ORIGINAL ARTICLE

Korean J Intern Med 2016;31:125-133
http://dx.doi.org/10.3904/kjim.2016.31.1.125

KJIM

Advanced chronic kidney disease: a strong risk factor for *Clostridium difficile* infection

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Received: March 7, 2014
Revised : August 5, 2014
Accepted: September 3, 2014

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Background/Aims: It has been suggested that chronic kidney disease (CKD) is a risk factor for *Clostridium difficile* infection (CDI) and is associated with increased mortality among patients infected with *C. difficile*. However, recent studies of the clinical impact of CKD on CDI in Asians are still insufficient. We sought to determine the relationship between CKD and CDI in a Korean population.

Methods: This was a single-center, retrospective case-control study. In total, 171 patients with CDI were included as cases and 342 age- and gender-matched patients without CDI were used as controls. We compared the prevalence of CKD in the study sample and identified independent risk factors that could predict the development or prognosis of CDI.

Results: Independent risk factors for CDI included stage IV to V CKD not requiring dialysis (odds ratio [OR], 2.90) and end-stage renal disease requiring dialysis (OR, 3.34). Patients with more advanced CKD (estimated glomerular filtration rate < 30) and CDI showed higher in-hospital mortality and poorer responses to the initial metronidazole therapy.

Conclusions: More advanced CKD is an independent risk factor for CDI and is associated with higher in-hospital mortality and poor treatment responses in CDI patients. Thus, in CKD patients, careful attention should be paid to the occurrence of CDI and its management to improve the outcome of CDI.

Keywords: Renal insufficiency, chronic; Clostridium difficile; Dialysis; Risk factors

INTRODUCTION

Several studies have investigated risk factors for *Clostridium difficile* infection (CDI); antibiotic use, older age, gastric acid suppression therapy, admission to a healthcare facility, immunosuppression, and prolonged hospitalization have been identified [1-5]. The pathogenesis of CDI includes the transformation of the intestinal microbiota resulting from antibiotic use, pathogenic toxin production, and altered host inflammatory responses [6]. Since 2003, the propagation of a new strain of *C. difficile*, known as B1/NAP/027, has been reported in the United States (US), Canada, and Europe; the frequency of CDI with high recurrence and mortality rates has increased since [7-9]. In chronic kidney disease (CKD) patients, gastric acid suppression, impaired immune funcs tion, and increased antibiotic use can contribute to the development of CDI [10-13]. Additionally, recent studies demonstrated altered intestinal microbial flora in CKD patients, especially increased colonization with *Clostridium* sp., which may be associated with increased CDI [14]. A previous study using a national cohort of hospitalized patients in the US reported that CKD patients have a two-fold higher risk of CDI than non-CKD patients, and

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

end-stage renal disease (ESRD) patients requiring dialysis were at the highest risk of CDI [15]. They also reported that CDI was associated with longer hospital stays and higher mortality in CKD patients. However, the national database did not provide any information about potential confounders, such as antibiotics exposure, CDI treatment, comorbidities, and laboratory parameters. In addition, a case-control study by Eddi et al. [10] showed that ESRD patients requiring dialysis had a higher risk of CDI; however, CKD patients not on dialysis showed no increased risk of CDI. Previous studies investigating the clinical features of CDI in CKD patients not on dialysis have yielded conflicting results, and recent studies of the clinical impact of CKD on CDI in Koreans are still insufficient. We thus examined the association between CKD and CDI using a single-center cohort. We also investigated risk factors that could help predict the development or prognosis of CDI in advanced CKD patients.

METHODS

Study population

This retrospective case-control study was performed at the Korea University Anam Hospital, Seoul, Korea, and was approved by the Korea University Anam Hospital Institutional Review Board. From the computerized hospital database, we retrieved a list of all patients who had been admitted to the hospital between May 2010 and May 2013 and had tested positive for *C. difficile* toxin A or B in fecal specimens (TechLab Corp., Blacksburg, VA, USA). All patients who tested positive for *C. difficile* toxin A or B and had diarrhea were included. As we aimed to study patients admitted with CDI (inpatients), we included only patients who were admitted to our hospital for more than 3 days (in both case and control groups). In total, 219 patients admitted with CDI fulfilled these criteria; however, 48 patients who were receiving chemotherapy or had terminal malignancies with life expectancies of less than 3 months were excluded. Finally, 171 patients were included in the patient group, and twice as many patients who had been admitted during the same period with matching age and gender were included in the control group.

