Risk factors of the *Clostridium difficile* infection in patients with chronic kidney disease

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Abstract

Background. *Clostridium difficile* (*C. difficile*) is a Gram-positive bacillus responsible for diarrhea and colitis, mainly among hospitalized patients. It is a leading cause of nosocomial infections.

Objectives. The main goal of the study was to assess the risk factors of the *C. difficile* infection in patients with chronic kidney disease (CKD).

Material and methods. We evaluated the medical records of all patients treated at the Department of Nephrology and Renal Transplantation of the Research and Development Center in the Provincial Specialist Hospital in Wrocław, Poland, between February 2009 and May 2012, who developed diarrhea, abdominal pain and/or fever within 72 h after admission. In patients with these symptoms, an enzyme cassette immunoassay was performed to detect antigens of *C. difficile* toxins A and B in stool.

Results. There were 207 patients enrolled in the study, presented with the symptoms of the *C. difficile* infection. Out of these patients, 69 (33%) persons were positive for *C. difficile* toxins. Longer hospitalization time and lower initial serum albumin concentration significantly increased the risk of infection ($p < 0.05$). Apart from the *C. difficile* infection, age, the number of used antibiotics, longer hospitalization time, and lower initial serum albumin concentration significantly augmented the risk of death ($p < 0.05$).

Conclusions. In patients with CKD, longer hospitalization time and lower serum albumin concentration significantly increased the risk of the *C. difficile* infection. The *C. difficile* infection, age, the number of used antibiotics, longer hospitalization time, and lower initial serum albumin concentration notably augmented the risk of death. Although the incidence of the *C. difficile* infection did not correlate with the estimated glomerular filtration rate (eGFR), 67% of patients who tested positive were class 5 of CKD, whereas only 5.7% were class 1.

Key words: malnutrition, *Clostridium difficile*, chronic renal insufficiency, pseudomembranous enterocolitis

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Introduction

The *Clostridium difficile* (*C. difficile*, CD) infection is the most frequent cause of diarrhea in patients treated with antibiotics who were admitted to hospital.¹ Whereas the course of the disease is mild in most cases, in some instances it may lead to severe dehydration, septic shock or even death.² Damage to the intestinal mucosa, initiating colorectal inflammation is caused by toxins A, B and newly diagnosed, highly virulent, toxin C.³ Well-established risk factors of the CD infection include prolonged treatment with antibiotics, proton pump inhibitors (PPIs), antidepressants, advanced age, chemotherapy, immunosuppression, and long hospitalization time.^{4–6} In recent years, a number of reports have appeared, indicating an increased incidence and morbidity of CD-associated infections in patients with chronic kidney disease (CKD).^{7,8} These observations corroborated current clinical experience in our Department, which is why we sought to assess the incidence, morbidity and risk factors of the CD infection in our CKD patients.

Material and methods

We evaluated the medical records of the patients hospitalized in the Department of Nephrology and Renal Transplantation of the Research and Development Center in the Provincial Specialist Hospital in Wrocław, Poland, between February 2009 and May 2012, who during their hospital stay developed symptoms indicating CD-associated enterocolitis. Qualifying symptoms were as follows: diarrhea, abdominal pain and/or fever within at least 72 h after admission to hospital. In all

patients meeting these criteria, a rapid enzyme cassette immunoassay was performed, detecting antigens of toxins A and B of *C. difficile* in stool (TOX A/B QUIK CHEK®; Techlab, Blackburg, USA). The sample material was taken with a spatula to the test tube, transferred to the test cassette and read after 15 min of incubation at room temperature.

Detailed data was accrued, pertaining to the patients' age, gender, concomitant diseases, and pharmacotherapy with the emphasis on antibiotics, PPIs and antidepressants. Laboratory tests were done in the hospital lab, using standard methods, including the measurement of serum creatinine and albumin concentrations. The shortened Modification of Diet in Renal Disease (MDRD) equation was used to calculate the glomerular filtration rate (eGFR).

Numerical data was expressed as means and standard deviations (SD). Statistical analysis was performed utilizing the STATISTICA v. 12 software (StatSoft Inc., Tulsa, USA). Normal distribution verified with the Kolmogorov-Smirnov test enabled the assessment of the differences between the 2 groups with Student's t test, the homogeneity of variations being checked with Fisher's test. In the case of nonparametric distribution, statistical importance of the differences was evaluated with the use of the Mann-Whitney U test. For quantitative data, the χ^2 analysis was done. Statistical significance cut-off level was set at $p = 0.05$.

Results

A total of 207 patients were enrolled in the study (104 males and 103 females), aged 20–91 years (64.5 years ± 15.79), hospitalized at the Department of Nephrology

Table 1. Clinical features of patients tested positive and negative for CD (mean values)

Parameter	Positive result of the test for CD toxins (1)	Negative result of the test for CD toxins (2)	p-value (1) vs (2)
Number of patients	69	138	–
Age [years]	65.7	63.2	0.29
Gender, M/F	35/34	69/69	–
Body mass [kg]	73.8	77.5	0.29
Number of patients treated with antibiotics, n (%)	61 (88)	114 (82)	–
Number of antibiotics used	2.1	2.0	0.66
Duration of antibiotic therapy [days]	12.8	11.2	0.19
Number of patients with diabetes, n (%)	18 (26)	47 (34)	0.24
Number of patients treated with PPIs, n (%)	46 (66)	87 (63)	0.6
Number of patients treated with H2 blockers, n (%)	8 (11)	9 (6)	0.2
Number of patients treated with statins, n (%)	22 (31)	48 (34)	0.67
Number of patients treated with immunosuppressant drugs, n (%)	23 (33)	47 (34)	0.8
eGFR [mL/min/1.73 m ²]	30.2	39.9	0.24
Serum albumin concentration at admission [g/dL]	2.95	3.43	0.000079*
Duration of hospitalization [days]	33.2	24.3	0.004319*
Number of deaths, n (%)	20 (28)	12 (8.7)	0.0001*

