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Clostridium difficile infection in patients after solid organ transplantations

Zakażenie *Clostridium difficile* u chorych po przeszczepieniu narządu miąższowego

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Summary

Clostridium difficile is the most common identified pathogen causing nosocomial and antibiotic-associated diarrhea. The incidence of *Clostridium difficile* infection (CDI) has increased over the last decades. The occurrence of severe and recurrent CDI is also more often recently observed. Patients after solid organs transplantation are more prone to *Clostridium difficile* infection that the general population. This is associated mainly with immunosuppressive therapy, more frequent hospitalizations and frequent antibiotic therapy. Due to the growing number of CDI, it is important to correctly diagnose this infection and to implement the proper treatment. The main drugs used to treat CDI are vancomycin and fidaxomicin. In the case of CDI recurrence, fecal microbiota transplantation remains to be considered. The rationale use of antibiotics and avoiding proton pump inhibitors may also prevent CDI. Results of recent observational study suggest that one of the probiotics – *Lactobacillus plantarum 299v* prevents CDI in patients during immunosuppressive therapy. The efficacy and safety of using probiotics in CDI prophylaxis in this group of patients requires, however, further studies.

Keywords: **solid organ transplantations • immunosuppressive therapy • *Clostridium difficile* infections • *Lactobacillus plantarum 299v***

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INTRODUCTION

Clostridium difficile (reclassified to the *Clostridioides* genus in the year 2016 based on genetic analysis) is one of the most common identified pathogen causing nosocomial and antibiotic-associated diarrhea [3, 28]. *Clostridium difficile* is a gram-positive, anaerobic *bacillus*. The incidence of *Clostridium difficile* infections (CDI) has increased over the last decades. The occurrence of severe and recurrent CDI is recently more often observed. It may be due to a world-wide spread of the hypervirulent epidemic BI/NAP1/027 strain of *Clostridium difficile*. This strain is characterized by increased production of pathogenic toxins A and B and by production of additional binary toxin [10, 22]. In the United States, a double increase of the hospitalization number caused by CDI within 10-year period

was observed [24]. In some studies, the CDI is diagnosed at 15–25% of hospitalized patients [8]. Furthermore, colonization by *Clostridium difficile* is estimated at 5% in non-hospitalized adults and from 25 to 55% in hospitalized adults [23]. It should be stressed that CDI is associated with significantly increased mortality [40].

Clostridium difficile spreads through the fecal-oral route by the spores. The ability to sporulate allows to survive in the external environment due to the spores resistance to high temperatures, acids (among them gastric acid) and antibiotics [33]. Spores germinate into vegetative form in the colon. This can lead to asymptomatic colonization or symptomatic CDI. Toxigenic strains of *Clostridium difficile* produces toxins A, B and binary toxin which damage the intestinal mucous membrane [6, 26]. The main role in the CDI pathogenesis plays toxins A and B. Above mentioned toxins lead to: damage of intestinal epithelial cells by inactivation Rho GTP-ase, depolymerization of actin filaments and, in consequence, destabilization the cell cytoskeleton. In addition, toxins A and B also lead to: increase of tumor necrosis factor alpha (TNFα) and other proinflammatory cytokines and interleukins synthesis, initiation of neutrophil and macrophage recruitment, increase of vascular permeability and opening of epithelial cell junctions. The overall effect of toxins are: epithelial cell apoptosis stimulation and mucus secretion increase in response to epithelial damage [34]. CDI might manifest with: diarrhea, abdominal pain, fever, anorexia, nausea, vomiting and malaise. In some cases pseudomembranous colitis, toxic megacolon, perforation of the colon and death is observed [4, 13]. The diagnostics in a patient with suspected CDI is based on the presence of above described clinical symptoms and laboratory tests. Presence of diarrhea or toxic megacolon, confirmed by microbiological tests with absence of another cause of diarrhea might suggest CDI. Additionally, at least one of the following criteria must be fulfilled: detection of toxin A and/or B in stool samples or toxigenic strains of *Clostridium difficile* in stool culture or with another methods, endoscopic or surgical findings of pseudomembranous colitis or histopathological findings of pseudomembranous colitis. Diarrhea is defined as a 3 or more unformed stools (i.e. taking the shape of the container) within 24 hours, or more often than is normal in particular patient [7, 27]. Laboratory tests for *Clostridium difficile* detect microorganism or its toxin [15]. The multistep diagnostic algorithm is recommended. Firstly, test detecting GDH (glutamate dehydrogenase) antigen or NAAT (Nucleic Acid Amplification Tests) to detect the gene encoding GDH should be performed. The next step is immunoassay test for *Clostridium difficile* toxins A and B. In the case of a negative this test result, bacterial culture stool samples and test of bacterial colonies for toxin production should be done (Fig. 1).