Clinical data

Patient baseline characteristics included the gender, age, history of diabetes and hypertension, intensive care unit (ICU) admission, use of antibiotics or gastric acid-reducing drugs (GARDs) during the admission, CKD stage at admission, length of hospital stay, and in-hospital mortality. All patients were classified into (1) non-advanced CKD (estimated glomerular filtration rate [eGFR] ≥ 60 mL/min/1.73 m^2), (2) stage III CKD (eGFR = 30 to 59 mL/min/1.73 m^2), (3) stage IV to V CKD not requiring dialysis (eGFR < 30 mL/min/1.73 m^2), or (4) ESRD requiring dialysis according to baseline creatinine level at admission and previous laboratory data within 3 months. The patients who had acute kidney injury (AKI) at admission were not considered to have CKD when their eGFR improved to the normal range (≥ 60 mL/min/1.73 m^2). Patients with AKI on CKD were classified according to previous laboratory data or improved eGFR during admission. In all cases, the eGFR was calculated using the modification of diet in renal disease equation.

For subgroup analysis in the CDI patient group, fever (> 38.3°C), hypotension (systolic blood pressure < 90 mmHg), AKI, levels of albumin, hemoglobin A1c, and white blood cell (WBC) count when diagnosed with CDI were also recorded. In the subgroup analysis of CDI patients, the data collected on ICU admission in the previous 3 months, and use of antibiotics or GARD in the preceding 6 weeks were based on the date of diagnosis of CDI.

For prognostic evaluations, primary treatment regimen, recurrence of CDI, time from admission to diagnosis, time from diagnosis to discharge, length of hospital stay, and in-hospital mortality were analyzed. Recurrence of CDI was defined as the recurrence of diarrhea and a positive *C. difficile* toxin test result within 1 month after the termination of therapy. Treatment resistance was defined as the additional use of vancomycin for CDI treatment due to initial metronidazole resistance.

Statistical analysis

All analyses and calculations were performed using IBM SPSS version 20.0 (IBM Co., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range), according to the distribution. Pearson chi-square tests were used

http://dx.doi.org/10.3904/kjim.2016.31.1.125

to analyze nominal data. Continuous variables of the groups were analyzed using the independent-sample *t* test or the Mann-Whitney test, according to the distribution. In multivariate analysis, a binary logistic regression model was used to calculate adjusted odds ratios (ORs). A $p < 0.05$ was considered to indicate statistical significance.

RESULTS

Baseline characteristics

The baseline characteristics are shown in Table 1. The mean age of the CDI patients was 71 years. The mean time from admission to CDI diagnosis was 27.8 days, and most of the patients with CDI were diagnosed with hospital-acquired CDI (96.4%, data not shown). Patients with CDI had a higher prevalence of ICU admissions, emergency admissions, advanced CKD, antibiotics use, and GARD use. The prevalences of ESRD requiring dialysis and CKD stage IV to V not requiring dialysis were significantly higher among CDI patients than among patients without CDI. Patients with CDI had a significantly longer length of hospital stay (median, 43 days vs. 10 days; $p < 0.001$) and increased in-hospital mortality (8.2% vs. 2.6%, $p = 0.006$) than patients without CDI.

CKD stage as an independent predictor of CDI

We applied a multivariate logistic regression model with backward elimination to calculate an adjusted OR for CDI in patients with CKD (Table 2). Model 1 was ad-

Table 1. Baseline characteristics of the patients

Characteristic	CDI (n = 171)	Non-CDI (n = 342)	*p* value
Age, yr	71 (57.75–77)	71 (58–78)	0.907
Male sex	86 (50.3)	172 (50.3)	1.000
History			
Diabetes	56 (32.7)	94 (27.5)	0.219
Hypertension	103 (60.2)	175 (51.2)	0.060
ICU admission	64 (37.4)	58 (17.0)	0.000
Use of any antibiotics	157 (91.8)	240 (70.2)	0.000
GARD use	116 (67.8)	200 (58.5)	0.043
Advanced CKD (including ESRD) (eGFR < 60 mL/min/1.73 m^2)	49 (28.7)	59 (17.3)	0.004
CKD stages			< 0.001
Non-advanced CKD (eGFR ≥ 60 mL/min/1.73 m^2)	122 (71.3)	283 (82.7)	
Stage III CKD	17 (9.9)	41 (12.0)	
Stage IV–V CKD	10 (5.8)	8 (2.3)	
ESRD requiring dialysis	22 (12.9)	10 (2.9)	
Reason for admission			0.148
Surgical	57 (33.3)	137 (40.1)	
Nonsurgical	114 (66.7)	205 (59.9)	
Admission type			0.005
Elective	22 (12.9)	72 (21.1)	
Urgent	43 (25.1)	108 (31.6)	
Emergent	106 (62.0)	162 (47.4)	
Length of hospital stay, day	43 (21–74)	10 (5–19)	< 0.001
In-hospital mortality	14 (8.2)	9 (2.6)	0.006

