Review Paper

Clostridium Difficile Infection in the Nephrology Ward

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Key Words

Antibiotic therapy • Chronic kidney disease • *Clostridium difficile* • *Lactobacillus plantarum* 299v

Abstract

Clostridium difficile is currently the most frequently identified pathogen causing antibiotic-associated diarrhea and the main cause of nosocomial diarrhea. In recent years, increases incidence of infection, severe infection, recurrent infection and mortality from *Clostridium difficile* infection (CDI) have been observed. This may be a consequence of excessive antibiotic use and spread of the hypervirulent epidemic BI/NAP1/027 strain of *Clostridium difficile*. The main risk factors for CDI are: antibiotic therapy, previous hospitalizations and number of comorbid conditions. Prevention of CDI mainly is focused in two directions: reducing the exposure of patients to the disease pathogen by intensifying hygiene measures, and reducing the impact of risk factors. A meta-analyses of clinical studies (observational, cohort and case control) showed significantly higher risk of CDI and CDI recurrence in patients with chronic kidney disease and increased mortality risk in chronic kidney disease patients with CDI comparing those without CDI. Increased risk of CDI in patients with chronic kidney disease can be caused by: frequent antibiotic therapy associated with numerous infections resulting in intestinal microflora dysfunction, frequent hospitalizations, older age of the patients and an impaired immune system. Among preventative measures against CDI, the use of probiotics were also studied. In patients hospitalized in nephrology ward highly significant reduction of the CDI incidence was observed after the introduction of *Lactobacillus plantarum* 299v as CDI prophylaxis. Therefore, the use of *Lactobacillus plantarum* 299v seems to be a promising method of CDI prevention in chronic kidney disease patients hospitalized in nephrology ward.

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***Clostridium difficile* infection in the general population**

Clostridium difficile is currently the most frequently identified pathogen causing antibiotic-associated diarrhea and the main cause of nosocomial diarrhea [1]. *Clostridium difficile* is a Gram-positive, anaerobic spore forming bacillus. The ability to produce spores enables bacteria to survive in the external environment and facilitates infection. The spores are characterized by resistance to high temperatures, acids and antibiotics. Infection is transmitted by the faecal-oral route [2]. After ingestion, the spores being resistant to acid, pass through the stomach into the small intestine where they germinate into vegetative bacterial forms upon exposure to bile acids. The main factor determining the pathogenicity of *Clostridium difficile* is the production of bacterial toxins A and B which damage the intestinal mucous membrane. Both enterotoxin A and B inactivate Rho GTP-ase, leading to depolymerization of actin filaments and damage to colonic epithelial cells. The presence of these toxins in the intestinal lumen stimulate the synthesis of tumor necrosis factor alpha and proinflammatory interleukins, facilitates neutrophil and macrophage recruitment, increases vascular permeability, causes the opening of epithelial cell junctions and stimulates epithelial cell apoptosis [3]. Damage to the intestinal mucosa and excess mucus production lead to diarrhea, colitis and the formation of a pseudomembrane consisting of inflammatory cells, fibrinous exudates and necrotic cells.

Exposure to the toxinogenic strains of *Clostridium difficile* may result in asymptomatic colonization of the large intestine or lead to disease associated with *Clostridium difficile* infection (CDI). Clinical symptoms and signs of CDI are very diverse. It may cause diarrhea of varying degrees and severity without signs of inflammatory bowel disease, colitis without formation of a pseudomembrane, pseudomembranous colitis, fulminant colitis complicated by toxic megacolon or paralytic obstruction or perforation of the colon [4]. Typical clinical presentations of CDI include watery, non-bloody diarrhea, lower abdominal pain, fever, anorexia, nausea, vomiting and malaise [2]. The clinical presentation depends both on the virulence of the strain of *Clostridium difficile* and the general condition of the patient. Symptoms of infection tend to occur between the second and third day after exposure [2]. In 90% of cases, there is a history of antibiotic use in the period from one to eight weeks before the onset of CDI symptoms with clinical presentation usually occurring between the fifth and tenth day of antibiotic therapy [5]. In 20% of patients with CDI post-treatment recurrence of infections occurred. Causes of recurrence of CDI include: presence of spores in the gastrointestinal tract, unstable large intestine colonization by physiological bacterial flora and resistance of *Clostridium difficile* to antibiotics [6].

