



Clinical Practice Guidelines of the Scientific Society for the Clinical Study of Human Microbiome, of the Russian Gastroenterological Association and the Russian Society for the Prevention of Noncommunicable Diseases on the Diagnosis and Treatment of *Clostridioides difficile* (*C. difficile*)-associated Disease in Adults

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Aim: the clinical practice guidelines intended for gastroenterologists, internal medicine specialists, infectious disease specialists, general practitioners (family doctors), coloproctologists, surgeons and endoscopists present modern methods of diagnosis, prevention and treatment of *C. difficile*-associated disease.

Key points. *C. difficile*-associated disease is a disease that develops when the diversity of the intestinal microbiota decreases and *C. difficile* excessively colonizes the colon, the toxins of which damage the intestinal mucosal epithelial barrier, followed by the development of inflammation in the colon wall, with diarrhea being a characteristic clinical manifestation. The clinical presentation of the disease can vary from asymptomatic carriage, mild to moderate diarrhea that resolves on its own, to profuse watery diarrhea and pseudomembranous colitis with development of life-threatening complications. The diagnosis of *C. difficile*-associated disease is based on an assessment of the clinical presentation, medical history, an objective examination of the patient and laboratory stool tests. The disease severity is determined by clinical symptoms and laboratory findings. Additional diagnostic methods that are used according to indications and contribute to the assessment of severity include endoscopy of the colon and abdomi-

nal cavity imaging methods. Treatment should be initiated in cases of characteristic clinical presentation of *C. difficile*-associated disease and positive laboratory stool testing. The choice of drug and treatment regimen depends on the severity of the episode, the presence of complications, and whether the episode is initial, recurrent, or reinfection.

Conclusion. Determination of target groups of patients for the diagnosis of clostridial infection is important in preventing overdiagnosis and subsequent unnecessary treatment. Timely diagnosis and treatment of *C. difficile*-associated disease help avoiding the development of life-threatening complications and improve the prognosis and quality of life of patients.

Keywords: *C. difficile*-associated disease, pseudomembranous colitis, intestinal microbiota, antibiotic therapy, fecal microbiota transplant

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Практические рекомендации Научного сообщества по содействию клиническому изучению микробиома человека, Российской гастроэнтерологической ассоциации и Российского общества по профилактике неинфекционных заболеваний по диагностике и лечению *Clostridioides difficile* (*C. difficile*)-ассоциированной болезни у взрослых

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Цель: в клинических рекомендациях, предназначенных для врачей-гастроэнтерологов, врачей-терапевтов, врачей-инфекционистов, врачей общей практики (семейных врачей), врачей-колопроктологов, врачей-хирургов и врачей-эндоскопистов, представлены современные методы диагностики, профилактики и лечения *C. difficile*-ассоциированной болезни.

Основное содержание. *C. difficile*-ассоциированная болезнь — заболевание, развивающееся при снижении разнообразия кишечной микробиоты и избыточной колонизации *C. difficile*, токсины которой вызывают повреждение слизисто-эпителиального барьера с последующим развитием воспаления в стенке толстой кишки, а характерным клиническим проявлением служит диарея. Клиническая картина заболевания может варьировать от бессимптомного носительства, легкой или умеренной диареи, купирующейся самостоятельно, до обильной водянистой диареи, псевдомембранозного колита с развитием жизнеугрожающих осложнений. Диагностика *C. difficile*-ассоциированной болезни основана на оценке клинической картины заболевания, данных анамнеза, объективного осмотра пациента и лабораторного обследования образцов кала. Тяжесть заболевания определяется клиническими симптомами и данными лабораторного обследования. К дополнительным диагностическим методам, выполняющимся по показаниям и способствующим оценке степени тяжести, относятся эндоскопическое исследование толстой кишки и методы визуализации брюшной полости. Лечение следует назначать в случаях характерной клинической картины *C. difficile*-ассоциированной болезни и положительных результатов лабораторного тестирования образцов стула. Выбор препарата и схем лечения зависит от степени тяжести эпизода, наличия осложнений и того, является ли эпизод первичным, рецидивом или реинфекцией.

Заключение. Определение целевых групп пациентов для диагностики клостридиальной инфекции имеет важное значение в предотвращении гипердиагностики и последующего необоснованного лечения. Своевременная диагностика и лечение *C. difficile*-ассоциированной болезни позволят избежать развития жизнеугрожающих осложнений и улучшить прогноз и качество жизни пациентов.

Ключевые слова: *C. difficile*-ассоциированная болезнь, псевдомембранозный колит, кишечная микробиота, антибактериальная терапия, трансплантация фекальной микробиоты

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1. Brief information on the disease or condition (group of diseases or conditions)

1.1. Definition of the disease or condition (group of diseases or conditions)

Clostridioides difficile (*C. difficile*)-associated disease is a disease that develops when the diversity of the intestinal microbiota decreases and *C. difficile* excessively colonizes the colon, the toxins of which damage the intestinal mucosal epithelial barrier, followed by the development of inflammation in the colon wall, with diarrhea being a characteristic clinical manifestation [1].

Pseudomembranous colitis is a severe non-specific inflammatory disease of the colon, resulting from damage to the epithelium and a decrease in the blood flow to the mucous membrane. Its characteristic sign is fibrinopurulent plaques on the mucous membrane of the colon [2–5].

1.2. Etiology and pathogenesis of the disease or condition (group of diseases or conditions)

The main etiological factor in the development of *C. difficile*-associated disease is *Clostridioides difficile* (*C. difficile*), a gram-positive, obligate anaerobic, spore-forming bacillus. In 2016, there was an official reclassification, according to which *Clostridioides difficile* was reclassified as a separate species, which has taxonomic and phylogenetic differences from other representatives of the genus *Clostridium* [6, 7]. Non-toxigenic and toxigenic *C. difficile* strains were described. Non-toxigenic ones belong to ribotypes 847 and 032 and do not cause inflammation of the colon mucosa. Toxigenic strains can cause the development of *C. difficile*-associated disease. There are several toxigenic strains belonging to ribotypes 014, 015, 078, 244 and 027. Among them, ribotypes 027 and 078 are the most clinically significant and associated with severe forms of clostridial infection [8–10].

The main route of infection transmission is fecal-oral, and potential reservoirs include

asymptomatic carriers, infected patients and those ones treated earlier, contaminated environments, including surfaces (furniture, phones) and medical equipment [1, 5, 10, 11].

The life cycle of *C. difficile* involves spore germination to form vegetative cells, reproduction followed by the production of toxins, and ends with reverse formation of spores, which are necessary for transmission between hosts and preservation in the external environment. The spores can survive for several months and are resistant to heat, antibiotics, and gastric acid pH (5 or less). Vegetative forms of *C. difficile* can only survive in the gastric contents at pH equal to or greater than 5.

Spore maturation to vegetative forms occurs in the distal small intestine and large intestine due to the combined effect of primary bile salts (cholate, taurocholate, glycocholate, deoxycholate) and L-glycine. Secondary bile acids (deoxycholic acid and lithocholic acid), on the contrary, inhibit spore maturation and toxin production. Calcium ions (*in vivo*) contribute to the activation of signaling pathways that trigger spore germination, while inefficient absorption of calcium in the intestine increases the risk of developing *C. difficile*-associated disease [11, 12].

The gastrointestinal tract (GIT) is the natural habitat of toxigenic and non-toxigenic *C. difficile* strains in most newborns (15–70 %). Over time, when the microbiota composition becomes stable under the influence of natural factors, commensal microorganisms become predominant and provide a protective environment against toxigenic *C. difficile* strains due to competition for nutrients, synthesis of short-chain fatty acids (SCFA), bacteriocins, antimicrobial peptides and secondary bile acids. However, about 5 % of the adult population is colonized by toxigenic *C. difficile* strains [5, 11, 13].

But colonization of *C. difficile* does not always lead to the development of clinical symptoms or the disease, and it may remain asymptomatic. The composition of the intestinal microbiota in asymptomatic individuals is similar to that in healthy individuals. It is assumed that the daily risk of transition from asymptomatic colonization to *C. difficile*-associated disease decreases over time, which may be mediated by the reaction of the adaptive immune system, manifested by an increase in an anti-toxin A and B serum antibody titer [1, 5].

Risk factors for clostridial infection may be related to the patient's condition (e.g., immune status, polymorbidity), exposure to *C. difficile* spores (hospitalization, stay in residential care settings), and disruption of the intestinal microbiota (use of antibiotics, other medicinal products, surgery).

A change in the composition of the intestinal microbiota, primarily when taking antibacterial drugs, leads to colonization of the colon by toxigenic *C. difficile* strains, which is considered the first stage of infection. Other risk factors associated with changes in the composition of the intestinal microbiota include age > 65 years, use of proton pump inhibitors (PPIs), comorbidities (inflammatory bowel disease (IBD), diabetes, obesity) [5, 13]. The main changes in the composition of the intestinal microbiota are a decrease in its diversity, a decrease in the number of *Ruminococcaceae*, *Bifidobacterium*, *Faecalibacterium* and an increase in the number of *Proteobacteria*, *Bacteroidetes* and *Clostridium* spp., which increases the risk of developing *C. difficile*-associated disease by 10 times [1]. The pathogen itself is not invasive, its virulence is due to the production of toxins A (TcdA) and B (TcdB), as well as enzymes such as collagenase, hyaluronidase and chondroitin sulfatase [11]. Traditionally, toxin A has been considered an “enterotoxin” that plays a dominant role, disrupting the integrity of the intestinal mucosal barrier and allowing toxin B, the “cytotoxin”, to enter the enterocytes and lamina propria, exhibiting toxic effects. However, more recent evidence suggests that both toxins are capable of causing damage to the colon wall through direct destruction of epithelial cells and zonula occludens.

An increase in the permeability of the intestinal mucosal barrier contributes to the activation of the innate immune response and the production of pro-inflammatory cytokines, followed by apoptosis and necrosis of epitheliocytes. The disruption of the intestinal barrier, combined with the activation of the immune system, stimulates increased fluid secretion. Toxin B is thought to have a more potent pro-inflammatory activity and may cause more severe disease than toxin A, but both toxins can cause symptoms independently. The hypervirulent *C. difficile* strain NAP1/B1/027 is characterized by increased production of toxins A and B, and also produces a special binary toxin. The binary toxin is considered an “enterotoxin” and is able to increase

the virulence of *C. difficile* in the presence of toxins A or B, inducing colonization of the pathogen, the production of pro-inflammatory cytokines, and suppressing the protective eosinophilic response of the host. The production of this toxin, in addition to *C. difficile* toxins A and B, is associated with severe disease, higher mortality, and the risk of recurrence. Severe cases of *C. difficile*-associated disease caused by a strain that produces only a binary toxin have been described [3, 5]. Impaired immune response to *C. difficile* toxins, as well as new exposure to spores are considered to contribute to disease recurrence [5, 8]. *C. difficile* strains associated with the development of hospital and community-acquired infections do not differ [14, 15].

Toxigenic *C. difficile* is also the best known etiological factor in pseudomembranous colitis, which occurs in more severe *C. difficile*-associated disease. However, *C. difficile*-associated disease and pseudomembranous colitis are not interchangeable terms. Other infectious agents (*St. aureus* (Staphylococcus aureus), *E. coli* (*Escherichia coli*), cytomegalovirus, cryptosporidium), medicinal products (non-steroidal anti-inflammatory drugs (NSAIDs), chemotherapy drugs), certain diseases of the colon (microscopic colitis, inflammatory bowel disease (IBD), ischemic colitis) and systemic vasculitis (Behcet's disease) can also be possible etiological factors of pseudomembranous colitis. The disease develops due to a decrease in oxygenation, damage to the colon epithelium and impaired blood flow to the mucosa, followed by the formation of pseudomembranes on the mucosa, consisting of necrotic epithelial cells, fibrin, mucus and leukocytes [2–5].

1.3. Epidemiology of the disease or condition (group of diseases or conditions)

C. difficile is the leading cause of diarrhea in hospitalized individuals. At the end of the 20th century, the incidence of *C. difficile*-associated disease increased in many countries of the world and it is currently one of the most significant hospital-acquired infections [5].

C. difficile infection can manifest with a wide range of clinical signs, from asymptomatic carriage to mild to moderate diarrhea and fulminant life-threatening colitis [15, 16].

In the first days of hospitalization, the frequency of *C. difficile* infection with possible development of clinical symptoms of the disease ranges from 2.1 to 20 % and increases with the length of hospital stay. After one month of

hospital stay, the infection rate can increase up to 50 %. However, only 25–30 % of colonized patients develop diarrhea [5]. The prevalence of asymptomatic carriage among healthy individuals, hospitalized patients, and long-term hospitalized patients is < 2 %, 3–26 % and 5–7 %, respectively [10]. The probability of *C. difficile* infection in an uncolonized healthy person in a healthcare facility is 2.3 %, in a long-term care facility – 0.37%, and outside a healthcare facility – 0.12 %. The probability of infection of a healthy non-colonized individual from a patient with *C. difficile*-associated disease outside a healthcare facility is 0.1 %, and from an asymptomatic colonized person – 0.05 % [15].

