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Severe Clostridium difficile infection after liver and kidney transplantation

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Recent statistics have shown increased rates of morbidity and mortality from Clostridium difficile infection worldwide. This problem is mainly typical for surgical patients and is associated with an antibiotic therapy and a prolonged hospital stay. Recipients of solid organs are at a high risk of developing severe forms of C. difficile infection due to immunosupression. Existing recommendations for the treatment of C. difficile infection are based on the severity of the disease and do not consider patients after liver transplantation. The aim of this work is to determine an actual tactics for the diagnosis and treatment of C. difficile in organ recipients in clinical practice.

Keywords: Clostridium difficile, pseudomembranous colitis, solid organ transplantation

AAD, antibiotic-associated diarrhea

CDI, Clostridium difficile infection (clostridial infection)

INTRODUCTION

Antibacterial therapy is an essential measure for the prevention and treatment of infectious complications in a surgical patient population. The progress of pharmacology in the synthesis of new therapeutic agents has provided clinicians of today with an arsenal of powerful broad-spectrum antibacterial drugs. However, a prolonged and not always justified antibiotic therapy can cause serious adverse events. A specific role belongs to intestinal microbiota impairments, which may be accompanied by a clinically significant activation of opportunistic microflora with the development of antibiotic-associated diarrhea (AAD) or pseudomembranous colitis. It is known that half of diarrhea cases in hospitalized individuals and 90–100% of pseudomembranous colitis are caused by the Clostridium difficile pathogen [1].

In recent years, statistics have shown a rampant growth in morbidity and mortality from Clostridium difficile infection (CDI) worldwide [2]. In most cases (76.4%), CDI has been associated with medical interventions and antibacterial therapy [3]. At the same time, antibiotics are the most commonly prescribed drugs and are used in all areas of clinical medicine, which emphasizes the importance of doctors' orientation in this problem. In this regard, the article will present up-to-date information on the specific features of the epidemiology and pathogenesis of this infectious disease,

provide recommendations for the diagnosis and treatment of C. difficile-associated colitis, as well as describe the author's personal experience of CDI successful treatment in a patient after solid organ transplantation.

Etiology and risk factors

C. difficile is gram-positive spore-forming anaerobic bacterium that is part of the natural microbiota of the small intestine, mainly in newborns and the elderly [4], and is found in a count of no more than 10^7 CFU/mL [5]. According to the results of many observations, the incidence of an asymptomatic carriage among healthy adults is 3%, while in hospitalized patients, and patients who have been in hospital for a long time, this figure reaches 20–30%, and 50%, respectively [6]. These statistics can be explained by C. difficile resistance to physical and chemical exposures used as the main sterilization methods, as well as the resistance to most antibacterial drugs, which leads to the bacteria persistence in a hospital environment. The pathogen transmission occurs as acquired in everyday environment through a contact with contaminated medical equipment (for example, patient care items, a stethoscope, thermometer, etc.), as well as through a contaminated surface or through the hands of medical staff and caregivers. [7].

The main risk factors for CDI include a decreased resistance to colonization, and impaired intestinal microbiota, most often due to the impact of antibacterial therapy, as well as the contact with C. difficile, which most often occurs during hospitalization in a medical facility or institution with a long hospital stay. According to the data of Huang H. et al, in patients who have been hospitalized for more than two weeks, the probability of CDI occurrence is increased 3-fold (odds ratio = 3.29; confidence interval 95%:

1.59–6.80; p = 0.001) [8]. A significant risk factor is the patient's presence in a room previously occupied by a patient with CDI; it accounts for approximately 10% of all cases of this disease [9].

In case of antibiotic therapy, the time interval associated with a high risk of developing CDI has been determined. So, during the treatment period, it increases 10 times and significantly decreases within 3 months after discontinuation of drugs [10]. Impressive results were presented from a multicenter retrospective cohort study within the US National Veterans Affairs Health System to investigate the complications of the perioperative period in cardiac surgery patients, coloproctology patients, and those after joint replacement. It was found that each additional day of antibiotic therapy increased the risk of developing CDI by 1.5–2 times, while the incidence of infectious complications remained at the same level [11].