In recent years, an increase in incidence of CDI and of mortality from CDI have been observed worldwide. This may be a consequence of the spread of the hypervirulent epidemic BI/NAP1/027 strain of *Clostridium difficile*. This strain is characterized by increased production of toxins A and B, production of the binary toxin, increased ability to form spores and resistance to fluoroquinolones. In patients infected by the BI/NAP1/027 strain severe and complicated forms of CDI are frequently observed, as well as increased rates of disease recurrence and higher mortality (three times higher than in CDI due to strain 001 or 014) [7-9].

The diagnosis of CDI is based on the presence of diarrhea or toxic megacolon in the absence of another cause, and fulfillment of at least one of the following criteria: (I) detection of toxin A and/or B in stool samples, or toxigenic strains of *Clostridium difficile* in stool culture; (II) endoscopic or surgical findings of pseudomembranous colitis; (III) histopathological findings of pseudomembranous colitis [10]. Diarrhea is defined as when loose stools take the shape of the container and three or more defecations in 24 hours, or more frequently than is normal for that particular individual. Toxic megacolon is defined as radiological distension of the colon (transverse width of colon >6 cm) with signs of a severe systemic inflammatory response [11].

The most important risk factor for CDI is antibiotic therapy. In a healthy human, the

intestinal microflora present in the colon fulfills an immune function and prevents the colonization and growth of pathogenic bacteria. The use of antibiotics may lead to the disruption of the physiological intestinal flora, reduction in the diversity of bacteria, and colonization by pathogenic strains. The risk of CDI increases during antibiotic therapy and is maintained for up to several weeks after its completion. The highest risk is related to treatment with broad-spectrum antibiotics [12, 13]. The risk of CDI varies with different antibiotic. Antibiotics associated with a high risk of CDI include clindamycin, ampicillin, amoxicillin, cephalosporins and fluoroquinolones. Antibiotics associated with moderate risk of CDI include penicillins (except amoxicillin and ampicillin), sulfonamides, trimethoprim (as monotherapy or in combination with sulfamethoxazole) and macrolides. Antibiotics associated with low risk of CDI include aminoglycosides, bacitracin, metronidazole, teicoplanin, rifampin, chloramphenicol, tetracyclines, carbapenems, daptomycin and tigecycline [6]. It is worthy of note that in hospitals with a high incidence of CDI, a single dose of antibiotic given in the framework of perioperative prophylaxis may lead to the development of CDI [14].

An increased predisposition for CDI in patients receiving drugs reducing the acidity of gastric fluid, such as proton pump inhibitors and histamine type 2 receptor antagonists, has been observed. The low gastric pH is a physiologically defence mechanism against various pathogens, and increasing gastric pH results in colonization of the upper gastrointestinal tract by pathogenic bacterial species including *Clostridium difficile*. A similar situation occurs in disease states with reduced gastric secretion of hydrochloric acid, such as pernicious anemia [15, 16]. People over 65 years of age are particularly prone to CDI - data from the UK indicate that CDI occurred at an incidence of 200 cases per 100 000 population in patients over 65 years of age, and at an incidence of 30 cases per 100 000 population in those between 45 and 64 years of age [17].

Other important risk factors for CDI are previous hospitalization and prolonged current hospitalization; this also applies to people living in nursing homes or other long-term care facilities. CDI occurs in 20-30% of hospitalized patients as compared to 3% in the general population [18].

Additional risk factors for CDI are comorbidities such as: chronic kidney disease, liver cirrhosis, diabetes mellitus, cystic fibrosis, inflammatory bowel diseases, malignant disease and chemotherapy treatment, presence of malnutrition or hypoalbuminemia. Other groups that are more vulnerable to CDI are patients with dysfunction of the immune system such as those with genetics immunodeficiencies, HIV infection and those with solid organ or hematopoietic stem cell transplant or receiving immunosuppressive drugs for the other reasons. Patients after gastrointestinal surgery or endoscopic procedures, and those with gastrostomy or jejunostomy tubes are also at increased risk of CDI [12, 19].

As already mentioned, recurrence of CDI occurs in 20% of CDI patients. Recurrent CDI is defined as recurrence of the infection within eight weeks after the onset of a previous episode. Risk factors for recurrent CDI are: age over 65 years, severity of underlying disease and exposure to additional antibiotics after treatment of previous episodes of CDI. Risk factors for severe CDI are: age over 70 years, blood leukocyte count higher than $20 \times 10^9/L$, serum creatinine concentration higher than 2 mg/dL, serum albumin concentration lower than 2.5 g/dL, inflammatory changes of the large bowel on computed tomography, surgery during the last 30 days and previous treatment with immunoglobulins [20].