The increase in morbidity and the development of more severe forms of *C. difficile*-associated disease and mortality at the end of the 20th century are due to the emergence of the epidemic hypervirulent strain NAP1/B1/027, while other strains were detected in asymptomatic carriers [10, 15]. The risk of infection recurrence is 10–35 % with a subsequent increase in the risk of recurrence up to 65 % after each episode. Up to 75–85 % of recurrences of *C. difficile*-associated disease are associated with an excessive increase in colony-forming units (CFU) of the same strain. Reinfection is caused by a new strain [10, 15, 17].

In the Russian Federation, *C. difficile* infection was detected in 34.4 % of cases of antibiotic-associated diarrhea in patients in multidisciplinary hospitals in St. Petersburg [18].

In general, there is currently a decrease and stabilization of the overall incidence of *C. difficile*-associated disease worldwide, which is explained by the rapidly declining prevalence of the hypervirulent strain NAP1/B1/027 due to improved diagnostic algorithms and treatment regimens, as well as expanding rational antibiotic use programs. The total number of cases of *C. difficile*-associated disease worldwide decreased from 476,400 in 2011 to 462,100 in 2017. In the United States, 223,900 cases of *C. difficile*-associated disease and 12,800 deaths were reported in 2017. Nevertheless, overall mortality related to *C. difficile*-associated disease is estimated at 5 %, while mortality due to its complications reaches 15–25 %, and in intensive care units – up to 34 % [5, 13, 15]. The total number of cases of recurrence of *C. difficile*-associated disease has also decreased and remains stable. For example, in the US, this figure decreased from 93,400 to 69,800 between 2011 and 2017. However, the past decade has seen an increase

in community-acquired *C. difficile* infection [8, 10, 19], which accounts for 10–43 % of reported cases of *C. difficile*-infections [8, 10, 15]. According to the latest data in the United States, the incidence of community-acquired *C. difficile*-associated disease increased from 52.88 per 100,000 population in 2012 to 65.93 per 100,000 population in 2017. In Canada, this rate increased over 2005–2015 from 6.09 to 9.56 per 100,000 population per year [15, 20]. Patients with community-acquired infection tend to be younger (mean age – 50 years), have lower mortality rates (0.07 %), and a significant proportion (36 %) have no history of antibiotic use [15].

Thus, the expansion of risk groups for *C. difficile* infection both among patients and among healthy individuals, the possible development of complications, including fatal ones, the continuing risk of recurrence and reinfection, rather high rates of morbidity, mortality, and the growth of community-acquired infection determine the relevance of studying preventive and therapeutic measures for this disease [15, 16].

1.4. Characteristics of coding the disease or condition (group of diseases or conditions) according to the International Statistical Classification of Diseases and Related Health Problems

A04.7 Enterocolitis caused by *Clostridium difficile*

1.5. Classification of the disease or condition (group of diseases or conditions)

There is no generally accepted classification of *C. difficile*-associated disease.

Depending on the relationship of the onset of symptoms with the provision of medical care and/or hospital stay, community-acquired and hospital-acquired infections are distinguished. Hospital-acquired infection with *C. difficile* is characterized by onset of symptoms on day 4 after hospitalization and beyond. Community-acquired infection is manifested by development of symptoms outside the hospital. The onset of symptoms within 4 weeks of discharge is considered a community-acquired, healthcare-associated *C. difficile* infection. The onset of symptoms within the first 48 hours of hospitalization or at least 4 weeks after discharge is considered sporadic community-acquired *C. difficile* infection. This distinction focuses on the risks of developing clostridial infection, which is important from an epidemiological point of view [8, 10].

Depending on clinical symptoms, their severity and the presence of complications, asymptomatic carriage of *C. difficile*, mild/moderate and severe/complicated *C. difficile*-associated disease are distinguished [1, 5, 10, 21]. There are currently no validated criteria for assessing the severity of *C. difficile*-associated disease [10, 21]. Mild/moderate *C. difficile*-associated disease is usually characterized by diarrhea without signs of systemic infection [21]. Severe/complicated *C. difficile*-associated disease is characterized by fever ($> 38.5^{\circ}\text{C}$), leukocytosis ($> 15 \times 10^9/\text{L}$) and elevated creatinine level ($> 1.5 \text{ mg/dL}$) [10]. Table 1 summarizes the main signs that allow distinction between the different severity grades of clostridial infection.

Depending on the time of onset of symptoms and their relationship with previous episodes of clostridial infection, an initial episode, recurrence and reinfection are distinguished. An initial episode of *C. difficile*-associated disease is characterized by the onset of symptoms in combination with a positive diagnostic test for *C. difficile* toxins and no evidence of clostridial infection within the preceding 8 weeks [10]. Recurrence of *C. difficile*-associated disease is characterized by the onset of symptoms and a positive test after temporary resolution of symptoms with standard treatment of the initial episode in the previous 2–8 weeks, but most often within the first week after treatment [10]. Reinfection with *C. difficile* is occurrence of symptoms and a positive stool test for toxins with the standard treatment of the initial episode, associated with infection with a new strain of *C. difficile*. The time threshold for distinguishing between recurrence and reinfection is 8 to 20 weeks [8, 10, 15].

1.6. Clinical presentation of the disease or condition (group of diseases or conditions)

The clinical presentation of *C. difficile*-associated disease can vary from asymptomatic carrying, mild or moderate diarrhea that resolves on its own, to profuse watery diarrhea and pseudomembranous colitis with development of life-threatening complications [5, 15, 16, 21] (see Table 1).

The main clinical symptom of *C. difficile*-associated disease is diarrhea (≥ 3 episodes of loose stools, type 6–7 on Bristol stool chart, within 24 hours) [8].

C. difficile can affect any part of the colon, but it more often colonizes the distal parts [5].

Table 1. Manifestations of *C. difficile*-associated disease depending on its severity [8, 10, 22–26]
Таблица 1. Проявления *C. difficile*-ассоциированной болезни в зависимости от тяжести ее течения [8, 10, 22–26]

Course of the disease Течение заболевания	Main criteria Основные критерии	Secondary signs** Дополнительные признаки**
Asymptomatic carriage Бессимптомное носительство	Absence of diarrhea when carrying a toxigenic <i>C. difficile</i> strain and/or presence of toxins in stool samples Отсутствие диареи при носительстве токсигенного штамма <i>C. difficile</i> и/или наличии токсинов в образцах кала	
Mild/moderate Легкое / умеренной тяжести	Diarrhea (loose stools ≥ 3 times a day, type 6–7 on the Bristol stool chart), including those associated with abdominal pain Диарея (неоформленный стул ≥ 3 раз в сутки, тип 6–7 по Бристольской шкале), в том числе в сочетании с болью в животе	<ul style="list-style-type: none"> – mucus in the stool – white blood cells $< 15 \times 10^9/L$ – creatinine < 1.5 mg/dL – positive fecal occult blood test – nausea – decreased appetite – low-grade fever may be observed, moderate tenderness on palpation of the abdomen, nonspecific erythema on endoscopic examination – примесь слизи в стуле, – лейкоциты $< 15 \times 10^9/л$, – креатинин $< 1,5$ мг/дл, – положительный тест на скрытую кровь в кале, – тошнота, – снижение аппетита, – может наблюдаться субфебрильная лихорадка, умеренная болезненность при пальпации живота, неспецифическая эритема при эндоскопическом исследовании
Severe Тяжелое	Watery diarrhea with two or more of the following <ul style="list-style-type: none"> – hypoalbuminemia (serum albumin < 30 g/L) – leukocytosis $< 15 \times 10^9/L$ – fever (> 38.5 °C) – creatinine > 1.5 mg/dL (or more than 1.5 times baseline creatinine or 25 % decrease in glomerular filtration rate from baseline) – abdominal pain and tenderness on palpation Водянистая диарея в сочетании с двумя и более признаками: <ul style="list-style-type: none"> – гипоальбуминемия (альбумин сыворотки < 30 г/л), – лейкоцитоз ($> 15 \times 10^9/л$), – лихорадка ($> 38,5$ °C), – креатинин $> 1,5$ мг/дл (или более чем в 1,5 раза выше исходного уровня креатинина, или снижение скорости клубочковой фильтрации на 25 % по сравнению с исходным уровнем), – абдоминальная боль и болезненность при пальпации 	<ul style="list-style-type: none"> – nausea – fatigue – bloating – dry mucous membranes – decreased skin turgor – presence of pseudomembranes in endoscopic examination – тошнота, – общая слабость, – вздутие живота, – сухость слизистых оболочек, – снижение тургора кожи, – наличие псевдомембран при эндоскопическом исследовании
Complicated Осложненное	Criteria for severe disease* in combination with one or more signs: <ul style="list-style-type: none"> – hypotension – shock – ileus – megacolon – altered level of consciousness – serum lactate level > 2.2 mmol/L – organ failure (the need for artificial lung ventilation, renal insufficiency, etc.) 	<ul style="list-style-type: none"> – nausea – bloating – anterior abdominal wall muscle stiffness – hepatic enzyme increase – тошнота,

Continuation of the table 1 / Продолжение таблицы 1

Complicated Осложненное	Критерии тяжелого течения* в сочетании с 1 и более признаком: – гипотензия, – шок, – илеус, – мегаколон, – изменение сознания, – уровень сывороточного лактата > 2,2 ммоль/л, – органная недостаточность (необ- ходимость искусственной вентиляции легких, почечная недостаточность и др.)	– вздутие живота, – ригидность мышц передней брюшной стенки, – повышение печеночных ферментов
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Примечание. * – Водянистая диарея отсутствует у пациентов с илеусом и токсическим мегаколоном. ** – Суммированы дополнительные симптомы, которые могут возникать у пациентов с различной степенью тяжести *C. difficile*-ассоциированной болезни.

Note. * – no watery diarrhea in patients with ileus and toxic megacolon; ** – summarizes additional symptoms that may develop in patients with varying severity of *C. difficile*-associated disease.

The incubation period can last more than one week (up to 28 days), averaging 2–3 days. In most patients, the main clinical symptom is mild diarrhea (up to 5 times a day), spontaneous recovery occurs 5–10 days after antibiotics are discontinued. Most often, diarrhea develops during or immediately after antibiotic therapy [8, 10, 25].

In addition to diarrhea, abdominal pain, fever, nausea and vomiting, weakness, and loss of appetite may occur. Fecal occult blood test is often positive, although active intestinal bleeding is rare. In rare cases, there may be signs of reactive arthritis. In the most severe cases, symptoms such as dehydration, hypoalbuminemia with peripheral edema and subsequent hypovolemic shock come to the fore in the clinical presentation. Severe complications of *C. difficile*-associated disease include toxic megacolon, colonic perforation, intestinal paresis, renal failure, systemic inflammatory response syndrome, septicemia, and death [5, 10].

The clinical presentation of pseudomembranous colitis is characterized by diarrhea, cramping abdominal pain, and fever. The disease can cause complications, such as electrolyte imbalance, ileus, megacolon, intestinal bleeding, colon perforation [2, 4, 5].

It is worth noting that colonized patients may also have diarrhea unrelated to *C. difficile*-associated disease. Clinical signs suggestive of an alternative diagnosis include failure to respond to treatment in mild cases, atypical course (including chronic diarrhea), periodicity and no worsening of symptoms without treatment, a history of alternating diarrhea and constipation [27].

2. Diagnosis of the disease or condition (group of diseases or conditions), medical indications and contraindications for the use of diagnostic methods

The diagnosis of C. difficile-associated disease is based on an assessment of the clinical presentation, medical history, an objective examination of the patient and laboratory stool tests. Determining target patient population for the diagnosis of clostridial infection is important in preventing overdiagnosis and subsequent unnecessary treatment. Screening for C. difficile-associated disease should only be done in patients with a first onset of diarrhea within 24 hours (loose stools, Bristol stool chart type 6–7, at least 3 times a day) with no other obvious cause of diarrhea. If ileus is suspected, it is acceptable to obtain a rectal swab sample. An important diagnostic feature is the presence of a proven risk factor (in particular, recent antibiotic therapy, advanced age, hospital stay). The disease severity is determined by clinical symptoms and laboratory findings. Additional diagnostic methods that are used according to indications and contribute to the assessment of severity include endoscopy of the colon and abdominal cavity imaging methods. When diagnosing the C. difficile-associated disease, it is necessary to evaluate not only the severity, but also whether the episode is initial, recurrent, or reinfection [5, 8, 10, 21, 25, 27].