CDI is a significant problem for patients after transplantation of solid and hollow organs. The CDI incidence makes 3–7% among liver recipients, 3.5–16% among kidney recipients, 1.5–7.8% among pancreas and 9% among small intestine recipients, 15% among heart and 7–31% among lung recipients [12]. The fulminant form of colitis caused by C. difficile occurs in 8% of cases among immunocompetent individuals and in 13% of solid organ recipients [13]. The risk of CDI is the highest in the first 3 months after transplantation, which is due to high doses of immunosuppression, an intensive antibiotic therapy, and prolonged hospital stay [14].

Additional risk factors for infection include age > 65 years [15]; concomitant pathology: cancer, chronic kidney disease, inflammatory bowel disease, immunosuppression, hypoalbuminemia [16, 17]; the use of proton pump inhibitors [18]; endoscopic examination of the gastrointestinal tract; and enteral nutrition [19].

Traditionally, the highest risk of developing CDI is associated with the following antibacterial agents: clindamycin, third-generation cephalosporins, penicillins, and fluoroquinolones [20]. Based on the analysis of the data from the FDA Adverse Effects Reporting System (FAERS) report for the period from 2015 to 2017, it was found that the maximum number of CDI cases was observed with the use of a group of lincosamides (clindamycin), and to a lesser extent, with monobactams, combination drugs with penicillin, carbapenems and cephalosporins of III – IV generations. The least CDI incidence was recorded with macrolides, sulfanilamides, and tetracycline [21].

Diagnostic modalities

It is known that the C. difficile detection in a culture study of intestinal microflora is not the evidence of the disease. CDI is caused only by toxicogenic strains of C. difficile. The main pathophysiological impact of C. difficile is realized through exotoxins A (TcdA), B (TcdB), and a binary toxin. The impact of TcdA and TcdB aims at disrupting the actin cytoskeleton of enterocytes, which leads to mucosa inflammation and necrosis, loss of tight contacts between cells, and an increase in epithelial permeability. The cytopathic effect of TcdB is 10 times stronger than the similar effect of TcdA. Initial investigations of CDI found that a severe course of the infectious process is characteristic of C. difficile strains producing both TcdA and TcdB. And in case of absent toxin A synthesis, the disease is not clinically significant [22, 23]. Binary toxin has been described relatively recently in highly virulent C. difficile strains of NAP1/BI/027. It enhances the adhesion and colonization of C. difficile, and also intensifies

the production of TcdA and TcdB by 16–23 times. In this regard, this strain is associated with severe forms of CDI [24, 25].

The CDI manifestations can vary from mild diarrhea to severe and fatal forms of colitis. The classic symptoms of the disease are watery stools ≥ 3 times a day, cramping abdominal pains, and in some cases, an elevated body temperature. A toxic megacolon developments, on the contrary, may be associated with stool reduction, accompanied by the symptoms of peritoneal irritation, the effusion in the abdominal cavity, and hypovolemia. Further progression of CDI may lead to a bowel perforation, peritonitis, septic shock, and multiple organ failure [26].

In general, the diagnosis of CDI is based on specific signs at clinical presentation in combination with laboratory test results; and the decision on the need for therapy should be clinically-based and can be justified even in case of negative results of all laboratory tests [27]. The use of rapid diagnosis algorithms can reduce unnecessary therapeutic intervention and timely take the infection control measures. However, an optimal method for laboratory diagnosis of CDI has not yet been determined. International recommendations offer two-stage diagnostic algorithms: the determination of glutamate dehydrogenase or the amplification of nucleic acids in a stool sample followed by the examination of A/B toxins. However, currently in the Russian Federation, the only diagnostic test available in routine practice is the rapid test for the determination of C. difficile toxins [28]. This method partially meets the requirements of a reference screening test. The advantages of this technique are its easy reproducibility, rapid implementation, and a high specificity of the test (~ 95%). However, the sensitivity of the test can vary between 60–90% [4].