CDI IN PATIENTS AFTER SOLID ORGANS TRANSPLANTATION

The results of clinical studies suggest that, patients after solid organs transplantation (SOT) are more prone to CDI than patients from general population. This is associated with immunosuppressive therapy, more frequent hospitalizations and frequent antibiotic therapy among SOT patients [2, 25]. Paudel et al. completed a meta-analysis including studies from 1991 to 2014 to estimate the prevalence of CDI after SOT. 21 683 patients after SOT were included in the analysis. The overall incidence of CDI in the SOT population was 7.4% and differed depending on the transplant organ. The highest CDI prevalence was among lung and liver recipients (10.8% and 9.1%). In other groups of organ transplant recipients, the prevalence of CDI were as follows: heart (5.2%), kidney (4.7%) and pancreas (3.2%). The risk of severe disease in this population was 5.3% regardless of the type of transplanted organ, and the risk of recurrence was approximately 20% [32]. In the study conducted by Boutros et al., in the group of 1331 SOT the prevalence of CDI was 12%. Depending on the transplanted organ, the CDI prevalence were 19% of liver recipients, 11% of kidney recipients, 9% of kidney-pancreas recipients and 8% of heart recipients [5]. The CDI risk in SOT patients is highest in the first 3 months after the transplantation. Most likely this is due to more frequent antibiotic therapy, intensive immunosuppression treatment and more frequent hospitalizations. Late-onset CDI occurs up to years after transplantation and is usually associated with antibiotic therapy or intensified immunosuppression due to acute graft rejection treatment [11, 16]. Moreover, severe CDI and complications are more common in SOT patients. Pant et al. found more frequent hospitalizations, colectomy, extended time of hospitalization and higher hospital mortality in SOT recipients with CDI in comparison to the patients from general population [31]. In addition, it was found that fulminant *colitis* was observe more frequently in the SOT patients than in the general population (13% vs 8%) [35]. SOT recipients are characterized by higher CDI recurrence rate. In a study involving heart and lung transplant recipients 29–33% patients experienced at least one CDI recurrence [9].

Important CDI risk factors often present in SOT patients are: antibiotic therapy, advanced age, hospitalization and increased duration of hospitalization, malnutrition, hypoalbuminemia, gastrointestinal surgery, gastric acid-suppressing medications (histamine-2 receptor antagonists and proton-pump inhibitors- PPI) [17, 37]. In SOT patients there is additional CDI risk factor- immunosuppressive therapy [32]. Immunosuppressive drugs, such as cyclosporine, azathioprine, and mycophenolate mofetil, can also damage to the gastrointestinal mucosa facilitate the development of CDI [9]. The use of antithymocyte globulin (ATG) in induction therapy was also associated with higher CDI risk [5]. An important component of the body's immune response to *Clostridium difficile* toxins is humoral response after infection. Hypogammaglobulinemia is commonly associated with lung, heart and liver transplants and may cause an impaired immune response and increase the incidence of CDI in this group of SOT patients. In a retrospective study of 235 heart transplant recipients, severe hypogammaglobulinemia (IgG levels <400 mg/dl) was associated with increased CDI