Criteria for establishing a diagnosis/condition: the diagnosis and severity of *C. difficile*-associated disease is established on the

basis of clinical signs, medical history, and findings of investigations.

2.1. Complaints and history

Complaints characteristic of patients with *C. difficile*-associated disease are described in Table 1 (Section 1.5 “Classification”) and Section 1.6 “Clinical presentation”.

- A careful history taking is recommended to rule out other causes of diarrhea and to identify risk factors for clostridial infection in patients with diarrhea to determine if a laboratory diagnosis of clostridial infection is warranted.

Grade of recommendation — B

(level of evidence — 5)

Comment. First of all, laxatives should be avoided within the previous 48 hours after the onset of symptoms. Other noninfectious causes of diarrhea include chemotherapeutic agents, enteral nutrition, abdominal surgery, and comorbidities such as IBD and irritable bowel syndrome (IBS). However, these conditions and diseases may themselves be risk factors for clostridial infection [8, 25]. It is believed that the main risk factors for *C. difficile*-associated disease are advanced age, hospitalization and antibiotic therapy. The use of antibiotics is the most important modifiable risk factor that directly affects the composition of the intestinal microbiota. Almost all classes of antibiotics have been associated with *C. difficile*-associated disease, but clindamycin, penicillins, third/fourth generation cephalosporins, carbapenems, and fluoroquinolones present the highest risk, followed by macrolides and sulfonamides/trimethoprim [16, 25]. It is believed that the disruption of the composition of the intestinal microbiota by antibiotics is of a long-term nature, and the risk of developing a *C. difficile*-associated disease increases both during therapy and within 3 months after its completion. During antibiotic therapy and the first month after it, the risk of developing clostridial infection increases 7–10 times, and 3 times — in the next 2 months. The risk of clostridial infection is directly proportional to the duration of use and the number of antibiotics. However, even brief exposure to an antibiotic, such as a prophylactic measure in surgery, increases the risk of *C. difficile* colonization and symptom development in the patient [5, 8, 10, 13, 28]. Proven risk factors for the development of *C. difficile*-associated disease also include: immunodeficiency conditions (IBD, HIV, cancer,

conditions after organ transplantation and, accordingly, the use of immunosuppressive and chemotherapeutic drugs), surgical interventions on the gastrointestinal tract (especially colon resection), enteral nutrition, presence of competing diseases (renal failure, diabetes mellitus, cystic fibrosis, diseases of the cardiovascular and respiratory systems), reduced acidity of gastric juice (primarily use of PPIs, as well as H₂-histamine receptor blockers) [5, 8, 10, 25]. Long-term use of PPIs has been shown to reduce gut microbiota diversity and may double the risk of *C. difficile* infection. The incidence of *C. difficile*-associated disease in individuals taking PPIs is 65–75 % higher than in the population of healthy individuals. However, this risk factor for the development of *C. difficile*-associated disease remains controversial. First, diarrhea is one of the side effects of PPIs. Second, those studies and systematic reviews that have shown an association with an increased incidence of clostridial infection in patients receiving PPIs did not take into account other factors, such as older age, comorbidities, and antibiotic use, which may distort the results [27]. Risk factors for recurrence of *C. difficile*-associated disease include antibiotic use during or after treatment of the first episode, older age (≥ 65 years), female gender, history of *C. difficile*-associated disease episodes (risk of developing after one, two and three episodes is 20 %, 40 % and 65 %, respectively), concomitant diseases (chronic kidney disease, IBD), taking immunosuppressive drugs, feeding through a nasogastric tube, reduced gastric acidity (long-term use of PPIs, H₂-histamine receptor blockers) [10, 15]. Predictive risk factors for severe/complicated disease course are listed in Section 7 (Supplementary Information).

2.2. Physical examination

Physical examination findings differ depending on the severity of *C. difficile*-associated disease (Table 1). In the case of mild/moderate disease, patients may have impurities of mucus or blood in the stool, low-grade fever, moderate tenderness on abdomen palpation. In the case of severe/complicated *C. difficile*-associated disease, various clinical symptoms are observed, including fever, diffuse abdominal pain, abdominal distension, hypovolemia (dry skin and mucous membranes, decreased skin turgor). When examining the abdomen, bloating, diffuse pain on palpation, and tympanitis on percussion can be determined. It is important to note that

patients with severe *C. difficile*-associated disease may develop dynamic intestinal obstruction, which is clinically manifested not by watery diarrhea, but by the absence of stools, and therefore the diagnosis may be delayed, which, in case of progression of the condition can lead to toxic megacolon or colonic perforation. Patients with complicated disease are hemodynamically unstable, signs of hypotension, shock, impaired consciousness, peritonitis, systemic inflammatory response syndrome can be observed [21, 25, 26].

2.3. Laboratory diagnostic tests

- It is recommended that only loose stool samples (type 6–7 on Bristol stool chart) be used for laboratory diagnosis in patients with first-onset diarrhea of unknown origin within 24 hours (≥ 3 episodes per day) for testing for clostridial infection [5, 10, 25, 27].

Grade of recommendation — B (level of evidence — 4)

Comment. In practice, it is not always possible to exclude the risk of *C. difficile* infection solely by the presence or worsening of clinical manifestations of diarrhea. If a patient has diarrhea, including associated with abdominal pain, which cannot be fully explained by the presence of a concomitant disease (IBD) or ongoing treatment (enteral nutrition, chemotherapy, laxatives), it is advisable to conduct a laboratory test for *C. difficile*. Testing is indicated when symptoms persist despite discontinuation of therapy (e.g., chemotherapy drugs, laxatives) or enteral nutrition [10, 25]. Patients with suspected ileus may be diagnosed by analysis of a rectal swab sample [5, 27]. If a patient with suspected clostridial infection but no diarrhea at the time of examination is taking antidiarrheal drugs (e.g., loperamide), it is advisable to discontinue the drug 24 hours prior to stool sample testing.

- Laboratory testing for *C. difficile* is not recommended in patients without diarrhea (asymptomatic) to prevent overdiagnosis and subsequent unnecessary treatment [5].

Grade of recommendation — B (level of evidence — 5)

Comment. It is not reasonable to screen patients without diarrhea for clostridial infection except for epidemiological purposes. This approach may be appropriate for infection control purposes, e.g., before admission to an oncology hospital or transplantation department [27].

- It is recommended that at least 2 laboratory tests be performed on stool specimens in patients with diarrhea of unknown origin to diagnose clostridial infection [5, 8, 10, 21, 25, 27, 29, 30].

Grade of recommendation — B (level of evidence — 3)

Comment. There are several laboratory tests for the presence of *C. difficile* in stool by detecting the pathogen itself, its toxins, or the glutamate dehydrogenase enzyme (GDH). These tests are based on culture, molecular genetic or serological methods (Table 2). The culture method using culture media allows not only detecting vegetative cells or *C. difficile* spores, but also evaluating cytotoxicity by detecting free *C. difficile* toxins using a cell cytotoxicity neutralization assay and determining the susceptibility to antibacterial drugs. The molecular genetic method is based on PCR (polymerase chain reaction). This method makes it possible to identify genes encoding toxins A, B and binary toxin, thereby confirming the presence of a toxigenic *C. difficile* strain. The serological method is based on immunochemical analysis (immuno-chromatographic assay (ICA), enzyme-linked immunosorbent assay (ELISA) and latex agglutination assay (LA assay)) using specific antibodies, the antigens to which are GDH or *C. difficile* toxins A and B.

Currently, none of the available laboratory tests is considered suitable as a stand-alone tool for the diagnosis of *C. difficile*-associated disease. Each of them has its own characteristics in conducting and interpreting the results, as well as different sensitivity, specificity, and, accordingly, predictive value (Table 3). Culture-based tests are considered as a reference method in the diagnosis of clostridial infection. The toxigenic culture/spore isolation method has high sensitivity and specificity. The method for determining cytotoxicity in a cell cytotoxicity neutralization assay has a high specificity, but it is not standardized in terms of the processing of stool samples and interpretation of the results, which reduces its sensitivity. The culture method is laborious, time consuming, should only be carried out in well-equipped laboratories by qualified personnel and, despite being reliable, is rarely used in routine practice [8, 10]. In this regard, the reference method has been replaced by more user-friendly and faster tests, such as

Table 2. Methods for diagnosing *C. difficile* [8, 10, 25–27, 29, 30]Таблица 2. Методы диагностики *C. difficile* [8, 10, 25–27, 29, 30]

Method Метод	Assay Анализ	Test time Время исследования	Test purpose Цель исследования
Culture Культуральный	Isolation of toxigenic culture on a culture medium Выделение токсигенной культуры на питательной среде	48–72 hours 48–72 часа	Vegetative cells or spores of <i>C. difficile</i> , toxins A and B Вегетативные клетки или споры <i>C. difficile</i> , токсины А и В
	Determination of cytotoxicity in a cell cytotoxicity neutralization assay Определение цитотоксичности в реакции нейтрализации на культуре клеток	24–48 hours 24–48 часов	Toxins A and B Токсины А и В
Molecular genetic Молекулярно-генетический	PCR ПЦР	2–4 hours 2–4 часа	Genes encoding toxins A, B, binary toxin Гены, кодирующие токсины А, В, бинарный токсин
Serological Серологический	ICA ИХА	15–30 minutes 15–30 минут	GDH, toxins A and B ГДГ, токсины А и В
	ELISA ИФА	1–4 hours 1–4 часа	GDH, toxins A and B ГДГ, токсины А и В
	LA РАЛ	30 minutes 30 минут	GDH, toxins A and B ГДГ, токсины А и В

Примечание. ГДГ — фермент глутаматдегидрогеназа.

Note. GDH — glutamate dehydrogenase.

PCR, ELISA, ICA. LA tests also belong to the older generation and are rarely used in routine practice. Assessment of presence of *C. difficile* by PCR is highly sensitive and specific. This test allows confirming the presence of a toxigenic strain of *C. difficile*, but has limitations in use, namely high cost and difficulties in interpreting the results. PCR is a qualitative method (positive or negative) and cannot characterize the bacterial load and viability of *C. difficile*. Identification of genes encoding toxins does not always mean that the strain is currently producing them. If the diarrhea has a different origin, the detection of such a strain can be misleading [5, 8, 27, 29]. The serological method (ELISA, ICA) is currently the most popular due to its low cost and ease of implementation. Its advantages also include the possibility to use minimal amounts of the test material, as well as to automate all stages of the test, which is important in data interpretation. The disadvantage is that this test can have a high false positive rate and interlaboratory differences. There are reports that a positive ELISA correlates with clinical symptoms and outcomes but may be negative in the early stages (due to lower bacterial load) and in patients with complicated disease. When testing a stool sample by

serological method, the rules of transportation and storage must be observed. Once a stool specimen has been obtained, it must be stored at +4 °C (refrigerator) and used for testing within the next 24 hours. This is extremely important because the toxin present in the sample easily degrades at room temperature, and after about 2 hours it cannot be detected in the obtained material [5, 8, 10, 25, 27, 29]. It is also possible to determine the presence of GDH in the stool using a serological method; however, this does not allow differentiating the presence of the toxigenic strain in a patient, since GDH is an enzyme also produced by non-toxigenic strains. In view of this, this test is recommended only as a screening. Commercial ICA test systems have been developed for rapid testing in the form of plastic plates with slots for introducing material, recording the result and control, allowing determination of not only the presence of GDH in the stool, but also of toxins A and B. These tests are easy to use, allow to quickly get a result and do not require specially trained healthcare professionals, but are inferior in sensitivity to other immunoassay methods and there are no clear criteria for data interpretation [5, 8, 10, 27, 30, 31]. The lack of consensus on the best method for laboratory diagnosis is also due to the fact that the

culture method, which has never been standardized, is used as a reference standard or reference method in most of the literature [10].

According to the State Register of Medical Devices and Organizations (Individual Entrepreneurs) engaged in the production and manufacturing of medical devices (www.roszdravnadzor.gov.ru), 1 set of reagents (rapid test) for the determination of *C. difficile* GDH + toxin A + toxin B antigens in stool samples by ICA, 2 sets of reagents (rapid test) for the determination of toxin A + toxin B antigens in stool samples by ICA, 4 sets of reagents for *in vitro* diagnostics of toxins A and B by ELISA and 1 set of reagents for *in vitro* diagnostics of toxins A and B using a PCR analyzer are currently authorized in Russia. Culture media, additives and components of culture media for microbiological diagnosis of *C. difficile* are also authorized.

• It is recommended to use a two- or three-step algorithm for laboratory diagnosis of stool samples in patients with diarrhea and presence of risk factors for clostridial infection to increase the diagnostic value of a positive laboratory test result [5, 8, 10, 21, 25, 27, 29, 30].

