University).
Contact information: ulyanin_a_i@staff.sechenov.ru;
119435, Moscow, Pogodinskaya str., 1, bld. 1.
ORCID: https://orcid.org/0000-0001-5506-5555

Ульянин Анатолий Игоревич — врач-гастроэнтеролог отделения хронических заболеваний кишечника и поджелудочной железы клиники пропедевтики внутренних болезней, гастроэнтерологии и гепатологии им. В.Х. Василенко ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: ulyanin_a_i@staff.sechenov.ru;
119435, г. Москва, ул. Погодинская, д. 1, стр. 1.
ORCID: https://orcid.org/0000-0001-5506-5555

Arkadiy A. Sheptulin — Dr. Sci. (Med.), Professor; Chair of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, First Moscow State Medical University (Sechenov University).
Contact information: sheptulin_a_a@staff.sechenov.ru;
119435, Moscow, Pogodinskaya str., 1, bld. 1.
ORCID: https://orcid.org/0000-0002-1395-9566

Шептулин Аркадий Александрович — доктор медицинских наук, профессор кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии ФГАОУ ВО «Первый Московский государственный университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информации: sheptulin_a_a@staff.sechenov.ru;
119435, г. Москва, ул. Погодинская, д. 1, стр. 1.
ORCID: https://orcid.org/0000-0002-1395-9566

* Corresponding author / Автор, ответственный за переписку

Oleg S. Shifrin — Dr. Sci. (Med.), Professor; Chair of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology; Head, Department of Chronic Intestinal and Pancreatic Diseases, Vasilenko Clinic of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, Sechenov First Moscow State Medical University (Sechenov University).
Contact information: shifrin_o_s@staff.sechenov.ru;
119435, Moscow, Pogodinskaya str., 1, bld. 1.
ORCID: https://orcid.org/0000-0001-8148-2862

Шифрин Олег Самуилович — доктор медицинских наук, профессор кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии Института клинической медицины им. Н.В. Склифосовского, заведующий отделением хронических заболеваний кишечника и поджелудочной железы клиники пропедевтики внутренних болезней, гастроэнтерологии и гепатологии им. В.Х. Василенко ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: shifrin_o_s@staff.sechenov.ru;
119435, г. Москва, ул. Погодинская, д. 1, стр. 1.
ORCID: https://orcid.org/0000-0001-8148-2862

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