Instrumental investigation tools are informative only to diagnose the severe forms of CDI. With an X-ray examination, the intestine dilatation can be observed. Computed tomography reveals a thickening of the intestinal wall, abnormalities of the adipose tissue surrounding the intestine, ascites, and hydrothorax [29]. Endoscopy of the lower gastrointestinal tract can be used as a part of the diagnostic examination to visualize the colon mucosa, detect the presence of inflammation or pseudomembranes, and take the tissue or stool samples in case of high clinical alertness, with unconvincing laboratory studies [30].

Treatment recommendations

In recent years, therapeutic approaches to the treatment of C. difficile infection have changed significantly. According to current recommendations, the therapeutic tactics should be chosen by initially assessing the severity of the process, and also excluding the previous history of the infection episodes. The CDI relapse is defined as the resumption of typical symptoms of the disease within 8 weeks after the previous episode with laboratory-confirmed convalescence. The severity of the course of the disease caused by C. difficile is ranked on the basis of laboratory parameters and clinical symptoms. This classification distinguishes the following grades [31]:

- an uncomplicated ("mild-to-moderate") infection course excludes the presence of one of the manifestations of a severe and fulminant process; laboratory results: leukocytosis $\leq 15x10^3$ and creatinine <1.5 mg/dL (133 μmol/L), is clinically characterized by moderate abdominal pain and diarrhea up to 4 times a day;

- a severe course is accompanied by a symptom complex: watery stool up to 20 times/day, signs of dehydration, leukocytosis >15x10^3, increased creatinine over 1.5 of the upper limit of normal or exceeding 1.5 mg/dL (133 μmol/L);

- a fulminant course that can be diagnosed if at least one of the following conditions develops: vascular collapse, shock, sepsis, megacolon, intestinal perforation, and also when there is a need for resuscitation and/or for a colon resection.

According to the recommendations of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) for the treatment of infection caused by C. difficile [32], in case of the first episode of uncomplicated and antibacterial therapy-associated CDI, it is advisable to withdraw the causative drug and observe for a clinical response for 48 hours. However, the patients should be closely monitored for any signs of clinical deterioration, in case of which the treatment should be given immediately. In this situation, an oral antibiotic therapy should include oral metronidazole, 500 mg 3 times a day for 10 days; or oral vancomycin, 125 mg 4 times a day for 10 days; or oral fidaxomycin[1], 200 mg 3 times a day for 10 days. If oral therapy is not possible, metronidazole is administered intravenously at a dose of 500 mg 3 times a day for 10 days.

In severe CDI, one should start antibacterial therapy with oral vancomycin, 125 mg 4 times a day for 10 days; or fidaxomycin, 200 mg 2 times a day for 10 days. The possibility of increasing the dose of vancomycin to 500 mg 4 times a day for 10 days may also be considered.

For a fulminant form, the preferred option is oral vancomycin at a dose of 500 mg 4 times a day. In intestinal obstruction, vancomycin can also

[1] At present, fidaxomycin is not registered in the Russian Federation.

be administered rectally: 500 mg dissolved in 100 ml of physiological saline, injected every 6 hours in the form of a retained enema.

At the first relapse, 125 mg vancomycin is used 4 times a day for 10 days, if metronidazole was used to treat the initial episode. If vancomycin was used to treat the initial episode, a dose-reduction therapy or pulse therapy with vancomycin are recommended: 125 mg 4 times a day for 10-14 days, 2 times a day for a week, once a day for a week, and further once every 2 or 3 days for 2-8 weeks; or fidaxomycin 200 mg 2 times a day for 10 days. In the second and subsequent episodes, vancomycin is used with a dose reduction or pulse therapy; or vancomycin, 125 mg 4 times a day orally for 10 days with a further conversion to rifaximin, 400 mg 3 times a day for 20 days; or fidaxomycin 200 mg twice a day for 10 days. In some cases, fecal microbiota transplantation may be used.

For patients after solid organ transplantation in case of severe CDI forms developed, as well as in CDI relapses, the immunosuppression dose reduction and the exclusion of prophylactic therapy with sulfamethoxazole-trimethoprim may be required (Table).