Grade of recommendation — B
(level of evidence — 3)

Comment. There is currently no standardized algorithm for diagnosing clostridial infection. It is assumed that it is advisable to use two- and three-stage algorithms to optimize the diagnosis of clinically significant *C. difficile*-associated

disease and differentiate between colonization and active infection (see Appendix B) [10, 25]. As a primary step/screening, it is advisable to perform a test with a high negative predictive value, i.e., with a high probability of absence of the disease if the test is negative (e.g., the determination of GDH (ICA) or genes encoding toxins A and B, binary toxin (PCR)). If the result is negative, clostridial infection is ruled out. When a positive result is obtained, the next step is to conduct a test with a high positive predictive value, i.e., a high probability of presence of the disease (toxins A and B (ELISA, ICA)). A positive second test confirms the presence of clostridial infection. In case of a negative result of the second test, a clinical assessment is necessary, such a laboratory result can be obtained in three situations: *C. difficile* with a toxin level below the detection threshold, a false-negative ELISA/ICA result for toxins A and B, or carriage of *C. difficile*. Stool samples that are negative for GDH but positive for toxins should be retested as this result is not valid (Figure 1, Appendix B) [5, 27].

An alternative algorithm for the laboratory diagnosis of clostridial infection is based on serological analysis (ELISA/ICA) to determine the *C. difficile* toxins A/B in stool together with GDH or PCR to identify genes of toxins A, B, binary toxin. If the first two laboratory tests are negative, clostridial infection is excluded, and if the results are

Table 3. Characteristics of methods used to diagnose *C. difficile* [8, 10, 26, 27, 29, 31]

Таблица 3. Характеристики методов, использующихся для диагностики *C. difficile* [8, 10, 26, 27, 29, 31]

Test Тест	Sensitivity (%) Чувствительность (%)	Specificity (%) Специфичность (%)	Differentiation of colonization from active infection Дифференциация колонизации от активной инфекции
Culture method: Isolation of toxigenic culture Культуральный метод: Выделение токсигенной культуры	90–100	90–99	yes да
Determination of cytotoxicity Определение цитотоксичности	65–100	90–98	
PCR (genes encoding toxins A, B, binary toxin) ПЦ (гены, кодирующие токсины А, В, бинарный токсин)	77–100	87–100	no нет
ELISA (toxins A and B) ИФА (токсины А и В)	43–100	84–100	yes да
ICA (GDH) ИХА (ГДГ)	29–86	76–100	no нет
ICA (toxins A and B) ИХА (токсины А и В)	29–79	89–100	yes да

positive, then it is confirmed. In the case when ELISA/ICA is used for the determination of *C. difficile* toxins A/B in combination with GDH, but one of the tests is negative and the second one is positive, testing for the genes encoding toxins A and B, binary toxin, is carried out to confirm the result (PCR), the result of which confirms or excludes clostridial infection, this being a three-stage algorithm. In patients with suspected recurrent infection, testing may be performed, including the determination of *C. difficile* toxins A/B (ELISA, ICA) (Fig. 2, Appendix B) [8, 10, 21, 25, 26].

- It is recommended to conduct a complete blood count and chemistry panel with an assessment of the level of white blood cells, CRP, creatinine, total protein, albumin and electrolytes in patients with confirmed clostridial infection to determine the severity and identify complications.

Grade of recommendation — A
(level of evidence — 4)

Comment. Depending on the severity and presence of complications in the complete blood count an increase in the level of white blood cells (leukocytosis) may be observed, and in the biochemical blood test — an increase in the level of C-reactive protein, hypoalbuminemia, signs of acute renal failure. In the case of mild/moderate *C. difficile*-associated disease, leukocytosis up to $15 \times 10^9/L$ and a creatinine level $< 1.5 \text{ mg/dL}$ can be observed in the blood tests. In case of severe/complicated *C. difficile*-associated disease, the complete blood count shows signs of leukocytosis (over $15 \times 10^9/L$). The biochemical blood test may reveal signs of impaired function of target organs, namely an increase in creatinine $> 1.5 \text{ mg/dL}$ or more than 1.5 times above the baseline. Signs of electrolyte imbalance consistent with hypovolemia and signs of lactic acidosis can be detected in such patients. If complications develop, there may also be signs of systemic inflammation, such as hypoalbuminemia. When hypotension develops, there may be signs of end-organ dysfunction secondary to hypoperfusion, such as elevated liver enzymes [10, 25, 27].

- It is not recommended to retest stool specimens in patients with diarrhea and an initially negative laboratory test performed to diagnose clostridial infection [5, 8, 10, 25].

Grade of recommendation — B
(level of evidence — 3)

Comment. Retesting within 7 days of an initial negative result is not recommended due to high risk of false positives, a very low diagnostic value (2 %), and potential for unnecessary treatment [5, 8, 10, 25]. Retesting for *C. difficile* should only be considered if the condition worsens in patients with a characteristic clinical presentation and a negative initial laboratory test [10].

- It is not recommended to assess the level of fecal biomarkers of inflammation (calprotectin, lactoferrin) in patients with suspected clostridial infection to determine the severity of the disease or the risk of recurrence [10, 25].

Grade of recommendation — C
(level of evidence — 5)

Comment. Biomarkers of inflammation such as calprotectin and lactoferrin may distinguish inflammatory causes of diarrhea (e.g., IBD) from non-inflammatory causes (e.g., IBS). Lactoferrin is an iron-binding glycoprotein found in neutrophils and its concentration in stool is proportional to the neutrophil count in it. Calprotectin is a calcium-binding protein found in the cytosol of neutrophils; its concentration is also proportional to the severity of inflammation in the intestine [10]. However, these markers are non-specific, therefore testing for these markers is not an informative method [8]. Currently, there is insufficient evidence to support their use as an additional method for diagnosing clostridial infection, due to the small cohort of patients in studies, the small number of prospective studies, and the use of different laboratory testing methods, which complicates the interpretation of data. Despite this, inflammation biomarkers may serve as an additional tool to identify patients at high risk for severe *C. difficile*-associated disease [10, 25].

2.4. Diagnostic investigations

- It is recommended to use abdominal imaging methods (radiography, ultrasound, multispiral computed tomography (MSCT)) in patients with clostridial infection in severe/complicated cases for timely diagnosis of the condition and selection of treatment approach [5, 8, 25].

Grade of recommendation — B
(level of evidence — 5)

Comment. Abdominal imaging methods (X-ray, ultrasound, MSCT) are not the methods of choice in the diagnosis of clostridial infection. Patients with mild/moderate *C. difficile*-associated disease do not require

additional imaging. If these methods are used in such patients, swelling of the colon loops and thickening of its wall can be determined. Their use is of great importance in the diagnosis of complications. Ultrasound imaging is a particularly good method for monitoring the width of the colonic lumen. Plain abdominal radiography can reveal the dilation of the loops of the small intestine and colon, the presence of fluid and air levels in the loops of the intestine, the presence of free air in the abdominal cavity. Computed tomography of the abdomen and pelvis with oral and intravenous contrast enhancement is useful in patients with severe clostridial infection to detect toxic megacolon, intestinal perforation, or other signs requiring surgical intervention. Detection of the colon wall thickening on MSCT in patients with an unclear clinical presentation and inconclusive laboratory findings has a high prognostic value.

- It is recommended to perform a colonoscopy with a biopsy and subsequent morphological examination of biopsies of the colon mucosa in cases of no response to treatment, progressive condition deterioration, or a suspected alternative diagnosis to clarify it and determine further treatment approach [5, 8, 25, 27].

Grade of recommendation — B
(level of evidence — 5)

Comment. Colonoscopy is not indicated for patients with mild/moderate *C. difficile*-associated disease, confirmed by laboratory tests as a routine method. The investigation is indicated when there is difficulty in diagnosing *C. difficile*-associated disease, namely, a typical clinical presentation, but negative results of laboratory testing of stool samples, in the absence of a response to the standard course of treatment, or when an alternative diagnosis is suspected, when direct imaging and/or a biopsy of the colonic mucosa are necessary. Colonoscopy may be performed when the disease worsens rapidly to determine the urgency of surgery, e.g., if intestinal obstruction is suspected. If the investigation is performed, limited flexible sigmoidoscopy with minimal or no air insufflation is preferred to avoid perforation of the inflamed colon. Pseudomembranes found during the procedure are white or yellow raised plaques, usually about 2 cm in diameter, that are unevenly distributed and separated by normal mucosa. They are not removed by washing the intestinal walls. The

*distribution of pseudomembranes may vary. Not all patients with *C. difficile* disease have pseudomembranes, and their absence does not rule out *C. difficile* infection. For example, pseudomembranes are rarely seen in recurrent clostridial infections or in patients with inflammatory bowel disease. On the other hand, pseudomembranous colitis can be caused by a number of different causes, such as Behcet's disease, microscopic colitis, IBD, ischemic colitis, and other infections (e.g., cytomegalovirus (CMV) or *E. coli*). Morphological examination of the colonic mucosa is not mandatory for the diagnosis of *C. difficile*-associated disease. This examination may be useful in the differential diagnosis of diarrhea, particularly in symptomatic colonized patients, to rule out other causes (e.g., microscopic colitis or IBD). With normal results on both endoscopy and morphology, *C. difficile* colonization is unlikely to be the cause of diarrhea.*

2.5. Other diagnostic tests

- It is recommended to consult an infectious disease specialist in patients with diarrhea, including in the absence of a response to treatment or the onset of a clinical recurrence after treatment, to rule out another infectious cause of diarrhea.

Grade of recommendation — A
(level of evidence — 5)

Comment. In such cases, it is necessary to exclude an alternative cause of diarrhea, e.g., another infection [26].

3. Treatment, including drug and non-drug therapies, diet therapy, pain relief, medical indications and contraindications to treatment methods

Treatment should be initiated in cases of characteristic clinical presentation of *C. difficile*-associated disease and positive laboratory stool testing. Patients with complicated *C. difficile*-associated disease should be treated in the intensive care unit. Empirical treatment is possible in cases of a characteristic clinical presentation, including fulminant onset and progression of symptoms, but negative results of initial laboratory tests (ELISA) or inability to conduct a diagnostic investigation in time. Empiric therapy increases the risk of false-negative PCR tests 1–3 days after treatment [5, 8]. The choice of drug and treatment regimen depend on the severity of the episode,

the presence of complications, and whether the episode is initial, recurrent, or reinfection (See Section 1.5 “Classification”). Previously, metronidazole was the drug of choice as the first line of treatment, while vancomycin was the second one. However, there is currently sufficient evidence to support the efficacy of vancomycin as a first-line treatment for *C. difficile*-associated disease [32]. In addition to being less effective in achieving clinical remission compared to vancomycin, treatment with metronidazole often requires prolongation of treatment up to 14 days due to a delayed response to treatment, recurrences are more common within 30 days after treatment, and various side effects may be observed, including neurotoxicity with repeated and long-term use [8, 26]. There are two dosage forms of vancomycin, capsules and powder for solution. All international guidelines for the treatment of clostridial infection are based on the use of capsules. There is no significant difference in the efficacy between the two forms, but a higher standard daily dose (1000 mg) is required when using the solution for the treatment of *C. difficile*-associated infection. In addition, vancomycin solution can be used in patients that cannot swallow the capsule. The cost of capsules is a limitation to the prescription [33]. In foreign guidelines, fidaxomicin is the first-line drug in addition to vancomycin, but this drug is not authorized in the Russian Federation. The goal of treatment is clinical improvement, normalization of laboratory parameters, abdominal imaging parameters (if any), endoscopic presentation (in pseudomembranous colitis) and prevention of recurrence of the disease.

3.1. Conservative management

3.1.1. General recommendations

- It is recommended to discontinue antibiotic therapy that is a risk factor (see Section 2.1 “History”) in patients with *C. difficile*-associated disease to improve clinical response to treatment and reduce the risk of recurrence [8, 10].

Grade of recommendation — A
(level of evidence — 3)

Comment. The early discontinuation of antibacterial drugs that have a causal and temporal relationship with the development of clinical symptoms plays a key role in the treatment of clostridial infections of any severity, since their continued use reduces the clinical

response to treatment and increases the risk of recurrence. Discontinuation of antibiotic therapy should be considered in all patients with clostridial infection unless it interferes with the treatment of other diseases and conditions. Patients with mild diarrhea, normal white blood cell and creatinine levels, who do not have risk factors for severe/complicated disease (see Section 7) may be monitored for several days to assess the need for additional treatment in addition to discontinuation of antibiotic therapy [26].

- It is recommended to start therapy for *C. difficile*-associated disease empirically in the presence of characteristic signs of severe/complicated disease or in the absence of the possibility of rapid laboratory testing for timely medical care [10].