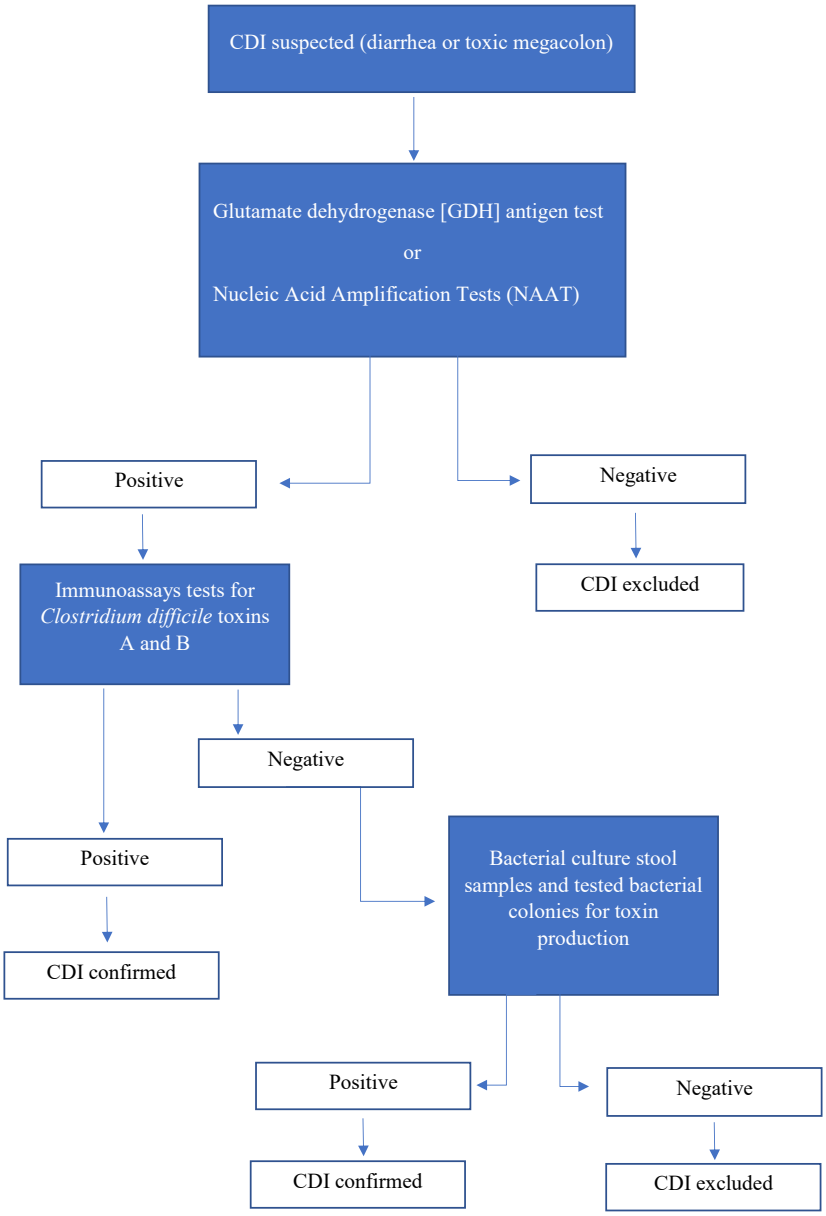

Fig. 1. CDI diagnostic algorithm (based on McDonald et al. [27])

risk. In these patients after intravenous immunoglobulin administrations a reduction of CDI cases number was observed [29]. The consequences of CDI among patients after SOT might be serious. In the observational study, Szewieczek et al. in the group of 13 kidney or kidney and pancreas recipients described deterioration of kidney graft function in 10 recipients. In 5 of them the deterioration of renal graft function was irreversible [20].

CDI PREVENTION AND TREATMENT IN PATIENTS AFTER SOLID ORGANS TRANSPLANTATION

Due to the increase rate of incidence, recurrence and mortality of CDI among SOT patients, it is important to use effective methods of CDI preventions in these group of patients. The main goal is to reduce the number of CDI by eliminating the pathways of the infection spread. These methods includes: hand washing with water, use of contact precautions like disposable gloves and an apron, and environmental disinfection. If a case of diagnosed CDI, isolation of the patient is necessary [33]. It is suggested that in the prevention of CDI, it is also recommended to administer probiotics during antibiotic therapy. This action is intended to prevent the disruption of the intestinal flora (i.e. prevent dysbiosis) which is one of the cause of CDI. The data about the efficacy and safety of probiotics in CDI prevention in SOT are limited. Dudzicz et al. observed in retrospective study, done among the patients hospitalized in the nephrology and transplantation ward, significant decrease of

the CDI incidence rate during twelve-month observation period (from 44.9 to 7.2 per 1000 patients hospitalized; p = 0.005) after implementation of *Lactobacillus plantarum 299v* (LP299v) strain as prevention of CDI in patients on immunosuppression and during antibiotic therapy. In this study, the daily LP299v dose was one capsule contains at least $10x10^9$ colony forming units (CFU). After cessation of the above-mentioned prevention action, the number of CDI significantly increased (from 7.2 to 34.0 per 1000 hospitalized patients; p = 0.025) (Fig. 2) [12].

During the entire observation period including all hospitalized patients in the group of 34 CDI patients severe CDI was diagnosed in three patients (9%). It should be noted, that there were no cases of severe CDI in the period of LP299v prophylaxis. Till now however, there is no randomized, placebo controlled study analyzing the use of probiotics in the SOT patients group [12, 19].