Values are presented as median (confidence interval 25%–75%) or number of patients (%).
CDI, *Clostridium difficile* infection; ICU, intensive care unit; GARD, gastric acid-reducing drug; CKD, chronic kidney disease; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate.

justed for all parameters with a p value < 0.10, with the exception of in-hospital mortality in a univariate model, and model 2 with a p value < 0.20. Patients with advanced CKD (eGFR < 60 mL/min/1.73 m^2) had an increased risk of CDI in model 1 (OR, 2.10; p = 0.003) and model 2 (adjusted OR, 1.98; p = 0.007). When advanced CKD patients were classified into two groups according to dialysis (CKD stage III to V not on dialysis, ESRD on dialysis), advanced CKD (stage III to V) not on dialysis was not associated with CDI (data not shown). However, when classified into three groups according to CKD stages (CKD stage III, CKD stage IV to V not on dialysis, and ESRD on dialysis), patients with more advanced CKD (stage IV to V) showed a 2.8- to 2.9-fold higher risk of CDI even though they were not on dialysis. Patients with ESRD requiring dialysis were at the highest risk of CDI (OR, 3.34 to 3.68), compared with non-advanced CKD.

Characteristics of CDI patients according to CKD stage

In this study, patients with stage IV to V CKD had a significantly higher risk of CDI (regardless of whether they were undergoing dialysis) than non-advanced CKD patients (eGFR ≥ 60 mL/min/1.73 m^2). Thus, we further analyzed the CDI characteristics according to CKD stage. For this analysis, CDI patients were classified into two groups based on the eGFR value (> 30 or < 30 mL/min/1.73 m^2) (Table 3). Patients with more advanced CKD (eGFR < 30 mL/min/1.73 m^2) had a significantly higher prevalence of hypertension and many of these patients were men; moreover, they had significantly higher WBC counts. More advanced CKD was also associated with higher in-hospital mortality. However, there was no significant difference between the two groups regarding the use of antibiotics or GARD, the recurrence of CDI, the initial treatment regimen, the length of hospital stay from admission to diagnosis, or the time from diagnosis to discharge. Treatment resistance was significantly higher in the group with more advanced CKD (28.1% vs. 12.2%, p = 0.031).

Table 2. Risk-adjusted analysis to evaluate CKD as an independent predictor of *Clostridium difficile* infection

Variable	Odds ratio	95% Confidence interval	p value
All advanced CKD (eGFR < 60 mL/min/1.73 m^2)			
Model 1[a]	2.10	1.29–3.42	0.003
Model 2[b]	1.98	1.20–3.25	0.007
CKD stages			
Non-advanced CKD			
Model 1[a]	-	-	-
Model 2[b]	-	-	-
Stage III CKD			
Model 1[a]	1.33	0.68–2.62	0.396
Model 2[b]	1.27	0.64–2.50	0.485
Stage IV–V CKD (non-dialysis)			
Model 1[a]	2.84	1.02–7.89	0.044
Model 2[b]	2.90	1.01–8.31	0.048
ESRD requiring dialysis			
Model 1[a]	3.68	1.58–8.57	0.003
Model 2[b]	3.34	1.42–7.87	0.006

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.
[a]Model 1 is adjusted for hypertension, intensive care unit admission, use of any antibiotics, gastric acid-reducing drug use, admission type, length of hospital stay.
[b]Model 2 is adjusted for all variables in model 1 plus reason for admission.