Grade of recommendation — C
(level of evidence — 5)

Comment. The decision to prescribe treatment for clostridial infection empirically depends on the severity of the disease and the possibility of rapid laboratory testing. In case of a characteristic clinical presentation, but a negative result of the initial laboratory test (ELISA), empirical treatment is also possible [5]. In other cases, antibiotic therapy for clostridial infection should be started after laboratory confirmation of the diagnosis to prevent unreasonable use of antibiotics and the associated growth of multidrug-resistant strains [10].

- Anti-motility agents (e.g., loperamide) are not recommended in patients with *C. difficile*-associated disease to reduce the risk of complications [8, 10].

Grade of recommendation — C
(level of evidence — 5)

Comment. The use of anti-motility agents is not recommended due to the risk of complications such as colonic dilatation, perforation and, consequently, increased mortality. Despite the fact that, according to the results of several cohort studies, there was no significant increase in the risk of complications with the use of these drugs, and there are no prospective and randomized studies, the international clinical guidelines do not recommend the use of anti-motility agents in patients with *C. difficile*-associated disease [34].

- Rehydration therapy is recommended for patients with clostridial infection in the presence of signs of impaired water and electrolyte balance [8, 26].

**Grade of recommendation — A
(level of evidence — 5)****3.1.2. Mild/moderate
C. difficile-associated disease**

• Vancomycin (125 mg orally 4 times a day for 10 days) is recommended for patients with a first episode of mild *C. difficile*-associated disease as a first-line treatment [5, 10, 24, 27, 32, 35].

**Grade of recommendation — A
(level of evidence — 2)**

Comment. Compared to metronidazole, vancomycin has minimal systemic absorption, so it can be prescribed to pregnant and lactating women. Vancomycin at a standard dose is recommended as a first-line drug for patients with IBD and immunodeficiency conditions. Wherein, in IBD, the duration of therapy should be at least 14 days and it is advisable to consider dose escalation of the current immunosuppressive therapy in the absence of a clinical response to the treatment of clostridial infection [27].

• Metronidazole (500 mg 3 times a day orally for 10–14 days) is recommended for patients with the first episode of mild *C. difficile*-associated disease if first-line vancomycin is not available [8, 10, 24, 26, 27].

**Grade of recommendation — A
(level of evidence — 2)**

Comment. If vancomycin is not available or contraindicated, metronidazole can only be used as an alternative for non-severe disease and absence of risk factors for severe disease (see Section 7).

• Rifaximin is not recommended as first-line treatment for patients with the first episode of mild/moderate *C. difficile*-associated disease.

**Grade of recommendation — C
(level of evidence — 4)**

Comment. Rifaximin has shown *in vitro* antimicrobial activity against *C. difficile* and is therefore considered a possible alternative treatment. In addition, it does not adversely affect the intestinal microbiota, and promotes the growth of *Lactobacillus*. However, there is currently insufficient evidence to recommend it as a first-line alternative for the treatment of patients with mild/moderate clostridial infection. There is also no evidence of its superiority over vancomycin or metronidazole [8]. In one cross-sectional study, rifaximin showed efficacy in this group of patients in the absence

of response to treatment with metronidazole [36]. Further qualitative studies are needed.

3.1.3. Severe *C. difficile*-associated disease

• Vancomycin (125 mg orally 4 times a day for 10 days) is recommended for patients with the first episode of severe *C. difficile*-associated disease as a first-line treatment [5, 8, 10, 26, 27].

**Grade of recommendation — A
(level of evidence — 3)**

• Parenteral metronidazole 500 mg 3 times a day every 8 hours is recommended for patients with a first episode of severe *C. difficile*-associated disease who cannot be prescribed oral vancomycin as an alternative first-line treatment [8, 26].

**Grade of recommendation — A
(level of evidence — 4)**

Comment. In patients with severe clostridial infection and impaired passage through the small intestine, intravenous metronidazole may be prescribed, since the drug is metabolized in the liver and excreted through the biliary tract into the small intestine.

**3.1.4. Complicated
C. difficile-associated disease**

• Vancomycin 500 mg orally or gavage 4 times a day is recommended for patients with complicated clostridial infections as first-line conservative treatment [8, 10, 24, 26, 27, 29].

**Grade of recommendation — A
(level of evidence — 4)**

Comment. High-dose oral vancomycin has long been the drug of choice in patients with complicated clostridial infections, but high-quality evidence is lacking despite this [10]. This is due to, first of all, the lack of well-conducted randomized studies because complicated clostridial infection is rare [29].

• Vancomycin rectally 500 mg in 100 ml saline every 6 hours is recommended in patients with complicated clostridial infection with suspected intestinal obstruction as the first-line conservative treatment [8, 10, 27, 29].

**Grade of recommendation — B
(level of evidence — 5)**

Comment. Vancomycin enemas should be administered with caution due to the risk of colonic perforation [8]. It is also not well understood whether a sufficient amount of the drug passes beyond the left colon with this route of administration [10].

• Metronidazole 500 mg parenterally 3 times a day every 8 hours is recommended in combination with oral or rectal vancomycin in patients with complicated clostridial infection as the first line of conservative treatment [8, 10, 24, 26, 27, 29].

Grade of recommendation — B
(level of evidence — 4)

Comment. *When administered intravenously, metronidazole can reach therapeutic concentrations in the inflamed colonic wall [10].*

3.1.5. Relapsing *C. difficile*-associated disease

It is estimated that a quarter of patients will have at least one more episode after treatment with metronidazole or vancomycin. Subsequent episodes may be due to a previously treated strain (recurrence) or colonization with a new strain (reinfection) if risk factors are present (see Section 2.1. "History"). Regardless of the strain, the treatment will be the same [8, 26]. To determine the optimal treatment approach, it is important to differentiate the first recurrence from a recurrent course with more than one episode [29].

Treatment of the first recurrence of *C. difficile*-associated disease

• Vancomycin is recommended in a taper or pulse regimen (125 mg four times a day for the first 10–14 days, then 125 mg twice a day for 7 days, then 125 mg once a day for 7 days, then 125 mg every 2 or 3 days for 2–8 weeks) in patients with the first recurrence of clostridial infection if the standard course of vancomycin or metronidazole was used to treat the first episode [8, 10, 24, 26, 27, 29].

Grade of recommendation — A
(level of evidence — 4)

Comment. *Several studies have shown that pulse therapy and gradual tapering of vancomycin in patients with recurrent clostridial infections provide treatment efficacy of up to 74 %, especially when a standard course of vancomycin or metronidazole at standard doses for 10 days was used to treat the first episode [8, 37]. Prolonged therapy with vancomycin involves the destruction of dormant vegetative spores during the 10-day course of treatment [8]. Metronidazole is not recommended for the treatment of recurrent clostridial infections because initial and sustained response rates are lower than those for vancomycin [10].*

• The standard 10-day course of vancomycin is recommended in patients with the first

recurrence of clostridial infection if metronidazole was used to treat the first episode [10, 24, 26, 29].

Grade of recommendation — B
(level of evidence — 4)

Treatment of subsequent recurrences of *C. difficile*-associated disease

• Vancomycin is recommended in a taper or pulse regimen for the treatment of patients with recurrent clostridial infection [10, 24, 26].

Grade of recommendation — C
(level of evidence — 4)

• Vancomycin is recommended as a standard 10-day course followed by rifaximin in patients with recurrent clostridial infection [10, 24, 26].

Grade of recommendation — C
(level of evidence — 4)

Comment. *Studies suggest that rifaximin after the main course of treatment may be an effective measure to reduce the frequency of recurrences. According to international guidelines, rifaximin should be prescribed after the main course of treatment at a dose of 400 mg 3 times a day for 20 days. However, the appropriateness, dose and duration remain controversial, especially among patients with a high risk of recurrence [38]. In a small RCT, patients received rifaximin 400 mg three times a day or placebo for 20 days immediately after completion of standard therapy. Recurrences occurred in 5 of 33 (15 %) patients treated with rifaximin and 11 of 35 (31 %) patients treated with placebo ($p = 0.11$) [39]. In another study, a 4-week course of rifaximin (400 mg 3 times a day for 4 weeks, or 400 mg 3 times a day for the first 2 weeks, and then 200 mg 3 times a day for the next 2 weeks) significantly reduced the risk of recurrences over the next 12 weeks [38]. Further high quality studies are needed. One of the potential problems associated with the use of rifaximin is the possibility of resistance [10, 40].*

3.2. Surgical treatment

• Patients with complicated clostridial infection are recommended to consult a surgeon in the absence of clinical improvement or an increase in lactate levels (≥ 2.2 mmol/L) or leukocytosis ($\geq 20 \times 10^9$ /L), to decide on surgical treatment [8, 10].

Grade of recommendation — A
(level of evidence — 5)

Comment. *Surgical intervention affects the prognosis of a patient with complicated*

clostridial infection. Indications for surgical treatment are toxic megacolon, ileus, colonic perforation, peritonitis, septic shock, systemic inflammatory response syndrome. Additional factors associated with increased mortality and serving as markers, additional markers of severity and indications for surgical treatment, are leukocytosis $\geq 25 \times 10^9/L$ and increased lactate levels $\geq 5 \text{ mmol/L}$. Surgical treatment may be considered in cases where all conservative treatments have failed [26]. A systematic review showed that the strongest predictors of postoperative mortality were preoperative intubation, acute renal failure, multiple organ failure, and shock requiring vasopressors. Total colectomy with ileostomy was associated with the lowest mortality and reoperation rates. However, less extensive surgery may be considered for patients with early disease [8].

- Subtotal colectomy with terminal ileostomy and preservation of the sutured rectal stump is recommended in patients with complicated clostridial infection to improve the patient's prognosis [10, 26, 27].

Grade of recommendation — A
(level of evidence — 3)

Comment. Subtotal colectomy is a common surgical option in patients with megacolon, colonic perforation, acute abdomen, and in patients with septic shock and associated multiple organ failure, reducing the risk of mortality [10, 26]. Despite the significant volume (removal of most of the infected colon), this method of surgical treatment allows avoiding anastomosis with the remaining part of the rectum by applying an ileostomy, and in the future, closing the patient's stoma [27].

- A diverting loop ileostomy with intraoperative antegrade colonic lavage and subsequent intraluminal administration of vancomycin is recommended as an alternative method of surgical treatment in patients with complicated clostridial infection to improve treatment outcomes.

Grade of recommendation — C
(level of evidence — 4)

Comment. This alternative method of surgical treatment was proposed not so long ago, in 2011. It includes the creation of a diverting loop ileostomy with intraoperative antegrade colonic lavage followed by 10 days of postoperative intraluminal administration of vancomycin through the ileostomy. This method preserves the colon and is less invasive (performed

laparoscopically). Despite the advantages of this method and its efficacy, further studies are needed to confirm its efficacy [10, 26, 41]. The results of a retrospective study including 3201 patients with *C. difficile*-associated disease were published, among which 613 underwent loop ileostomy and 2408 — subtotal colectomy. There were no significant differences in in-hospital mortality (25.96 % and 31.18 %, respectively; $p = 0.28$) [42]. The decision on the extent of surgical treatment is made by the surgeon.

3.3. Other treatment

Fecal microbiota transplantation (FMT) has gained popularity over the past few decades, thanks to numerous studies, and is now a rapidly growing field of therapy [8]. The fundamental concept is the delivery of normal fecal microbiota from the stool of a healthy donor to the intestine of a patient with clostridial infection to manage the imbalance of the intestinal microbiota. Since its first description in 1983, numerous systematic reviews and RCTs have demonstrated the efficacy and safety of this treatment in patients with recurrent clostridial infection. FMT was included in earlier international clinical practice guidelines for the treatment of recurrent clostridial infection, and it is also expected to be effective in patients with severe/complicated disease who do not respond to standard therapy when surgical treatment is not possible [10, 24, 27]. Several methods of delivery of samples from a healthy donor have been studied: through a tube (oro-, nasogastric, nasoduodenal, nasojejunal, colonic transendoscopic), infusion using colonoscopy, enemas and oral capsules with frozen or freeze-dried microbiota. All methods have been shown to be safe and have similar success rates (between 82 and 95 % after one or two transplants in most studies) [8]. However, it is not entirely clear from published studies, which route of administration is more effective, as there are no randomized studies. Each of the methods has its own advantages and disadvantages. For example, low cost and no need for sedation, but inability to examine the colonic mucosa when using a probe, need for sedation and invasiveness, but possibility of examining the colonic mucosa and taking a biopsy when using colonoscopy, simple use and non-invasiveness, but inability to reach the left sections when using enemas, and non-invasiveness and

simple use, but high cost when using capsules. As a rule, FMT is well tolerated by patients and has minimal short-term side effects, such as abdominal pain, bloating, diarrhea, and constipation. More severe complications associated with transplantation of stool samples have also been described, such as colonic microperforation, gastrointestinal bleeding (GIB), and peritonitis [43]. The long-term consequences of altering the intestinal microbiota through FMT are unknown. Given the diversity of donor stool sources, there may be an increase in bacteria of currently unknown significance and non-culturable bacteria that may lead to unexpected health consequences for the recipient. In 2012, a study was conducted involving 77 patients, in which FMT recipients were followed up for 3 months. Four of them (5 %) developed autoimmune or rheumatic diseases. However, there is no reliable evidence of a causal relationship between FMT and the development of these diseases, which requires further study [44]. The difficulty of performing FMT lies in the lack of standardized protocols for screening and stool sampling, as well as standardized criteria for selecting donors. Careful selection of a healthy donor is a critical step in preventing iatrogenic transmission of infections [8, 43]. Phase III clinical studies are currently ongoing to further investigate the efficacy and feasibility of using FMT as a first-line treatment for clostridial infection [8].

