Kidney Res Clin Pract 32 (2013) 27–31

Kidney Research and Clinical Practice

journal homepage: http://www.krcp-ksn.com
Contents lists available at ScienceDirect

Original Article

Clostridium difficile-associated diarrhea in dialysis patients ☆

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Article history:
Received 2 April 2012
Received in revised form
14 September 2012
Accepted 20 November 2012
Available online 31 December 2012

Keywords:
Antibiotics
Chronic kidney disease
Clostridium difficile
Dialysis

Abstract

Background: Dialysis patients have impaired host defense mechanisms and frequently require antibiotics for various infective complications. In this study, we investigated whether dialysis patients have greater risk for *Clostridium difficile*-associated diarrhea (CDAD).

Methods: During the 4-year study period (2004–2008), 85 patients with CDAD were identified based on a retrospective review of *C difficile* toxin assay or histology records. Nosocomial diarrheal patients without CDAD were considered as controls ($n=403$). We assessed the association between renal function and the prevalence and clinical outcomes of CDAD.

Results: There was a significant difference in the prevalence rate of chronic kidney disease (CKD) between CDAD and non-CDAD patients ($P<0.001$). Sixteen patients (18.8%) of the CDAD group were treated with dialysis, whereas 21 patients (5.2%) of the non-CDAD group were treated with dialysis. There was a significant association between renal function and CDAD in patients on dialysis [odds ratio (OR)=4.44, 95% confidence interval (CI) 2.19–8.99, $P<0.001$], but not in patients with CKD stage 3–5 (OR=1.10, 95% CI 0.63–1.92, $P=0.73$). In multivariate analysis, CKD stage 5D was an independent risk factor for the development of CDAD (OR=13.36, 95% CI 2.94–60.67, $P=0.001$).

Conclusion: Our data indicate that dialysis patients might be at a greater risk of developing CDAD, which suggests that particular attention should be provided to CDAD when antibiotic treatment is administered to dialysis patients.

Introduction

Clostridium difficile is the well-known causative organism of antibiotic-associated diarrhea, and is one of the most common hospital-acquired infections. It accounts for 10–25% of all cases of antibiotic-associated diarrhea and virtually all cases of antibiotic-associated pseudomembranous colitis [1]. The major predisposing factor of *C difficile*-associated diarrhea (CDAD) is antimicrobial therapy, especially involving treatment

☆ Support and Financial Disclosure Declaration: None

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http://dx.doi.org/10.1016/j.krcp.2012.12.002

with broad-spectrum antibiotics such as penicillins, penicillin plus beta-lactamase inhibitor combinations, cephalosporins, and clindamycin [2]. However, other factors leading to the disturbance of the normal intestinal flora may also contribute to the development of CDAD. These include older age, severe underlying disease, gastrointestinal surgery, acid suppression, nonsteroidal anti-inflammatory drug use, and enteral feeding [3–4].

Patients on maintenance dialysis often need antibiotics for treatment of a variety of infective complications. In addition, a severely compromised host immune system may put dialysis patients at particularly high risk for *C difficile* infection. Although there have been a few reports suggesting a relationship between CDAD and chronic kidney disease (CKD) [5–8], it is still unclear whether dialysis treatment is a risk factor for CDAD. Here, we investigated whether dialysis patients are at greater risk for CDAD.

Methods

This study was conducted at the Hallym University Kangnam Sacred Heart Hospital in Korea from March 2004 to February 2008. During the 4-year period, 85 patients with CDAD were identified on the basis of a retrospective review of *C difficile* toxin assay or histology records. Tests for *C difficile* infection were performed in patients with nosocomial diarrhea and fever. The diagnosis of CDAD was established either by *C difficile* toxin A positivity in stool samples or by the presence of pseudomembranous colitis (identified by endoscopic examination). Stool samples were examined for *C difficile* toxin A using an enzyme-linked fluorescent assay (ELFA; VIDAS CD II, bioMérieux, France). An aerobic bacterial culture (*Salmonella* and *Shigella*) of stool specimens and an examination of ova and parasites were also performed to exclude other forms of infectious diarrhea. Hospitalized patients who showed diarrhea but were negative for *C difficile* toxin or showed negative endoscopy findings were considered as controls (non-CDAD, $n=403$).