Due to the increase CDI incidence, an important issue has become the economic dimension and significant increase of the hospitalization costs. The mean treatment costs of CDI case vary from $8911 to $30.049 for hospitalized patients in the United States and is estimated at over €4 billion in 2015 in European Union [30, 36]. Dudzicz et al. based on the result of above mentioned study calculated that the cost of single case of CDI prevention using the LP299v is 262.5 PLN (61.5 €). This is caused by low cost of LP299v (1.25 PLN/0.3 € per dose; 17.5 PLN/4.1 € per patients undergoing prevention) and low number needed to treat (i.e., 15 patients) [12]. Therefore, CDI prevention with LP299v in the nephrology and transplantation ward is economically justified.

Because of the common availability of probiotics and their association with food, they are considered to be safe products for use in the general population. However, due to the potential for bacteraemia and the development of infection (among this endocarditis), data on the treatment with probiotics in immunocompromised patients have been analyzed. Several cases of sepsis and other infection causing by probiotics bacteria have been reported [18, 21]. In a meta-analysis of 57 studies including patients with immunosuppression (patients after SOT or receiving immunosuppressive drugs from any other reason, immunocompromised patients, HIV infection patients) Van den Nieuwboer et al. stated that there were no the increased risk in this group of side effects during probiotic treatment [38]. Probably the different probiotic strains are characterized with various risk of bacteremia. In this context, LP299v seems to be safe, because of specific properties to the gut mucosa colonization associated with mannose-dependent mechanism of adhesion only to the human intestinal epithelium. Adawi et al. studied the risk of endocarditis after intravenous administration of LP299v in animal model. Ninety six hours after intravenous infusion in the sectional examination of rats, LP299v in the tissue samples of heart and in microbiological blood culture was not found [1]. Moreover, Dudzicz et al. in observational study in patients on immunosuppression therapy with LP299v did not found any case of bacteremia due to this probiotics strains prophylaxis. Therefore, the use of LP299v in the group of immunocompromised patients seems to be safe.

CDI treatment guidelines in SOT patients are the same as in the general population. Current treatment is based on 2017 Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines (Tables 1, 2). In the case of non-severe, initial episode it is recommended to use of vancomycin in 125 mg dose given orally four times

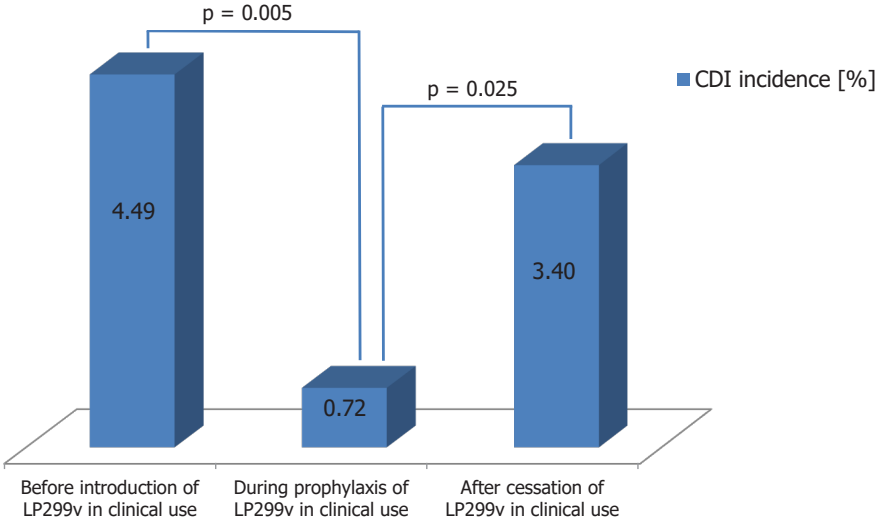

Fig. 2. The incidence of CDI before, during and after cessation of LP299v administration as a routine prophylaxis in the nephrology and transplantation ward among patients during immunosuppressive therapy hospitalized there (based on [12])