- FMT is recommended for patients with severe and complicated clostridial infection, refractoriness to conservative treatment and impossibility of surgical treatment [27].

Grade of recommendation — A
(level of evidence — 4)

Comment. There is strong evidence to consider FMT for the treatment of patients with severe/complicated clostridial infection who do not respond to standard treatment (within 48–72 hours) and who are not candidates for surgical treatment. FMT can not only increase the efficacy of treatment, but also reduce the risk of colectomy, sepsis and mortality. A single FMT treatment may not be sufficient to achieve a sustained response, several consecutive treatments in short sequence (every 3–5 days) are required. There is currently no clear protocol on FMT regimens. There are clinical data on the possibility of resuming vancomycin therapy between FMT procedures

in this group of patients to increase the efficacy of treatment or performing FMT early after diagnosis while receiving the main course of treatment [27].

- FMT is recommended for patients with recurrent clostridial infection with failure of standard antibiotic therapy [8, 10, 24, 26, 27, 29, 45].

Grade of recommendation — A
(level of evidence — 4)

Comment. Clinical studies in patients with recurrent clostridial infection have shown a significant imbalance of intestinal microbiota diversity as well as the relative size of the bacterial population [10]. FMT has been shown to be superior to standard antibiotic therapy in terms of clinical efficacy and lower recurrence rate [8, 46, 47]. In addition, FMT after vancomycin treatment is superior to vancomycin alone in patients with recurrent clostridial infection [8, 47].

- FMT is recommended for patients with a second (or more) episode of clostridial infection to reduce the risk of subsequent recurrences [10, 27].

Grade of recommendation — A
(level of evidence — 3)

- FMT is recommended for patients with a second (or more) episode of clostridial infection, using a colonoscope or capsules with frozen or freeze-dried microbiota [27].

Grade of recommendation — A
(level of evidence — 3)

- FMT is recommended for patients with a second (or more) episode of clostridial infection using enemas when other methods of administration are not available to improve the efficacy of the procedure [27].

Grade of recommendation — B
(level of evidence — 4)

- Repeated FMT is recommended for patients with recurrent clostridial infection within 8 weeks of the first transplant to improve the efficacy of the procedure and reduce the risk of subsequent recurrences [27].

Grade of recommendation — B
(level of evidence — 4)

3.4. Treatment efficacy assessment

- Assessment of clinical symptoms and, if there are changes, of laboratory and investigation results in patients treated for *C. difficile*-associated disease is recommended to determine the efficacy of treatment [26].

**Grade of recommendation — A
(level of evidence — 4)**

Comment. Depending on the severity of clostridial infection, the assessment of the efficacy of treatment includes an assessment of the clinical symptom changes (normalization of stool, relief of abdominal pain, normalization of body temperature, disappearance of signs of dehydration), laboratory results (in particular, normalization of the level of white blood cells), additional investigation results (thickness of the wall and lumen of the intestine according to ultrasound, MSCT). Non-specific fecal markers of inflammation (calprotectin, lactoferrin) are not suitable as a tool to assess the efficacy of treatment.

- It is not recommended to retest stool specimens in patients treated for clostridial infection in order to assess the efficacy of treatment to prevent false positive results.

**Grade of recommendation — A
(level of evidence — 3)**

Comment. Retesting as a test of treatment efficacy is not recommended due to the high risk of false positives, very low diagnostic value (2 %), and the potential for unnecessary long-term treatment, as more than 60 % of patients may have positive results even after treatment because of asymptomatic shedding of spores for 6 weeks [5, 8, 10, 25]. Also, in about 25 % of cases, after treatment of clostridial infection, post-infectious irritable bowel syndrome, diarrhea-predominant or mixed variant, may develop [27].

4. Medical rehabilitation and health resort treatment, medical indications and contraindications to medical rehabilitation methods, including those based on the use of natural curative resources

Medical rehabilitation measures are aimed at preventing complications and adverse sequelae of surgical treatment.

With mild or moderate disease, treatment is carried out on an outpatient basis. Severe or complicated disease requires hospitalization in a hospital with an intensive care unit.

In patients who require surgical treatment of *C. difficile*-associated disease, rehabilitation in three stages is possible.

Stage 1 — early rehabilitation, carried out immediately after surgical treatment from day 2 to day 14. The main task of stage 1 of rehabilitation is to restore the normal functioning of

the gastrointestinal tract after surgery. It is at this stage that urination disorders are most often detected and should be managed. Importance is also assigned to the control of homeostasis, measures aimed at the healing of postoperative wounds, relief of postoperative pain syndrome and activation of the patient. During this period, a complete blood count, blood chemistry tests, coagulation tests, and urinalysis are performed.

Stage 2 of rehabilitation begins after 15 days and continues as needed further on. It is aimed at the final healing of postoperative wounds with control over the activity of the gastrointestinal tract and other body systems. This stage can be carried out both on an outpatient basis and in a day or round-the-clock hospital setting.

Stage 3 of rehabilitation is carried out in the late rehabilitation period in patients before reconstructive surgery. The main task at this stage is to compensate the gastrointestinal function, measures aimed at identifying and improving the function of the rectal sphincters.

5. Prevention and clinical observation, medical indications and contraindications to the use of prevention methods

Preventive measures include prevention of *C. difficile*-associated disease (primary prevention) and the recurrence of the disease (secondary prevention). Considering that *C. difficile* infection is the most common hospital-acquired infection, and *C. difficile* spores are highly contagious, preventive measures are also taken against the spread of infection in a hospital with an established case of the disease.

5.1. Prevention of *C. difficile*-associated disease (primary prevention)

- Rational use of antibiotic therapy is recommended strictly according to indications to reduce the risk of *C. difficile*-associated disease [10, 25–27, 48].

**Grade of recommendation — A
(level of evidence — 3)**

Comment. The rational use of antibiotics, namely, minimizing the frequency, duration and amount of drugs taken, is the main measure for the prevention of clostridial infection. The main aspects of such use of antibiotics include prescribing them for the treatment of bacterial, but not viral infections, strictly for indications, taking the antibiotic by the patient exactly as prescribed by the attending physician, and

also it is preferable to choose an antibacterial drug that acts on a specific microorganism or group of microorganisms rather than a broad spectrum antibiotic [49]. In particular, the use of fluoroquinolones, clindamycin and cephalosporins should be limited [10]. It has also been shown that the incidence of clostridial infection increases together with an increase in the amount of antibiotics taken. The rational use of antibiotics has been proven to be the most cost-effective method to significantly reduce the incidence of clostridial infection [8].

- The addition of the probiotic strain *Saccharomyces boulardii* CNCM I-745 to patients receiving antibacterial drugs is recommended for the prevention of *C. difficile*-associated disease [50].

Grade of recommendation — B
(level of evidence — 2)

Comment. An earlier meta-analysis and systematic review showed a significant reduction in the risk of developing *C. difficile*-associated diarrhea with antibiotics, especially in hospitalized patients, when using probiotic strains of *Lactobacillus*, *Saccharomyces* and a mixture of probiotic strains [51]. A recent meta-analysis evaluated 19 RCTs including 6261 patients treated with *Saccharomyces boulardii*, *Lactobacillus* spp., *Bifidobacterium* spp., and *Streptococcus* spp., of which the probiotic strains of *Lactobacillus* spp., *Bifidobacterium* spp., and *Streptococcus* spp. were used alone or in combination. The study showed promising results with a > 50 % reduction in clostridial infection in patients receiving probiotics concomitantly with antibiotics (without specifying the probiotic strain). Moreover, the efficacy was higher when probiotics were initiated closer to the first dose of the antibiotic [52].

Saccharomyces boulardii (*Saccharomyces boulardii* CNCM I-745) has a direct inhibitory effect on *C. difficile* toxins. This probiotic strain has been shown to inhibit the adhesion of *C. difficile* toxin A to epithelial cells by producing a protease that inactivates the receptor for *C. difficile* toxin A, prevents *C. difficile* toxin A biofilm formation (in vitro), and stimulates the production of antibodies against *C. difficile* toxin A. In addition, *Saccharomyces boulardii* CNCM I-745 helps to normalize the composition of the intestinal microbiota, increase the production of SCFAs, reduce the inflammatory response by inhibiting the production of the pro-inflammatory cytokine IL-8 and suppressing the nuclear transcription factor κ B

(NF- κ B), as well as the formation of secondary bile acids, capable of inhibiting vegetative forms of *C. difficile* [53–56]. *Saccharomyces boulardii* is stable over a wide pH range, including low values, when exposed to bile salts and gastrointestinal enzymes, and is also resistant to antibacterial drugs, as it is a fungus (yeast) [57].

Results of a large meta-analysis confirm the positive effect of *Saccharomyces boulardii* in preventing the first episode of *C. difficile*-associated disease [58]. In a recent large cohort study of 8763 hospitalized patients, patients who received *Saccharomyces boulardii* concomitantly with antibiotics were shown to have a lower risk of developing clostridial infection (OR = 0.57, 95 % CI: 0.33–0.96), compared with patients who did not receive *Saccharomyces boulardii* ($p = 0.035$), while the efficacy was significantly higher with early administration of *Saccharomyces boulardii* [59].

In the Russian Federation, the probiotic with the strain *Saccharomyces boulardii* CNCM I-745 is authorized as a medicinal product (according to the State Register of Medicinal Products, <https://grls.rosminzdrav.ru/Default.aspx>). It is included in the Clinical Practice Guidelines of the Scientific Community for the Promotion of Clinical Research of the Human Microbiome (SCPCRHM) and the Russian Gastroenterological Association (RGA) on the use of probiotics, prebiotics, synbiotics and functional foods enriched with them for the treatment and prevention of gastroenterological diseases in children and adults as a drug for prevention of antibiotic-associated diarrhea and *C. difficile*-associated disease [50]. The recommended dose of *Saccharomyces boulardii* CNCM I-745 is 5×10^9 CFU 2 times a day. The limitation of taking this probiotic is the possible fungemia in immunocompromised patients, as well as in patients with CVC (central venous catheter) [57].

- It is not recommended to discontinue PPI treatment in patients with indications in order to reduce the risk of clostridial infection [10, 25].

Comment. Despite clinical data suggesting an increased risk of developing *C. difficile* with PPIs, the data heterogeneity, the role of confounding factors, the lack of dose-response relationships, and other methodological considerations significantly limit their practical application. As with any drug, PPIs should be prescribed strictly if there are indications,

especially in patients at high risk of developing clostridial infection.

5.2. Prevention of recurrence of *C. difficile*-associated disease (secondary prevention)

- It is recommended to choose an antibacterial drug associated with a lower risk of developing *C. difficile*-associated disease for patients who have had a successful treatment of the first episode with vancomycin or metronidazole, but require further treatment with systemic antibacterial drugs, to prevent further recurrences [5].

Grade of recommendation — C (level of evidence — 5)

Comment. The use of additional antibiotics (other than those used to treat clostridial infection) is associated with an increased risk of prolonged diarrhea and recurrence of clostridial infection and should therefore be discontinued. However, if such therapy is necessary, it is preferable to choose antibiotics that are associated with a lower risk of clostridial infection, such as macrolides, aminoglycosides, sulfonamides, vancomycin, or tetracyclines.

- Empiric low-dose oral vancomycin is recommended in patients treated for clostridial infection, including those with recurrent clostridial infection who are at risk for further recurrence but who require continued systemic antibiotics to prevent further recurrence of clostridial infection [27, 60, 61].