The increasing rate of infection and the mortality from CDI makes the prevention of CDI important. This should be focused in two directions: reducing the exposure of patients to the disease pathogen by intensifying hygiene measures, and reducing the impact of risk factors. One of the most important measures to reduce the number of infections and spread of *Clostridium difficile* is frequent hand washing. Appropriate disinfection of the environment of the patient (floors, cabinets, bed, bedding) and of medical equipment is also important. If a case of CDI is diagnosed, isolation of the patient in a room with a separate bathroom should be implemented immediately. This isolation should last for up to about 48 hours after

the resolution of diarrhea. Before entering the room the medical staff should be obliged to put on disposable gloves and an apron. Another important issue in the prevention of CDI is the restriction of the use of antibiotics. Antibiotic therapy should begin only if significant clinical indications occur and, if possible, the use of antibiotics associated with a low risk of CDI should be preferred. It is also recommended to use proton pump inhibitors and histamine type 2 receptor antagonists only if there are important clinical indications. The duration of such treatment should not be prolonged and it should be discontinued during hospitalization, if possible [2, 17].

The first step in the treatment of CDI is to consider discontinuation of the antibiotic therapy that led to the development of the infection, if clinically possible; in mild cases, this may be sufficient to allow recovery. Monitoring of the patient's hydration and plasma electrolyte concentrations, and appropriate replacement of fluids and electrolytes is crucial in the prevention of cardiovascular and kidney complications [10, 12]. It is recommended to avoid anti-motility medications as prolongation of the intestinal transit leads to increased growth of *Clostridium difficile* and exposure to bacterial toxins [10, 21]. In patients with CDI discontinuation of proton pump inhibitor and histamine type 2 receptor antagonists should also be considered [10]. Antibacterial agents that may be used for CDI include metronidazole, vancomycin and fidaxomicin. Metronidazole is an inexpensive and effective medication recommended for the treatment of mild to moderate forms of CDI. The oral form is recommended for mild CDI. Metronidazole has similar efficacy to vancomycin in the treatment of mild forms of the disease (90% in the metronidazole group vs 98% in the vancomycin group) [22]. The standard metronidazole dose is 500 mg, 3 times a day for 10 to 14 days. Compared to the use of vancomycin, there is a low risk of selection of vancomycin-resistant enterococci (VRE). In the treatment of severe CDI, it has been demonstrated that there is an advantage for vancomycin over metronidazole (success of the therapy in 97% of patients treated with vancomycin vs 76% patients treated with metronidazole) [22]. Vancomycin administered orally is poorly absorbed from the gastrointestinal tract and results in high therapeutic concentrations in the intestinal lumen with few systemic adverse effects [12]. The standard vancomycin dose is 125 mg 4 times a day for 10 to 14 days. Fidaxomicin is a macrolide antibiotic possessing a narrow spectrum of activity against aerobic and anaerobic gram-positive bacteria. After oral administration, it is not absorbed from the gastrointestinal tract and it has no adverse effect on the intestinal microflora [12]. In 2011, it was registered by the Food and Drug Administration (FDA) of the USA for the treatment of CDI. In clinical studies, fidaxomicin has shown therapeutic efficacy similar to vancomycin (88% in fidaxomicin group vs 86% in vancomycin group). However, after fidaxomicin treatment there is lower risk of recurrence compared to vancomycin (15% in fidaxomicin group vs 25% in vancomycin group) [23]. Fidaxomicin is more effective in patients who are unable to stop previous antibiotic therapy (90% in fidaxomicin group vs 79% in vancomycin group) [24]. The standard fidaxomicin dose is 200 mg 2 times a day for 10 days. Currently, the cost of fidaxomicin treatment is significantly higher than the cost of both metronidazole and vancomycin treatment [25]. First line therapies of CDI are summarized in Table 1.