Table. Recommendations on the therapy for colitis caused by Clostridium difficile in adults after liver transplantation [33]

Clinical presentation	Recommended therapy	Alternative treatment regimen	Comments
First episode, uncomplicated course mild-to-moderate	Metronidazole 500 mg x 4 times a day, 14 days	Vancomycin 125 mg 4 times a day for 10 days, oral form	The diagnosis is based on the determination of A and B toxins by ELISA, or the toxigenic culture study, or PCR for C.difficile Exclusion of other pathogenic factors (e.g. CMV infection) In case of negative test results, consider colonoscopy or CT

First episode, severe / fulminant course	Vancomycin 250 mg 4 times a day, oral form or via a nasogastric tube and Metronidazole 500 mg iv 4 times a day	For intestinal obstruction, add rectal administration of vancomycin Consider the additional admininstrations of rifaximin 400 mg 2 times a day	Reduce immunosuppression Consider indications for colectomy
Relapse	Vancomycin, oral form, prolonged therapy may be needed: 250 mg 4 times a day for 3-4 weeks or therapy with a dose reduction: 250 mg x 4 times a day for- 2 weeks, 125 mg x 4 times a day for 2 weeks, 125 mg x 2 times a day for 4 weeks	-	Consider discontinuation of prophylactic antibiotic therapy (sulfamethoxazole-trimethoprim) Decrease immunosuppression

Currently, the probiotics value for the CDI prevention and treatment has not been clearly defined. According to international recommendations, there are no indications for using probiotics. The Russian Association of Gastroenterologists proposes the formulae containing Bifidobacterium bifidum, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus rhamnosus, for a period of at least 3 months only after having completed the course of specific antibacterial therapy against C. difficile. The world literature sources report several meta-analyses that have shown a decreased risk of CDI development by > 50% in hospitalized adult individuals with the adminitration of probiotics immediately before the start of antibacterial therapy [34–36].

According to the recommendations, the surgical treatment should be performed in the extent of total colectomy with ileostomy in case of the colon perforation, toxic megacolon, the development of an “acute abdomen” and severe intestinal obstruction, as well as in the presence of a systemic inflammation syndrome and a worsening clinical condition resistant to antibiotic therapy. In authors' opinion, the surgery is preferable to be performed before the colitis course has become very severe. A serum lactate

level (exceeding 5 mmol/L) can serve as the marker of the course severity [37].

In our practice, there have been cases of the postoperative CDI development in patients early after liver and kidney transplantation.

Clinical Case Report

Male, 46 years old. From the medical history: in March 2014, he underwent orthotopic liver transplantation for liver cirrhosis in the outcome of viral hepatitis. The immunosuppressive therapy with tacrolimus and mycophenolate mofetil was chosen. A gradual increase in azotemia and the progression of chronic renal failure was observed over the following years. In October 2018, he started renal replacement therapy with program hemodialysis, and in December 2018, he underwent kidney allotransplantation from a cadaveric donor. A three-component immunosuppressive therapy was prescribed: the patient was switched to an extended release tacrolimus in combination with mycophenolic acid and prednisolone at a dose of 30 mg with a gradual decrease to a maintenance dose of 4 mg. After 3 months, the leukopenia development up to 2.7 $x10^3$ was the reason to withdraw the mycophenolic acid.

In the postoperative period, the patient experienced the fever episodes associated with the stricture formation in the ureteropelvic segment of the kidney transplant, and urinary infection. Within 3 months, the patient was admitted several times in a surgical hospital for invasive procedures: percutaneous puncture nephrostomy, ureteral stenting. Antibacterial therapy with sulfamethoxazole-trimethoprim, fluoroquinolones and meropenem was used to treat and prevent infectious complications.