We assessed renal function by measuring serum creatinine levels before the onset of diarrhea. We also calculated the estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease (MDRD) study equation [9]. We defined CKD as eGFR <60 mL/minute/1.73 m^2. Patients with acute kidney injury (AKI) during the episodes of diarrhea were excluded.

MDRD study equation: $eGFR = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742, \text{if patient is female})$

We assessed the association between renal function and prevalence and clinical outcomes of CDAD. We also evaluated comorbid conditions, recently prescribed antibiotics (within 8 weeks), laboratory parameters, treatment regimens, and the relapse of CDAD.

According to the CDAD severity scoring system [10], patients with $\geq$ 2 points were considered to have severe disease. One point each was given for age $>$ 60 years, body temperature >38.3 °C, peripheral white blood cell (WBC) count $>$ 15,000 cells/mm^3, and serum albumin level <2.5 g/dL within 48 hours. Two points were given for endoscopic evidence of pseudomembranous colitis or treatment in the intensive care unit. Relapse was defined as complete abatement of CDAD symptoms while on initial antibiotic therapy with subsequent return of diarrhea within 4 weeks after completion of treatment.

Results were presented as average $\pm$ standard deviation. Mann–Whitney *U* test was used to compare differences in continuous variables such as age, serum creatinine, and albumin levels. Differences in proportions were assessed using Fisher exact test. Stepwise multivariate logistic regression analysis was performed for a few variables investigated in univariate analysis. A significant level of 5% was considered statistically significant. Data were recorded using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and statistical analyses were performed using the SAS package (version 6.10; SAS institute, Cary, NC, USA).

Table 1. Renal function of study groups

Renal function	CDAD ($n=85$)	Non-CDAD ($n=403$)	*P*
eGFR $\geq$ 60 mL/min/1.73 m^2	65 (76.5%)	316 (78.4%)	<0.001
eGFR 15–59 mL/min/1.73 m^2	4 (4.7%)	66 (16.4%)	
Dialysis treatment	16 (18.8%)	21 (5.2%)	

CDAD, *Clostridium difficile*-associated diarrhea; eGFR, estimated glomerular filtration rate.

Table 2. Baseline characteristics of study groups

	CDAD	Non-CDAD	*P*
All patients			
n	85	403	
Age (y)	61.8 ± 12.7	62.0 ± 17.3	0.93
Male gender (*n*, %)	40 (47.1%)	196 (48.6%)	0.81
Serum creatinine (mg/dL)	1.67 ± 2.00	1.23 ± 1.42	0.02
eGFR (mL/min/1.73m^2)	87.5 ± 50.4	84.8 ± ± 41.4	0.6
Serum albumin (g/dL)	3.1 ± 0.7	3.3 ± 0.7	0.03
Diabetes mellitus (*n*, %)	22 (25.9%)	102 (25.3%)	0.89
CKD stage 3–5			
n	20	87	
Age (y)	62.1 ± 11.3	69.4 ± 14.0	0.03
Male gender (*n*, %)	7 (35.0%)	44 (50.6%)	0.23
Serum creatinine (mg/dL)	4.75 ± 2.12	2.82 ± 2.49	0.002
eGFR (mL/min/1.73m^2)	14.6 ± 9.5	33.4 ± 17.9	<0.001
Serum albumin (g/dL)	2.7 ± 0.7	3.0 ± 0.7	0.17
Diabetes mellitus (*n*, %)	13 (65.0%)	39 (44.8%)	0.14
CKD stage 5D			
n	16	21	
Age (y)	60.4 ± 10.7	65.1 ± 12.6	0.24
Male gender (*n*, %)	6 (37.5%)	17 (81.0%)	0.02
Serum creatinine (mg/dL)	5.37 ± 1.83	6.17 ± 2.98	0.35
eGFR (mL/min/1.73m^2)	10.9 ± 3.9	9.8 ± 4.0	0.41
Serum albumin (g/dL)	2.7 ± 0.7	2.7 ± 0.7	0.99
Diabetes mellitus (*n*, %)	11 (68.8%)	15 (71.4%)	1