daily for 10 days or fidaxomicin in 200 mg dose given orally twice daily for 10 days. If both above mentioned antibiotics are unavailable, metronidazole may be used as an alternative treatment. Recommended dose is 500 mg orally 3 times per day for 10 days. Despite recommendation in the current guidelines, it should be mentioned that metronidazole is still the first-line CDI treatment in many centers in Poland. If this is the initial episode with severe course (defined as white blood cell count of ≥15 000 cells/mL or a serum creatinine concentrations >1.5 mg/dL) it is advisable to use vancomycin or fidaxomicin in the doses mentioned above. In fulminant initial episode (CDI with hypotension or shock, ileus or toxic megacolon) vancomycin 500 mg 4 times per day orally or by nasogastric tube should be used. In the case of ileus, rectal administration of vancomycin and intravenous infusion of metronidazole in the 500 mg dose every 8 hours should be administered. Treatment of first recurrence of CDI depends on the treatment method chosen for the first episode. In clinical practice, treatment of CDI relapses was initiated with a drug that was effective at the last episode. However, according to the latest recommendations if the patient received metronidazole, in the case of recurrence, vancomycin in the 125 mg dose given orally 4 times daily for 10 days is recommended. If standard treatment was previously used, treatment should be started as a prolonged tapered and pulsed dosing of vancomycin. The proposed dosage and duration of this type of treatment is: 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks. Instead of vancomycin, fidaxomicin 200 mg given orally twice daily for 10 days may be considered. In the case of second or subsequent recurrence instead of the above scheme, the use of vancomycin in dose 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days or fecal microbiota transplantation (FMT) may be considered (Tables 1, 2) [27].

As mentioned above, FMT is another therapeutic option in the treatment of recurrent CDI [27]. In 2013 van Nood et al. compared the effectiveness of vancomycin and FMT in prevention of CDI recurrence. The study included 43 patients with two or more recurrent episodes of CDI. Patients were divided into 3 groups: with 14-day course of oral vancomycin without and with bowel lavage and 4-day course of vancomycin, bowel lavage and subsequent FMT. The appearance of recurrence in 10-week period was assessed. In 81% patients in group with FMT no relapse was observed compare to

Table 1. Therapy of initial Clostridium difficile infection (based on [27])

Therapy of initial Clostridium difficile infection		
Non-severe CDI	**Severe CDI**	**Fulminant CDI**
Vancomycin 125 mg p.o. four times per day for 10 days	Vancomycin 125 mg p.o. four times per day for 10 days	Vancomycin 500 mg p.o. by nasogastric tube four times per day
Fidaxomicin 200 mg p.o. twice a day for 10 days	Fidaxomicin 200 mg p.o. twice a day for 10 days	In case of ileus: consider rectal administration of vancomycin. Additionally: metronidazole 500mg i.v. three times a day
If the above are unavailable: metronidazole 500 mg p.o. three times a day for 10 days		

Table 2. Therapy of recurrent Clostridium difficile infection (based on [27])

Therapy of recurrent Clostridium difficile infection	
First recurrence	**Second or next recurrence**
In case of metronidazole use for the initial episode: vancomycin 125 mg p.o. four times per day for 10 days	Vancomycin pulse/taper therapy eg, 125 mg four times per day for 10–14 days, twice a day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks
In case of standard therapy use for the initial episode: vancomycin pulse/taper therapy eg, 125 mg four times per day for 10–14 days, twice a day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks	Vancomycin 125 mg p.o. four times per day for 10 days and subsequently rifaximin 400 mg p.o. three times a day for 20 days
Fidaxomicin 200 mg p.o. twice a day for 10 days	Fidaxomicin 200 mg p.o. twice a day for 10 days
	Fecal microbiota transplantation

27% patients without recurrence of CDI from two other studied groups (P <.001) [39]. Friedman-Moraco et al. described two cases of patients after kidney transplantation and lung transplantation, respectively, with recurrent CDI in whom FMT treatment was safe and effective [14]. In another study Lin et al. describes his experience in the use of FMT in the CDI treatment. The observation includes 5 patients after organ transplantation (four patients after kidney transplantations and one patient after pancreas transplantation) with recurrent CDI. After FMT procedure no recurrent in 80% of patients was observed. The most common adverse effect was cramping and constipation after FMT [25].

CONCLUSIONS

Due to the growing number of CDI, also in SOT patients, it is important to correctly diagnose the infection and implement the proper treatment. In the case of CDI recurrence, FMT remains to be considered. The rationale use of antibiotics and avoiding proton pump inhibitors may also might reduce the number of CDI among SOT patients. Results of recent observational study suggest that one of the probiotics – *Lactobacillus plantarum 299v* might prevent CDI in patients during immunosuppressive therapy. The efficacy and safety of using probiotics in CDI prophylaxis in SOT patients requires, however, further studies.

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