Table 1. First line therapies for *Clostridium difficile* infection

First line therapy of <i>Clostridium difficile</i> infection			
Non-severe CDI	Severe CDI	First CDI recurrence	Multiple recurrences of CDI
If it is clinically possible, stop antibiotics and observe the clinical response for 48 h	Vancomycin 125mg p.o. 4x day for 10 days	Vancomycin 125mg p.o. 4x day for 10 days	Vancomycin 125mg p.o. 4x day for 10 days in pulse/taper therapy
	or	or	or
Metronidazole 500mg p.o. 3x day for 10 days	Fidaxomicin 200mg p.o. 2x day for 10 days	Fidaxomicin 200mg p.o. 2x day for 10 days	Fidaxomicin 200mg p.o. 2x day for 10 days

The results of some clinical studies suggest that toxin binders, for example, anion exchange resins such as cholestyramine, may be useful in the treatment of CDI. In the mild form of the disease, they can reduce the severity of the symptoms. However, anion exchange resins may also bind orally administered drugs [26]. Preliminary studies of a parenteral vaccine containing toxoid A and B are yielding promising results. The vaccine was administered to a group of three patients requiring continuous vancomycin therapy due to recurrent CDI; all patients were able to cease vancomycin treatment without any further recurrence [27].

***Clostridium difficile* infection in patients hospitalized in the nephrology ward**

CDI is frequent in patients in the nephrology ward, especially in patients after kidney transplantation. Risk factors for CDI in this group include frequent hospitalizations as well as immunosuppressive and antibiotic therapy. CDI in CKD patient groups may lead to many complications including CKD progression and impaired graft function.

A retrospective analysis of CDI cases among patients hospitalized in the Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland, found an increase in CDI prevalence in recent years (0.7% in 2011 and 1.3% in 2013). In this study, nosocomial infection was diagnosed in 70% of the cases. CDI occurred more frequently in elderly patients: 16% of CDI patients were below 40 years old, 16% were between 40 and 50 years old and 68% were above 50 years old. 78% of patients with CDI had been treated with antibiotics in the four weeks before the occurrence of the CDI symptoms. In addition, 51% of patients had been treated with more than one antibiotic. The most commonly used groups of antibiotics were: fluoroquinolones (46%), penicillins (32%), carbapenems and monobactams (27%) and cephalosporins (24%). The onset of CDI symptoms was on average nine days after starting antibiotic treatment [28].

Diarrhea associated with *Clostridium difficile* in patients with chronic kidney disease (CKD) was described in 1985 by Leung et al. [29] Numerous cases of epidemic CDI among CKD patients hospitalized in nephrological wards have subsequently been reported [30]. Results of epidemiological studies suggest that CKD is one of the potential additional risk factors for CDI. A meta-analysis of 20 clinical studies (observational, cohort and case control) including 162 million individuals showed significantly higher risk of CDI and CDI recurrence in patients with chronic kidney disease (1.95-fold and 2.61-fold increased risks, respectively). Moreover, in ten studies, a significantly increased CDI risk was demonstrated in patients with end-stage renal disease (2.63-fold increased risk) [31]. Similarly, a meta-analysis of 19 studies (case-control and 18 cohort studies) showed that patient with CKD have an increased risk of severe or recurrent CDI, and increased CDI mortality risk (1.51-fold, 2.73-fold and 1.76-fold increased risks, respectively) [32]. In another meta-analysis of four cohort studies including 8 million patients, Thongprayoon et al. demonstrated an increased mortality risk in non-dialyzed patients with CKD and CKD stage 5d patients with CDI versus those without CDI (1.73-fold and 2.15-fold increased risks, respectively) [33]. Kim et al. showed that patients with CKD in stages 4 and 5 or CKD patients on chronic dialysis treatment are characterized by increased CDI risk (OR=2.90 and OR=3.34, respectively). Furthermore, advanced CKD in patients with CDI is associated with increased CDI mortality [34]. Among patients with CKD hospitalized in the United States in the years 2005-2009, CDI occurred twice as often than in patients without CKD (1.49% vs. 0.70%, respectively; $P<0.001$). In addition, patients with CKD undergoing chronic dialysis treatment were more vulnerable to CDI than patients with CKD who were not on dialysis (OR, 1.33; 95% CI, 1.32-1.35; $P<0.001$) [35].

In a retrospective case-control study by Abdelfatah et al., disease recurrence was diagnosed in 10% of CDI patients. Multivariate analysis showed that the majority of relapses occurred in patients with comorbidities, including CKD (OR, 1.3; 95% CI, 1.0-2.4; $P = 0.039$).