M – male; F – female; PPIs – proton pump inhibitors; eGFR – glomerular filtration rate; * statistically significant.

and Renal Transplantation from February 2009 to May 2012. Patients were found to have CKD of various etiology: primary and secondary glomerulonephritis (23 cases – 11.1%); secondary nephropathies – ischemic, diabetic, obstructive (53 cases – 25.6%); acute kidney injury evolved to chronic kidney failure (24 cases – 11.6%). Of these patients, 77 (37.2%) were subjected to renal replacement therapy (RRT) (75 hemodialyses and 2 peritoneal dialyses) and 27 (13.0%) persons were kidney allograft recipients. The common feature of all these cases was impaired renal function (eGFR: 35.05 mL/min/1.73 m² ±12.3).

Among 207 patients demonstrating the symptoms of acute enterocolitis, in 69 (33%) persons, positive results of the cassette immunoassay for toxins A and B of CD were found.

In our study, longer hospitalization time and lower initial serum albumin concentration significantly increased the risk of infection (Table 1).

Moreover, it was demonstrated that the patients who died during the hospital stay not only more frequently tested positive for CD toxins (Table 1), but also had lower serum albumin concentration at admission, were older, were given more antibiotics during hospitalization, and their hospital stay lasted longer (Table 2). The mean morbidity coefficient for the CD infection was 12.5 per 1,000 hospitalizations.

It was not observed in the study group that lower eGFR, body weight, treatment with PPIs, H₂-receptor blockers, immunosuppression, or statins, and the presence of diabetes increased significantly the risk of the CD infection. Furthermore, the length of antibiotic therapy and the number of used antibiotics did not increase considerably the risk of infection.

The stratification of CKD patients with symptoms of acute enterocolitis referring to the classes of CKD is presented in Table 3.

Discussion

The prevalence of the CD infection in the results presented herein: 12.5/1000 hospitalizations is strikingly high when compared to the American (9/1000) and European (4.1/1000) populations, respectively.^{9,10} Similarly, in one of the few Polish publications related to the CD infection in nephrology wards, the prevalence of 9.9/1000 hospitalizations was reported.⁸ High prevalence of the CD infection in CKD patients of our Department confirms our observations, indicating a higher prevalence of the infection in nephrological patients when compared both to the general population and to patients hospitalized in other wards.^{6,11} It also indicates that CKD, especially class 5, is an independent risk factor of the CD infection. The duration of hospitalization and lower serum albumin concentration at admission are significantly related to a higher frequency of the CD infection, as demonstrated in our study. Moreover, we documented an increased risk of death in CD-infected

Table 2. Clinical characteristics of patients deceased during hospitalization (mean values)

Parameter	Patients who died during hospitalization	Patients discharged from hospital	p-value
Number of patients	32	175	–
Age [years]	76.7	61.8	0.000001
Number of antibiotics	2.84	1.88	0.000575
Hospitalization [days]	40.4	24.7	0.000101
Serum albumin concentration at admission [g/dL]	2.56	3.07	0.039297
eGFR at admission [mL/min/1.73 m ²]	17.5	34.5	0.11

eGFR – glomerular filtration rate.

Table 3. Classes of CKD in patients demonstrating the symptoms of acute enterocolitis

Class of CKD	Number of patients	%
1	12	5.7
2	11	5.3
3	27	13
4	21	10.1
5	136	65.7

CKD – chronic kidney disease.

patients. In our study, age, prolonged hospitalization time and lower serum albumin concentration were proven as risk factors of death. Some authors underline the importance of malnutrition, especially among older patients as one of the main agents of mortality. Thus, it is important to focus on proper nutritional therapy in patients with the CD infection.¹² On the other hand, the study under discussion failed to confirm the importance of many established risk factors of the CD infection, such as prolonged use of antibiotics, PPIs and immunosuppressant drugs.^{4,5,10,11} This may be attributable to the fact that the control group in our study consisted of CD-negative patients with diarrhea, instead of all persons hospitalized in the analyzed period (the available data on the treatment of these patients was incomplete).

Recent reports concerning the impact of CKD on the prevalence of the CD infection are inconsistent. A higher risk of infection has been observed in chronically dialyzed patients,⁷ whereas this relation has not been confirmed in CKD subjects not requiring RRT.¹³ At least 1 report showed a higher risk of the CD infection in patients with both acute and chronic renal injury.¹⁴ In the present report, it was not documented that reduced eGFR augmented the risk of the CD infection; however, the patients tested positive for CD toxins had on average eGFR lower by 9.7 mL/min/1.73 m². Moreover, the investigated group of patients was dominated by persons with class 5 CKD: 137 of 207 (65.7%) with 77 (37.2%) of them chronically dialyzed.

Compliance with ethical standards

All procedures applied in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent was not required.

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