Grade of recommendation — B (level of evidence — 2)

Comment. Patients who require further systemic antibiotics immediately or shortly after treatment for clostridial infection are at increased risk of clostridial infection recurrence and complications [10]. In such cases, prolongation of vancomycin treatment or its administration empirically, but at lower doses (e.g., 125 mg per day), is suggested. However, studies are scarce and their data are contradictory. In one retrospective study, extending the course of vancomycin for more than 10–14 days did not show a beneficial effect on reducing the risk of recurrence [62]. Two retrospective cohort studies have been published that investigated the risk of recurrence of clostridial infection after successful treatment of the first episode in patients receiving subsequent treatment with antibiotics in combination with or without vancomycin, the dose and regimen of which differed [63, 64]. Both studies showed

a reduced risk of recurrence with empiric use of vancomycin in combination with antibiotics for 90 days or with readmission within 1–22 months after treatment of an episode of *C. difficile*-associated disease. One study showed a reduced risk in patients with recurrent clostridial infection, but not in patients with a history of a single episode [64]. Currently, there are no prospective randomized studies of secondary prevention of clostridial infection that could serve as recommendations, but the use of low-dose vancomycin in combination with systemic antibiotics may be appropriate. Factors influencing the need for such prevention may include the time between treatment of an episode of clostridial infection and the need for systemic antibiotics, the number and severity of previous episodes and patient comorbidities [10].

- The addition of the probiotic strain *Saccharomyces boulardii* CNCM I-745 to the main course of treatment of recurrent clostridial infection is recommended to reduce the risk of subsequent recurrence [27, 45].

Grade of recommendation — C (level of evidence — 2)

Comment. Based on systematic reviews and meta-analyses, *Saccharomyces boulardii* CNCM I-745 showed good results in preventing further recurrence in patients with recurrent clostridial infection when added to the main course of treatment [45, 65, 66]. The recommended dose of *Saccharomyces boulardii* CNCM I-745 is 5×10^9 CFU 2 times a day.

- The addition of the prebiotic oligofructose to the main course of treatment of recurrent clostridial infection is recommended to reduce the risk of subsequent recurrence [45].

Grade of recommendation — C (level of evidence — 3)

Comment. The recommended dose of oligofructose is 4 g 3 times a day.

- Bezlotoxumab is recommended in combination with the standard course of treatment in patients with recurrent clostridial infection or presence of risk factors for recurrent clostridial infection to reduce the risk of subsequent recurrence [24].

Grade of recommendation — C (level of evidence — 2)

Comment. Bezlotoxumab is a fully humanized monoclonal antibody that neutralizes *C. difficile* toxin B. The drug was approved by the FDA (Food and Drug Administration,

USA) in 2016 to reduce the risk of recurrence in high-risk patients treated for clostridial infection [8, 26]. Also, the drug is authorized in the Russian Federation (according to the State Register of Medicinal Products, <https://grls.rosminzdrav.ru/Default.aspx>). Two phase III multicenter, placebo-controlled clinical studies showed that patients treated with bezlotoxumab experienced a significant reduction in the recurrence rate of *C. difficile*-associated disease after 12 weeks of treatment. Although the majority of patients received the drug within 6 days of starting standard antibiotic treatment, there was no difference in the recurrence rate of *C. difficile*-associated disease depending on the time of bezlotoxumab infusion [67]. The drug is administered at a dose of 10 mg/kg as an infusion over 60 minutes without the need for dose adjustment in renal or hepatic insufficiency. Despite good tolerability, adverse infusion-related reactions were noted in 10 % of patients, the drug should be used with caution in patients with cardiac insufficiency [8]. The results of studies have shown that the use of bezlotoxumab not only reduces the risk of recurrence, but also the need for FMT (fecal microbiota transplantation), helps to reduce readmissions within 30 days in patients with one or more risk factors for recurrence and reduce the duration of hospitalizations [68, 69]. The efficacy of this drug in reducing the risk of recurrence of clostridial infection does not depend on the choice of antibacterial drug for the standard course of treatment, the time of diagnosis and the time of infusion [70]. Despite the promising properties of the drug, further studies are needed to compare with FMT and the standard course of antibiotic therapy in terms of efficacy, safety and cost [8, 29].

- Discontinuation of PPI treatment in patients with clostridial infection in order to reduce the risk of recurrence is not recommended if there are indications for their use [27].

Grade of recommendation — A
(level of evidence — 4)

Comment. Patients with clostridial infection should be evaluated for the need for antisecretory therapy. Therapy must be continued if indicated.

5.3. Prevention of the spread of *C. difficile* in the hospital

- It is recommended to place patients diagnosed with clostridial infection in separate rooms with a separate toilet to prevent further

transmission of the infection in the hospital [5, 10, 25, 26].

Grade of recommendation — A
(level of evidence — 3)

Comment. In case of a limited number of single rooms with a separate toilet, preference should be given to patients with fecal incontinence. In addition, hand washing and showering should be available to reduce the number of spores on the patient's skin. If accommodation in a separate ward is not possible, contact between patients should be avoided (e.g., reading the same books/magazines, using the same phone), the patient should have separate furniture.

- It is recommended that *C. difficile*-infected patients be grouped and housed separately from patients infected with other multidrug-resistant organisms (e.g., methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococcus*) to prevent further hospital cross-infection [10, 25].

Grade of recommendation — A
(level of evidence — 3)

- The use of gloves and gowns by healthcare workers is recommended when entering the room and providing care to a patient with *C. difficile*-associated disease to prevent the risk of further spread of infection [5, 10, 25–27].

Grade of recommendation — A
(level of evidence — 3)

Comment. Wearing gloves in combination with hand hygiene should reduce the concentration of *C. difficile* on the hands of healthcare personnel. Care must also be taken to prevent contamination of hands when removing gloves. The use of gowns, preferably disposable, has been recommended because of the potential for *C. difficile* contamination of healthcare worker uniforms and the high quality of evidence about reducing the transmission of other multidrug-resistant enteric organisms.

- It is recommended that preventive measures be taken when contacting a patient with suspected clostridial infection until laboratory results are available [10, 25].

Grade of recommendation — A
(level of evidence — 3)

- It is recommended to continue to take precautionary measures for contact with a patient diagnosed with *C. difficile* infection for at least 48 hours after diarrhea has been stopped [10].

Grade of recommendation — C
(level of evidence — 5)

- It is recommended to practice hand hygiene after contact with a patient with clostridial infection or after removing gloves to prevent the risk of further spread of the infection [5, 10, 25–27].

Grade of recommendation — A
(level of evidence — 3)

Comment. Hygiene is considered the main measure to prevent the spread of infection and includes washing hands under running water with soap or an alcohol-based cleaner. However, *C. difficile* spores are highly resistant to alcohol, so during an outbreak of clostridium infection or if contact with patient stool specimens is possible, hand washing with soap and water before and after patient care should be preferred. An antiseptic containing chlorhexidine has also been shown to be more effective than soap in removing *C. difficile* spores from the hands of medical personnel. However, no well-conducted clinical studies have been conducted. It is believed that the degree of contamination of surfaces with *C. difficile* spores in a medical facility correlates with the degree of contamination of the hands of healthcare personnel.

- Thorough cleaning and disinfection of reusable medical equipment after use in a patient with clostridial infection is recommended to prevent the spread of infection [10, 25, 27].

Grade of recommendation — A
(level of evidence — 3)

Comment. It is recommended to use disposable medical equipment whenever possible. Reusable medical equipment should be placed in the patient's room. Cleaning and disinfection of reusable equipment should be carried out after each contact with a patient with clostridial infection. For this purpose, it is preferable to use a sporicidal disinfectant that is compatible with the equipment used.

- It is recommended to clean the ward with a sporicidal agent for outbreaks of clostridial infection in a hospital or for repeated cases in the same ward [5, 10, 25].

Grade of recommendation — C
(level of evidence — 5)

Comment. Daily cleaning with a sporicidal agent should be considered in conjunction with other measures to prevent clostridial infection during outbreaks or when there is evidence of recurrence in the same area. Chlorine-based solutions are generally recommended for environmental cleaning, with 1000 ppm chlorine being effective and 5000 ppm being the best

choice. After discharge, the patient's room must be thoroughly disinfected.

6. Organization of medical care

Indications for hospitalization: since the disease is acute, patients are hospitalized in a round-the-clock hospital on an emergency basis in the presence of the following:

- 1) intolerance to oral medications for treatment;
- 2) dehydration;
- 3) presence of risk factors for severe/complicated *C. difficile*-associated disease;
- 4) hospitalization or transfer to the intensive care unit is indicated for severe disease or complications (septic shock, sepsis, toxic megacolon, peritonitis, severe dehydration with hypotension and dysfunction of target organs).

Indications for discharge of the patient from the hospital:

- 1) reduced severity of clinical symptoms (normalization of stool, body temperature, relief of abdominal pain);
- 2) normalization of laboratory values;
- 3) normalization of investigation results, including imaging of the abdominal organs (colon wall thickness) and endoscopic examination (disappearance of pseudomembranes according to colonoscopy in pseudomembranous colitis);
- 4) normalization of the function of other organs and systems involved in the pathological process in complicated disease (e.g., kidneys in case of development of renal failure, etc.);
- 5) refusal of the patient or his legal representative to receive medical care in a round-the-clock hospital;
- 6) the need to transfer the patient to another healthcare facility with the relevant profile of medical care; the conclusion on the advisability of transferring the patient to a specialized healthcare facility is made after a preliminary consultation on the provided medical records and/or a preliminary examination of the patient by doctors of the healthcare facility to which the transfer is planned.

7. Additional information (including factors that affect the outcome of the disease or condition)

Prognostic factors for severe/complicated *C. difficile*-associated disease include: advanced age (≥ 65 years), leukocytosis ($> 15 \times 10^9/\text{L}$), hypoalbuminemia (serum albumin $< 30 \text{ g/L}$) elevated serum creatinine ($> 1.5 \text{ mg/dL}$ or more than 1.5 times baseline creatinine or 25 % decrease in glomerular filtration rate from baseline),

infection with the hypervirulent strain NAP1/B1/027. It is important to note here that among patients with malignant neoplasms, and hematological diseases, the leukocytes count and

creatinine level may tend to decrease. In this regard, not all of the above factors may be applicable to this group of patients and a personalized approach is needed [10, 29].

Appendix A. Clinical guidelines development methodology

Criteria for assessing the quality of medical care

No. №	Quality assessment criteria Критерии оценки качества	Performed (Yes/No) Оценка выполнения (да/нет)
1	Laboratory tests for <i>C. difficile</i> infection in a patient with diarrhea performed (at least 2) Проведены лабораторные тесты на наличие инфекции <i>C. difficile</i> у пациента с диареей (не менее 2-х)	Yes/No Да/нет
2	Complete blood count, blood chemistry tests (total protein, albumin, creatinine, alanine aminotransferase, aspartate aminotransferase, glucose, sodium, potassium, C-reactive protein) performed Проведены общий (клинический) анализ крови, биохимический общетерапевтический анализ крови (общий белок, альбумин, креатинин, аланинаминотрансфераза, аспаратаминотрансфераза, глюкоза, натрий, калий, С-реактивный белок)	Yes/No Да/нет
3	Abdominal ultrasonography performed Выполнено УЗИ органов брюшной полости	Yes/No Да/нет
4	Abdominal MSCT with intravenous contrast-enhancement performed in case of severe disease Выполнено МСКТ органов брюшной полости с в/в контрастированием при тяжелом течении заболевания	Yes/No Да/нет
5	Colonoscopy with biopsy of the colon mucosa performed (if indicated) Выполнена колоноскопия с биопсией слизистой толстой кишки (при наличии показаний)	Yes/No Да/нет
6	Morphological examination of biopsies of the colon mucosa performed (if indicated) Выполнено морфологическое исследование биоптатов слизистой толстой кишки (при наличии показаний)	Yes/No Да/нет
7	Plain abdominal radiography performed (if indicated) Выполнена обзорная рентгенография органов брюшной полости (при наличии показаний)	Yes/No Да/нет
8	Vancomycin prescribed Назначен Ванкомицин	Yes/No Да/нет
9	Metronidazole prescribed Назначен Метронидазол	Yes/No Да/нет
10	Adequate correction of water and electrolyte balance prescribed Назначена адекватная коррекция водно-электролитного баланса	Yes/No Да/нет
11	Surgeon consulted (if indicated) Проведена консультация хирурга (при наличии показаний)	Yes/No Да/нет
12	Measures taken to prevent the spread of <i>C. difficile</i> infection in the hospital Проведены меры профилактики распространения инфекции <i>C. difficile</i> в стационаре	Yes/No Да/нет

The proposed recommendations are intended to bring modern ideas about the etiology and pathogenesis of *C. difficile*-associated disease to practitioners, to introduce the currently used algorithms for diagnosis, assessment of severity, methods of prevention and treatment.

Target audience of these clinical guidelines:

- 1) gastroenterologists;
- 2) internal medicine specialists;
- 3) infectionists;
- 4) general practitioners (family doctors);
- 5) coloproctologists;
- 6) surgeons;
- 7) endoscopists.

In the proposed clinical guidelines, all information is ranked according to the level of reliability (evidence) depending on the number and quality of studies on this disease.