In this group of patients, more frequent use of proton pump inhibitors (OR, 1.65; 95% CI, 1.0-1.7; P=0.002) and glucocorticoids (OR, 1.65; 95% CI, 1.0-1.5; P=0.047) was also reported [36].

Increased risk of CDI in patients with CKD can be caused by: frequent antibiotic therapy associated with numerous infections resulting in intestinal microflora dysfunction, frequent hospitalizations, older age of the patients and an impaired immune system [31].

Use of a *Lactobacillus plantarum* 299v in the prophylaxis of *Clostridium difficile* infections in the nephrology ward

Because CKD patients are characterized by high CDI risk, CDI prevention in these group of patients is of great importance. Among preventative measures against CDI, the use of probiotics should be discussed. So far, it has not been proven in the general population that probiotics are effective in the prevention of CDI in patients undergoing antibiotic therapy. In a meta-analysis of 23 randomized controlled trials, including 4213 patients, Goldenberg et al. showed that probiotics can reduce the risk of *Clostridium difficile*-associated diarrhea by 64% (RR = 0.36, 95% confidence interval 0.26 to 0.51). However, in another analysis of 13 trials it was showed that there is no significant effect of probiotics on the incidence of CDI [37]. In the randomized placebo-controlled clinical study, PLACIDE (Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in older inpatients), Allen et al. evaluated the role of probiotics in the prevention of CDI prospectively in 2889 hospitalized patients over 65 years of age treated with antibiotics. The study did not show any evidence of the efficacy of the multistrain preparation of *lactobacilli* and *bifidobacteria* in the prevention of CDI [38].

Lactobacillus plantarum 299v (LP299v) is a gram-positive lactic acid bacterium occurring naturally on the surface of the human intestinal mucosa [39]. This strain has the specific property of colonization of human intestine due to mannose-dependent adhesion of LP299v to the epithelium [40], which leads to the inhibition of bacterial translocation from the intestinal lumen into blood vessels. In a double blind, placebo controlled study, Lönnemark E. et al. showed that the use of a strain LP299v can reduce the severity of gastrointestinal adverse effects (nausea and loose stools) during antibiotic therapy [41]. Klarin et al. in a study of 44 patients hospitalized in the intensive care unit showed a lower incidence of *Clostridium difficile* colonization in patients receiving LP299v compared to the group receiving standard therapy (0% vs 19%; respectively) [42].

In the Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland a retrospective study was performed with the aim to assess the efficacy of the LP299v strain in the prevention of CDI by analysing the incidence of CDI in hospitalized patients. A two-year observation period was divide into two twelve-month intervals: before and during the use of LP299v as a CDI routine prophylaxis in patients at high risk of CDI (patients during antibiotic therapy and receiving immunosuppressive treatment). Before the introduction of the LP299v strain, different probiotics containing *Saccharomyces boulardii*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Lactobacillus delbrueckii lactis* and *Bifidobacterium* were given to try to prevent antibiotic-associated diarrhea. Since December 2013, all patients with a high risk of CDI have been

Table 2. The incidence of CDI before and during *Lactobacillus plantarum* 299v prophylaxis in the Department of Nephrology, Transplantation and Internal Medicine, University of Silesia. Based on Kujawa-Szewieczek et al. [43]. *P.0001 vs period during LP299v prophylaxis

	Number of cases	Incidence [%]
Before LP299v prophylaxis	21	1.21
During LP299v prophylaxis	2	0.11*

given LP299v (one capsule orally per day containing at least 10×10^9 colony forming units (CFU) of LP299v) as a preventative measure for CDI. A highly significant reduction of the incidence of CDI was observed after the introduction of LP299v as prophylaxis of CDI (1.21% vs 0.11%, $P=0.0001$) (Table 2) [43]. The results of this retrospective study suggest that routine administration of *Lactobacillus plantarum* 299v during treatment with antibiotics prevents CDI in patients at high risk of CDI. The promising results of this retrospective observational study should be confirmed in future prospective, randomized, placebo controlled, double blind studies.

Conclusion

In summary, CDI is an important complication in patients hospitalized in the nephrology wards and the use of *Lactobacillus plantarum* 299v seems to be a promising method of CDI prevention in CKD patients.

Disclosure Statement

Marcin Adamczak received lecturer fee from Sanprobi. The other authors declare no conflict of interest.

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