http://dx.doi.org/10.3904/kjim.2016.31.1.125

Clinical features of patients with treatment resistance

Patients who experienced treatment resistance to initial metronidazole therapy had significantly higher prevalences of the use of more than two antibiotics, vancomycin use before CDI diagnosis, more advanced CKD (eGFR < 30 mL/min/1.73 m^2), and higher WBC counts than patients without treatment resistance. The recurrence of CDI was higher in the group with treatment resistance, although this difference was not statistically significant. In-hospital mortality also did not differ between the patients with treatment resistance and those without (Table 4). A logistic regression model was used for multivariate analysis to identify risk factors associated with treatment resistance. All parameters with a $p < 0.20$ in the univariate model were considered in the multivariate analysis. Considering the previous use of two or more antibiotics, carbapenem use, vancomycin use, WBC count > 15 × 10^3/μL, and more advanced CKD as variables for the multivariate logistic regression analysis (backward method), the previous use of two or more antibiotics (OR, 3.47; $p = 0.020$) or vancomycin (OR, 5.64; $p = 0.036$), WBC count > 15 × 10^3/μL (OR, 4.11; $p = 0.003$), and more advanced CKD (OR, 2.83; $p = 0.048$) were independent risk factors for treatment resistance (Table 5).

DISCUSSION

In this study, we observed the following: (1) stage IV to V CKD not requiring dialysis, as well as ESRD requiring dialysis were independent risk factors for CDI, and ESRD patients on dialysis had a much higher risk for CDI; (2) more advanced CKD (eGFR < 30 mL/min/1.73 m^2) was associated with higher in-hospital mortality due to CDI; and (3) patients who had treatment resistance showed significantly higher prevalences of previous use of two or more antibiotics, previous use of vancomycin, WBC count > 15 × 10^3/μL, and more advanced CKD.

Risk factors for CDI include antibiotic use, older age, gastric acid suppression therapy, admission to a healthcare facility, immunosuppression, and prolonged hospitalization [1-5]. CKD has also been suggested to be a risk factor for CDI and is associated with increased mortality, lower treatment response, and higher recurrence rates [10,15-17]. Although the reason for the association between CDI and CKD is unclear, recent studies have shown that CKD is associated with systemic chronic inflammation and subsequent acquired immunodeficiency that leads to increased susceptibility to infection [18,19]. Furthermore, gastric acid suppression or microorganism overgrowth caused by intestinal dysmotility is frequently observed in CKD patients; this may also contribute to increased risk of CDI [12,13]. These results suggest that CKD could also be an important risk factor for CDI and affect its prognosis. However, it is not clear whether CKD not requiring dialysis is also a risk factor for CDI, because previous studies have yielded conflicting results [10,15,16]. Eddi et al. [10] reported that the association between CKD and CDI was insignificant in patients with stage III to V CKD who were not on dialysis, whereas in a study by Keddis et al. [15], CKD patients not on dialysis had a higher incidence of CDI than non-CKD patients ($p < 0.001$). Thus, in this study, we investigated the CDI risk factors according to the CKD stage and found that stage IV to V CKD not requiring dialysis and ESRD requiring dialysis were significant independent risk factors for CDI. Thus, we suggest that the recent increase in the occurrence of CDI may be due to the increasing number of people with CKD.

Previous use of antibiotics is the most important cause of CDI. Almost all antibiotics can lead to the development of CDI, although second/third generation cephalosporins, clindamycin, and fluoroquinolones seem to play the most important role in its development [2,20]. In terms of CDI management, discontinuation of antibiotics that may cause CDI and initiating therapy with metronidazole or vancomycin according to CDI severity are recommended [21]. If there is no improvement in clinical symptoms after the initial therapy with metronidazole, switching to vancomycin or the addition of vancomycin is required. In our center, this clinical practice guideline is followed. In the analysis of the treatment response of CDI, we found that CKD was associated with poor clinical outcome among patients with CDI, similar to that in previous studies, showing that CKD patients have longer treatment periods [17] and higher in-hospital morbidity [15,16]. In this study, initial treatment resistance was more common in CKD patients. The in-hospital mortality rate was also significantly higher among patients with advanced CKD than in non-advanced CKD patients. These results suggest

Table 3. Characteristics of CDI patients according to the more advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m^2)