CDAD, *Clostridium difficile*-associated diarrhea; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Results

Data on renal function of CDAD ($n=85$) and non-CDAD patients ($n=403$) at presentation are presented in Table 1. There was a significant difference in the prevalence of CKD between CDAD and non-CDAD patients ($P<0.001$). In the CDAD group, 16 patients (18.8%) were treated with dialysis (12 hemodialysis, four peritoneal dialysis), and four patients (4.7%) had CKD stage 3–4 (eGFR, 15–59 mL/minute/1.73 m^2). In the non-CDAD group, 21 patients (5.2%) had end-stage renal disease (17 hemodialysis, four peritoneal dialysis), and 66 patients (16.4%) had CKD stage 3–4.

Table 2 shows the clinical characteristics of CDAD and non-CDAD patients and the data stratified by CKD stage. Taking all patients into account, the CDAD group had higher serum

Table 3. Risk factors associated with CDAD

Variables	OR	95% CI	*P*
Unadjusted			
CKD stage 3–5	1.1	0.63–1.92	0.73
CKD stage 5D	4.44	2.19–8.99	< 0.001
Age (y)	0.99	0.99–1.01	0.93
Diabetes mellitus	1.03	0.60–1.76	0.91
Male gender	0.91	0.59–1.50	0.79
Serum albumin (g/dL)	0.67	0.47–0.96	0.03
Serum creatinine (mg/dL)	1.19	1.02–1.31	0.02
eGFR (mL/min/1.73m^2)	1	1.00–1.01	0.6
Adjusted			
CKD stage 5D	13.36	2.94–60.67	0.001
Serum albumin (g/dL)	0.81	0.56–1.18	0.27
Serum creatinine (mg/dL)	0.77	0.58–1.02	0.07

CDAD, *Clostridium difficile*-associated diarrhea; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; OR, odds ratio.

creatinine level (1.67 ± 2.00 vs. 1.23 ± 1.42 mg/dL, $P=0.02$) than the non-CDAD group, but showed a significantly lower serum albumin level (3.1 ± 0.7 vs. 3.3 ± 0.7 g/dL, $P=0.03$). However, differences in serum albumin levels were not significant when CDAD and non-CDAD patients were compared by CKD stage.

Univariate and multivariate analysis of risk factors for CDAD are provided in Table 3. There was no significant association between renal function and development of CDAD in patients with CKD stage 3–5 [odds ratio (OR)=1.10, 95% confidence interval (CI)=0.63–1.92, $P=0.73$]. However, CKD stage 5D showed a significant association between renal function and development of CDAD (OR=4.44, 95% CI=2.19–8.99, $P<0.001$). Serum albumin (OR=0.67, 95% CI=0.47–0.96, $P=0.03$) and creatinine levels (OR=1.19, 95% CI=1.02–1.31, $P=0.02$) were significantly associated with CDAD. However, neither age nor diabetes mellitus or gender was related to CDAD. In multivariate analysis, CKD stage 5D was an independent risk factor for the development of CDAD (OR=13.36, 95% CI=2.94–60.67, $P=0.001$).