Table 1 (Appendix A). Grading of Level of Evidence (GLE for diagnostic methods (diagnostic interventions)
Таблица 1 (Приложение А). Шкала оценки уровней достоверности доказательств (УДД) для методов диагностики (диагностических вмешательств)

GLE УДД	Explanation Расшифровка
1	Systematic reviews of studies with reference method control or systematic review of randomized clinical trials using meta-analysis Систематические обзоры исследований с контролем референсным методом или систематический обзор рандомизированных клинических исследований с применением метаанализа
2	Individual studies with reference method control or individual randomized clinical trials and systematic reviews of studies of any design, excluding randomized clinical trials, using meta-analysis Отдельные исследования с контролем референсным методом или отдельные рандомизированные клинические исследования и систематические обзоры исследований любого дизайна, за исключением рандомизированных клинических исследований, с применением метаанализа
3	Studies without sequential control with a reference method or studies with a reference method that is not independent of the study method or non-randomized comparative studies, including cohort studies Исследования без последовательного контроля референсным методом или исследования с референсным методом, не являющимся независимым от исследуемого метода, или нерандомизированные сравнительные исследования, в том числе когортные исследования
4	Non-comparative studies, case reports Несравнительные исследования, описание клинического случая
5	There is only a rationale for the mechanism of action or expert opinion Имеется лишь обоснование механизма действия или мнение экспертов

Table 2 (Appendix A). Grading of Levels of Evidence (GLE) for prevention, treatment and rehabilitation methods (preventive, curative, rehabilitative interventions)

Таблица 2 (Приложение А). Шкала оценки уровней достоверности доказательств (УДД) для методов профилактики, лечения и реабилитации (профилактических, лечебных, реабилитационных вмешательств)

GLE УДД	Explanation Расшифровка
1	Systematic review of RCTs using meta-analysis Систематический обзор РКИ с применением метаанализа
2	Individual RCTs and systematic reviews of studies of any design, excluding RCTs, using meta-analysis Отдельные РКИ и систематические обзоры исследований любого дизайна, за исключением РКИ, с применением метаанализа
3	Non-randomized comparative studies, including cohort studies Нерандомизированные сравнительные исследования, в том числе когортные исследования
4	Non-comparative studies, case reports or case series, case-control studies Несравнительные исследования, описание клинического случая или серии случаев, исследования «случай — контроль»
5	There is only a rationale for the mechanism of action of the intervention (preclinical studies) or expert opinion Имеется лишь обоснование механизма действия вмешательства (доклинические исследования) или мнение экспертов

Таблица 3 (Приложение А). Шкала оценки уровней убедительности рекомендаций (УУР) для методов профилактики, диагностики, лечения и реабилитации (профилактических, диагностических, лечебных, реабилитационных вмешательств)

Table 3 (Appendix A). Grading of Recommendations (GoR) for methods of prevention, diagnosis, treatment and rehabilitation (preventive, diagnostic, therapeutic, rehabilitation interventions)

GoR УУР	Explanation Расшифровка
A	Strong recommendation (all efficacy measures (outcomes) considered are important, all studies are of high or satisfactory methodological quality, their conclusions on the outcomes of interest are consistent) Сильная рекомендация (все рассматриваемые критерии эффективности (исходы) являются важными, все исследования имеют высокое или удовлетворительное методологическое качество, их выводы по интересующим исходам являются согласованными)
B	Conditional recommendation (not all efficacy measures (outcomes) considered are important, not all studies are of high or satisfactory methodological quality, and/or their findings are inconsistent for the outcomes of interest) Условная рекомендация (не все рассматриваемые критерии эффективности (исходы) являются важными, не все исследования имеют высокое или удовлетворительное методологическое качество и/или их выводы по интересующим исходам не являются согласованными)
C	Weak recommendation (lack of good quality evidence (all efficacy measures (outcomes) considered are unimportant, all studies are of low methodological quality and their conclusions are inconsistent for the outcomes of interest) Слабая рекомендация (отсутствие доказательств надлежащего качества (все рассматриваемые критерии эффективности (исходы) являются неважными, все исследования имеют низкое методологическое качество и их выводы по интересующим исходам не являются согласованными)

Procedure for updating clinical practice guidelines

The mechanism for updating clinical practice guidelines envisages their systematic updating at least once every three years, as well as when new data appear from the point of view of evidence-based medicine on the diagnosis, treatment, prevention and rehabilitation of specific diseases, the presence of reasonable supplements/observations to previously approved CPGs, but not more than once every 6 months.

Reference materials, including compliance with therapeutic indications and contraindications, methods of administration and doses of medicinal products, instructions for use of the medicinal product

These clinical practice guidelines have been developed taking into account the following legal documents:

1. Article 76 of the Federal Law of the Russian Federation No. 323-FZ of November 21, 2011 On the fundamentals of Protecting the Health of Citizens in the Russian Federation, regarding the development and approval of clinical practice guidelines (treatment protocols) on the provision of medical care by medical professional non-profit organizations;
2. Order No. 906n of November 12, 2012 On Approval of the Procedure for Providing Gastroenterological Medical Care to the Population;
3. Order of the Ministry of Health of the Russian Federation No. 203n of May 10, 2017 On Approval of Criteria for Assessing the Quality of Medical Care;
4. Order of the Ministry of Health and Social Development of the Russian Federation No. 1024n of December 17, 2015 On the Classification and Criteria Used in the Implementation of Medical and Social Expert Evaluation of Citizens by Federal State Institutions of Medical and Social Expert Evaluation.

Appendix B. Doctor's action algorithms

Algorithms for laboratory examination of stool samples for the diagnosis of *C. difficile*-associated disease

Figure 1.

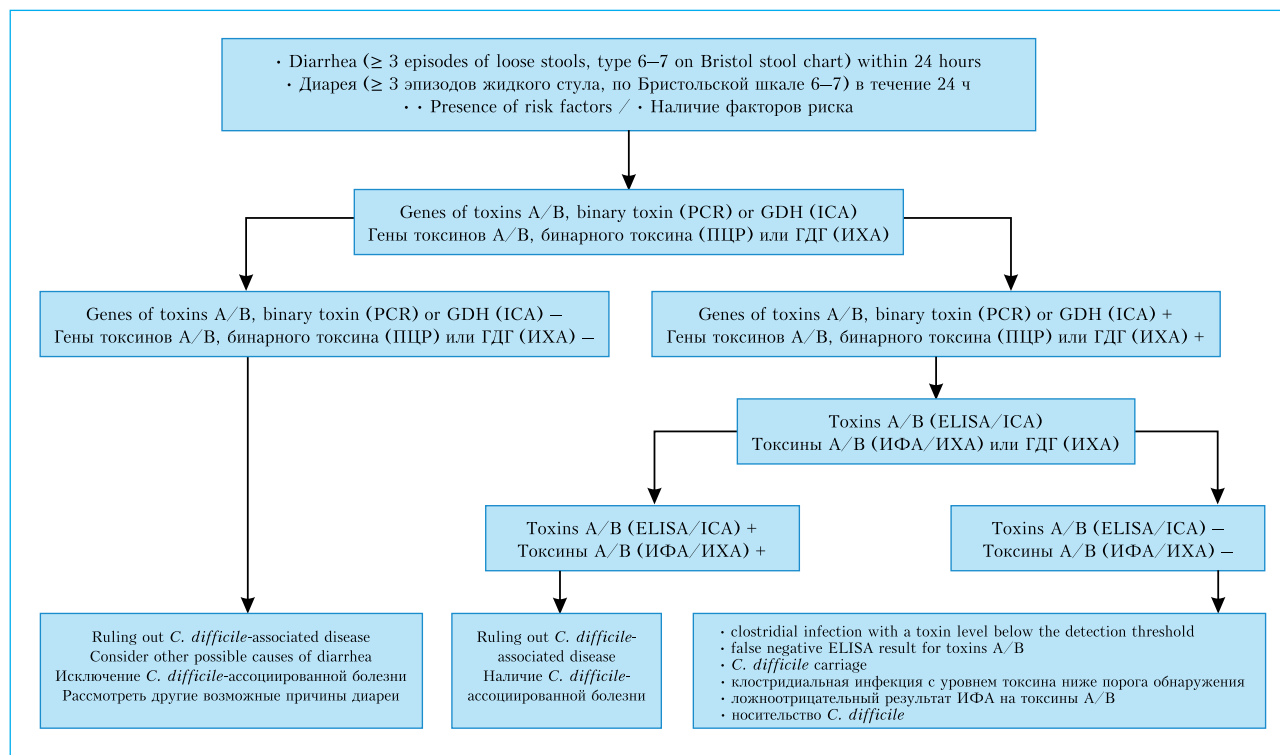
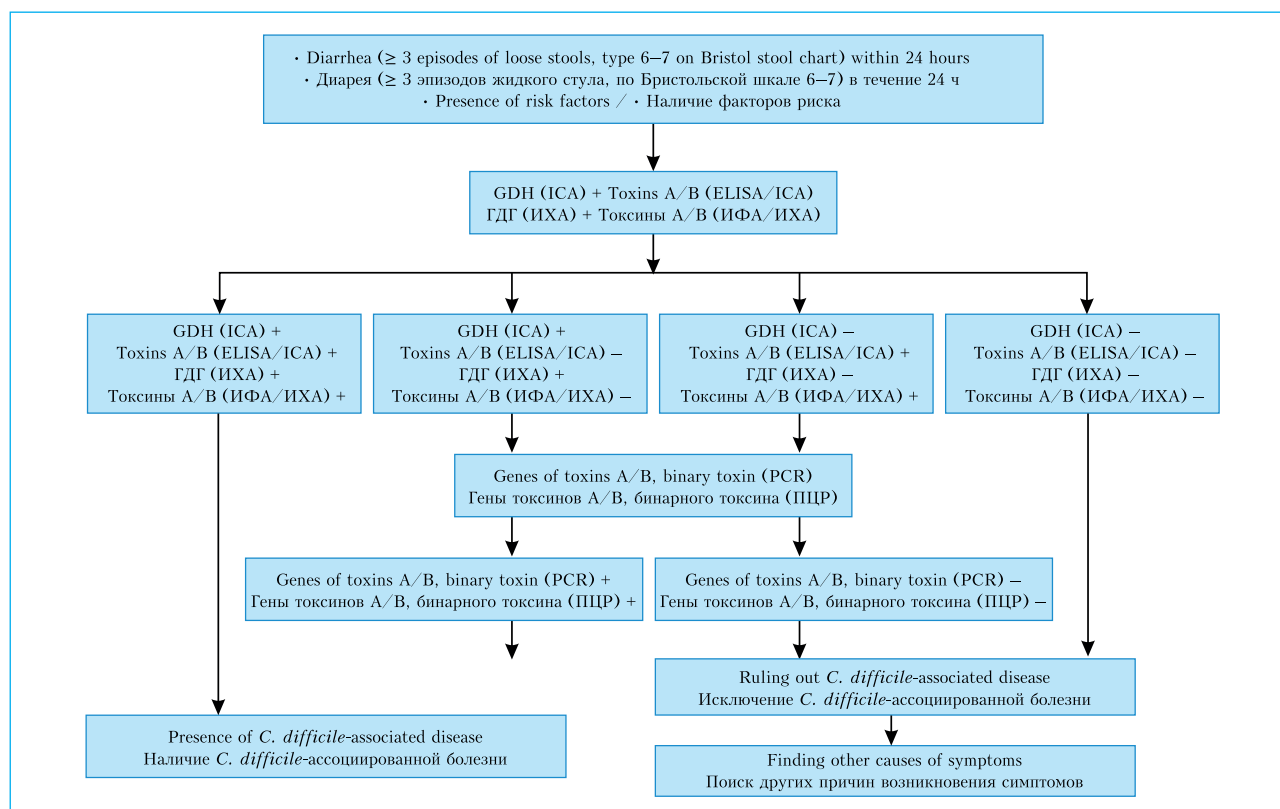


Figure 2.



Appendix C. Information for the patient

Dear Patient! Small numbers of *C. difficile* can comprise the normal microbiota in the intestines of a healthy individual. Spores of this bacterium can be found on any surface and enter the gastrointestinal tract by swallowing. Therefore, the infection can be prevented through proper personal hygiene (e.g., washing hands before eating, especially after visiting healthcare facilities, not eating unwashed foods). But even the presence of bacteria in the intestines or the entry of its spores into the gastrointestinal tract will not cause the disease if there are no factors contributing to their excessive growth. The use of antibiotics is the main factor in changing the normal composition of the microbiota. It is extremely important to take antibiotics when really necessary and only as prescribed by a doctor, just like other medicinal products. If you have diarrhea, then you should consult a doctor to decide on the necessary additional examinations and receive recommendations for treatment. Do not self-medicate. Timely and appropriate treatment will ensure complete recovery from the disease and allow avoiding complications.

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