In April 2019, after another episode of urinary infection, the patient was admitted in a surgical hospital for reconstructive surgery: pyeloureterostomy using the ureter of his native kidney. Intraoperatively, a massive adhesive process was revealed in the abdominal cavity. During adhesiolysis, the small intestine perforaion occurred, the perforation defect was sutured. On postoperative day 9, the suturing of the anterior abdominal wall was performed for an occurred eventration. The perioperative period was characterized with a long-term antibacterial and antifungal therapy that included the sequential administration of drugs: ceftriaxone, imipenem/cilastatin + metronidazole, cefoperazone/sulbactam, fluconazole in therapeutic doses based on the results of bacteriological cultures of urine, wound discharge (Klebsiella pneumonia, Candida albicans). On postoperative day 21, the patient reported complaints of bloating, spastic abdominal pain, and loose slurry stool up to 7 times a day without pathological impurities. AAD was suspected, the antibacterial therapy was discontinued; antispasmodics, enzymes, and probiotic preparations containing Lactobacillus acidophilus and Bifidobacterium animalis subsp. lactis were prescribed. Nevertheless, negative changes were observed over time: the frequency of bowel movements increased up to 20 times a day, the stool became watery, fever elevated up to 38° C, the volume of the discharge drained from the abdominal cavity increased significantly from 100 mL to 4800 mL per day, in the form of a transparent ascitic fluid; alongside, oligoanuria was recorded.

Laboratory test results demonstrated a gradually augmenting leukocytosis to 11,000 with a stab cell shift of 9%, *C*-reactive protein increased to 142 mg/dL, creatinine increased from 172 mmol/L to 350 mmol/L, and hypoalbuminemia progressed to 17 g/L. The blood tests

showed significant abnormalities of the acid-base and electrolyte status: hyponatremia (up to 124 mmol/L) and acidosis (up to 7.27). Ultrasonography demontrated the increased volume of free fluid in the abdominal cavity and the intestinal wall thickening to 14 mm (see Figure). The chext X-ray revealed bilateral hydrothorax. The blood test by polymerase chain reaction for the detection of cytomegalovirus DNA was negative. In order to exclude CDI, a rapid test was conducted to detect C. difficile toxins A and B. The test results confirmed the presence of TcdA and TcdB in the patient's stool sample.