In the CDAD group, 81 patients (95.3%) had a record of recent antibiotic therapy. Recently prescribed antibiotics for any infectious cause were cephalosporins ($n=52$), followed by penicillin plus beta-lactamase inhibitor combinations ($n=18$), quinolone ($n=17$), aminoglycoside ($n=10$), glycopeptide ($n=9$), antituberculosis medication ($n=2$), macrolide ($n=2$), and clindamycin ($n=2$). Thirty-six patients (42.4%) had received two or more antibiotics. In dialysis patients, cephalosporins and penicillin plus beta-lactamase inhibitor combinations were the most commonly implicated agents. There was no statistically significant interaction between the classes of antimicrobial agents and CDAD occurrence.

General characteristics of patients with CDAD stratified by dialysis treatment are shown in Table 4. The significantly different characteristics between dialysis and nondialysis group were the serum albumin level, peripheral WBC count, and the presence of diabetes. We did not find a difference in the severity of CDAD in dialysis patients (56.3%) compared with nondialysis patients (43.5%).

Initial antibiotic therapy for CDAD consisted of oral administration of metronidazole in all patients. The dose of oral metronidazole was 250 mg four times daily, and the duration of antibiotic treatment was 10–14 days. Treatment failure occurred in three patients treated with metronidazole.

Table 4. Comparisons of characteristics of CDAD patients by dialysis treatment

	Control ($n=69$)	Dialysis ($n=16$)	*P*
Age (y)	62.1 ± 13.2	60.4 ± 10.7	0.68
Male gender (*n*, %)	34 (49.3%)	6 (37.5%)	0.42
Serum creatinine (mg/dL)	0.81 ± 0.48	5.37 ± 1.83	< 0.001
eGFR (mL/min/1.73m^2)	104.4 ± 37.5	10.8 ± 3.9	< 0.001
Serum albumin (g/dL)	3.2 ± 0.6	2.7 ± 0.7	0.006
WBC count (/mm^3)	9837 ± 5615	$14{,}599 \pm 7547$	0.03
Temperature (°C)	37.3 ± 0.8	37.5 ± 0.8	0.34
Duration of antibiotic use (d)	22.1 ± 15.7	24.8 ± 21.3	0.64
Diabetes mellitus (*n*, %)	11 (15.9%)	11 (68.8%)	< 0.001
Severe disease (*n*, %)	30 (43.5%)	9 (56.3%)	0.41

CDAD, *Clostridium difficile*-associated diarrhea, eGFR, estimated glomerular filtration rate; WBC, white blood cell.

Metronidazole failure occurred in two dialysis patients and one nondialysis patient. However, these differences were not statistically significant. In three patients with refractory symptoms, oral vancomycin (250 mg four times daily) was administered. All patients showed complete resolution of symptoms. During the study period, CDAD relapse occurred in nine (10.6%) of the 85 patients treated with metronidazole. Dialysis patients did not show significantly higher relapse rates than controls. Eleven patients (12.9%) died during the study period. CDAD was considered to be the main cause of death in one patient.

Discussion

Our data showed that dialysis patients, but not patients with CKD stage 3–5, had a higher incidence of CDAD. Despite a few publications regarding patients with CKD or AKI, there have been limited clinical studies reporting the development of CDAD in dialysis patients. In a previous study conducted in a hospital environment, the incidence of CDAD in the nephrology department was significantly higher than in the remaining departments of the hospital [6]; this study included mainly patients with AKI. Jung et al [7] reported that it took a short period for patients with impaired renal function to develop CDAD.

By contrast, Yousuf et al [8] reported that CKD (serum creatinine level > 1.5 mg/dL) was not a risk factor for CDAD, but its presence was associated with increased recurrence of CDAD. In this study, we also evaluated whether dialysis treatment was a risk factor for CDAD. We found that CKD stage 5D but not CKD stage 3–5, was a significant independent risk factor for the development of CDAD. This observation is consistent with the results of the study by Eddi et al [5], who reported that the association between CKD and CDAD remained insignificant in patients with CKD who were not undergoing dialysis treatment. However, the end-stage renal disease group did show a significant association. The reasons for this are not clear. Uremic patients have impaired host defense mechanisms as compared with nonuremic patients, which are typically ascribed to the immunodeficient state associated with uremia [11]. In addition, exposure to the dialysis membrane or peritoneal dialysis solution, the presence of vascular access, and episodes of latent or overt peritonitis may chronically aggravate inflammatory processes in patients undergoing maintenance dialysis. As a consequence, they are more often treated with broad-spectrum antibiotics for various infective complications.

Previous studies have reported that CKD is associated with severe and recurrent disease [8,12–14]. Leung et al [15] also reported that uremic patients suffered from severe disease with explosive diarrhea and systemic toxicity. In this study, we did not observe increased severity or relapse of CDAD in dialysis patients. Although there was a significant difference in serum albumin levels between the dialysis and nondialysis groups, it seemed to be associated with decreased renal function. Rubin et al. [13] defined severe disease as clinical decompensation resulting in intensive care unit admission or death. CKD occurred more commonly in cases of severe CDAD (33%) than mild CDAD (10%). However, there is no consensus definition for severe CDAD, nor is there agreement on the most important clinical indicators that should be used to differentiate severity. As a result, comparison between studies might be problematic. This may account for our findings being different from those of other studies. The majority of cases were promptly treated and resolved without major sequelae. The development of relapse (10.6%) was lower in our overall population than that reported by others [16–18].

CDAD is mediated by two toxins: *C difficile* toxin A and toxin B. Diagnosis is generally based on the identification of toxin A or toxin B. The gold standard for diagnosis of CDAD is tissue culture or cytotoxin assay of stool infiltrates. However, these techniques are laborious. Instead, more rapid immunoassays [enzyme-linked immunosorbent assays (ELISAs)] with comparable sensitivity (70–90%) and specificity (99%) are now widely used [19]. In our study, stool specimens were examined for toxin A using ELFA. The sensitivities of ELFA and ELISA for toxin A are similar, but the specificity and positive predictive value of ELFA are higher than those of ELISA [20]. Sigmoidoscopy or colonoscopy is not generally recommended in patients with typical clinical findings and positive stool toxin assay results. The importance of early diagnosis of CDAD is emphasized because the incidence and severity appear to be increasing [21,22]. When patients have classic clinical findings but negative results in stool toxin assays, it is important to consider CDAD and refer the patient for early endoscopy. In our study, CDAD developed as early as 2 days after antibiotic treatment completion; this was especially true in the case of dialysis patients. Clinicians should have a high index of suspicion of CDAD in dialysis patients developing diarrheal disease, especially during or shortly after antimicrobial therapy. Particular attention should be paid in dialysis patients.

Standard treatment for CDAD consists of oral administration of metronidazole or vancomycin. Metronidazole is less expensive and has lower potential for the development of resistant organisms. For these reasons, it has been commonly recommended as first-line therapy [23–25]. In this study, metronidazole treatment failure occurred in two dialysis patients and one control. However, there was no significant difference between the two groups, possibly because of the small number of cases. The reasons for higher treatment failure in dialysis patients are poorly understood. We hypothesized that if the drug was being extensively removed by hemodialysis or peritoneal dialysis, less metronidazole was delivered to the mucosa and the colonic lumen [26]. The limitations of our study were that it was retrospective and the sample size was relatively small.

In conclusion, our data indicate that dialysis patients might be at greater risk for the development of CDAD. This suggests that particular attention should be provided to CDAD, especially if the symptoms develop in dialysis patients.

Conflict of Interest

No conflict of interest has been declared.

Acknowledgments

The authors wish to acknowledge the contributions of the following individuals to this study: Dr Jacop Lee and Dr Heo Jung Kim in Kangnam Sacred Heart Hospital, Mr Jang-Herm Choi in management information team and nephrology staffs in Hallym University Medical Center. We also thank Dr Dong-Hyun Kim and his colleagues for their statistical support.

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