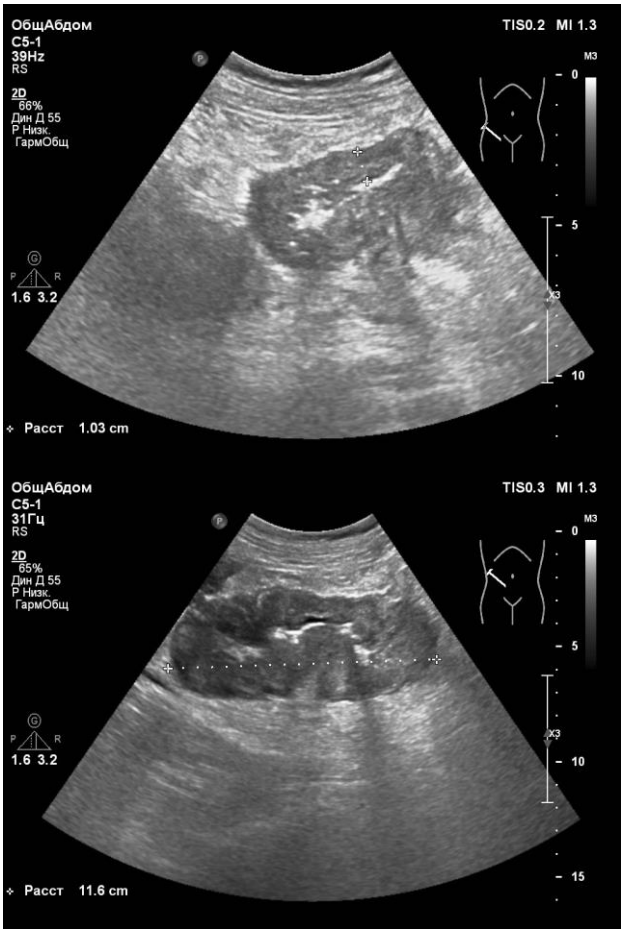

Figure. The colon wall thickening at abdominal ultrasonography examination

Based on the clinical picture, and the laboratory test results, the following diagnosis was made: antibiotic-associated colitis caused by C. difficile. A specific antibacterial therapy was adminihstered: a course of oral vancomycin, 500 mg 4 times a day for 10 days. Due to growing dyspnea, the left pleural cavity was drained. As a pathogenetic treatment, the patient received infusion of crystalloids, hypoalbuminemia correction by intravenous administration of albumin, fresh frozen plasma in accordance with the calculation of the protein loss of at least 8 g per 1 liter of eliminated transudate. Against the experienced diarrhea and developed anuria, the patient showed an increase in blood level of tacrolimus , which required an interrupion in the drug administration for 2 days, followed by the 2-fold reduction in immunosuppression dose until the diuresis was restored.

On the 3rd day of the therapy, a slight positive chnges were recorded: the fever was controlled, the stool frequency decreased to 6-10 times a day. Meantime, the occurred electrolyte abnormalities and hypoalbuminemia impeded coping with the anuria and massive losses of colloids via the drainages from the abdominal and pleural cavities.

On day 7 of the vancomycin therapy, the frequency of bowel movements did not exceed 6 times a day, the stool became mushy, spastic abdominal pain decreased, and the appetite restored. Rifaximinum at a dose of 400 mg 3 times a day was added to the therapy. The laboratory test results indictaed the resolution of the leukemoid reaction and leukocytosis, the increase in albumin to 23 g/L. Despite the persistent anuria and drained transudate from the abdominal and pleural cavities in the amount of up to 1 liter per day, a decision was made to remove draining tubes. On the first day after the manipulation, 2300 ml of urine were obtained. Later, diuresis was restored with the resolution of ascites and hydrothorax.

After completing the course of the 10-day vancomycin therapy, a repeated rapid test for the presence of TcdA and TcdB in a feces sample was performed that yielded a negative result.

On day 24 from the start of vancomycin therapy, the patient was discharged from the hospital with the stable liver and kidney graft functions: total bilirubin was 9.1 μmol/L, albumin 37 g/L, international normalized ratio 1.04, prothrombin 91%, alanine aminotransferase 15 U/L, aspartate aminotransferase 20 U/L, alkaline phosphatase 96 U/L, gamma-glutamine transpeptidase 28 U/L, creatinine 184 μmol/L, urea 14.7 mmol/L. The patient was given recommendations to continue immunosuppressive therapy: extended release tacrolimus, 15 mg per day; prednisolone, 5 mg; enoxaparin, 0.4 ml 2 times a day; antimycotic therapy; proton pump inhibitors. At the moment of writing the manuscript, 3 months have passed since the patient's discharge from hospital. In that period, a satisfactory function of the liver and kidney transplants was preserved; there were no CDI symptom resumption.

Conclusion

The review of literature and our experience have shown that Clostridium difficile infection becomes the most common nosocomial antibiotic-associated infection. Even uncomplicated forms in combination with severe concomitant pathology, especially in the postoperative period, can significantly complicate patient's condition. In this regard, most cases of clostridial infection are characterized by an aggressive course. For the prevention of Clostridium difficile infection development, it is necessary to avoid unreasonable administration of high-risk antibacterial drugs, to limit the duration of surgical antimicrobial prevention therapy to the period of

skin closure and, if possible, shorten hospitalization, especially for people over 65 years of age. If these recommendations are impossible to comply with, there should be alertness regarding the occurrence of Clostridium difficile infection. In case of a suspected clostridial infection development, it is mandatory to immediately take diagnostic measures to identify C. difficile toxins and start etiotropic therapy in a timely manner. An important anti-epidemiological measure is to isolate a patient with a confirmed diagnosis of Clostridium difficile infection, to use thorough routine and general cleaning using disinfectants, as well as to follow the sanitary and epidemiological rules and regulations as for the disinfection of medical personnel hands and medical equipment. The latter is becoming an increasingly important factor with the recognition that reducing the transmission of virulent strains is a key way to control Clostridium difficile infection in a hospital setting. The presented above clinical case report has confirmed the particularly severe nature of the Clostridium difficile infection course in patients after solid organ transplantation.

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