Characteristic	CDI patients with eGFR ≥ 30 (n = 139)	CDI patients with eGFR < 30 (n = 32)	*p* value
Age, yr	74 (64–79)	71 (57–74)	0.987
Male sex	64 (46.0)	22 (68.8)	0.030
History			
Diabetes	43 (30.9)	13 (40.6)	0.303
Hypertension	74 (53.2)	29 (90.6)	0.000
ICU admission in the past 90 days	47 (33.8)	17 (53.1)	0.067
Antibiotic use in the past 42 days			
Use of any antibiotic	128 (92.1)	29 (90.6)	0.728
Use of two or more antibiotics	74 (53.2)	15 (46.9)	0.560
Cephalosporin use	85 (62.1)	22 (66.8)	0.544
Quinolone use	46 (33.1)	7 (21.9)	0.290
Carbapenem use	23 (16.5)	2 (6.2)	0.172
Macrolide use	6 (4.3)	3 (9.4)	0.372
Trimethoprim/sulfamethoxazole use	7 (5.0)	1 (3.1)	1.000
Metronidazole use	9 (6.5)	1 (3.1)	0.690
Use of antifungal agents	10 (7.2)	0	0.211
Tazocin use	24 (17.3)	8 (25.0)	0.321
Vancomycin use	7 (5.0)	1 (3.1)	1.000
GARD use in the past 42 days	92 (66.2)	24 (75.0)	0.405
Fever (> 38.3°C)	47 (33.8)	8 (25.0)	0.405
Shock (SBP < 90 mmHg)	13 (9.4)	4 (12.5)	0.528
Acute kidney injury	12 (8.6)	4 (12.5)	0.505
Albumin	3.0 (2.7–3.3)	2.9 (2.6–3.0)	0.175
Hemoglobin A1c	5.9 (5.4–6.7)	6.0 (5.7–6.6)	0.924
WBC count > 15 × 10^3/μL	37 (26.6)	16 (50.0)	0.018
CDI treatment at diagnosis			
Metronidazole	129 (92.8)	30 (93.8)	1.000
Vancomycin	10 (7.2)	2 (6.2)	1.000
Switched from metronidazole to vancomycin	17 (12.2)	9 (28.1)	0.031
Recurrence of CDI	17 (12.5)	4 (14.8)	0.755
In-hospital mortality	7 (5.0)	7 (21.9)	0.006
Length of hospital stay, day	39.5 (19–68)	45 (25–72)	0.891
Time from admission to diagnosis	17(8–31)	23 (8–38)	0.632
Time from diagnosis to discharge	15.5 (6–44)	17 (9–38)	0.921

Values are presented as median (confidence interval 25%–75%) or number of patients (%).
CDI, *Clostridium difficile* infection; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; GARD, gastric acid-reducing drug; SBP, systolic blood pressure; WBC, white blood cell.

that careful management and follow-up of CDI is required, especially in CKD patients.

In summary, more advanced CKD, with an eGFR < 30 mL/min/1.73 m^2 is a risk factor for CDI even in CKD patients not on dialysis. Additionally, advanced CKD is associated with poor clinical outcome of CDI, particular-

http://dx.doi.org/10.3904/kjim.2016.31.1.125

Table 4. Characteristics of CDI patients with treatment resistance

Characteristic	Resistant (n = 26)	Non-resistant (n = 145)	*p* value
Age, yr	73.5 (55.25–75)	72 (64–79)	0.491
Male sex	12 (46.2)	74 (51.0)	0.676
History			
Diabetes	11 (42.3)	45 (31.0)	0.265
Hypertension	18 (69.2)	85 (58.6)	0.386
ICU admission in the past 90 days	11 (42.3)	53 (36.6)	0.661
Antibiotic use in the past 42 days			
Use of any antibiotic	26 (100.0)	131 (90.3)	0.132
Use of two or more antibiotics	20 (86.9)	69 (47.6)	0.010
Cephalosporin use	19 (73.1)	88 (60.7)	0.276
Quinolone use	9 (34.6)	44 (30.3)	0.652
Carbapenem use	7 (26.9)	18 (12.4)	0.070
Macrolide use	2 (7.7)	7 (4.8)	0.628
Trimethoprim/sulfamethoxazole use	0	8 (5.5)	0.609
Metronidazole use	2 (7.7)	8 (5.5)	0.650
Use of antifungal agents	2 (7.7)	8 (5.5)	0.650
Tazocin use	6 (23.1)	26 (17.9)	0.586
Vancomycin use	4 (15.4)	4 (2.8)	0.019
GARD use in the past 42 days	20 (76.9)	96 (66.2)	0.364
Fever (> 38.3°C)	11 (42.3)	44 (30.3)	0.258
Shock (SBP < 90 mmHg)	2 (7.7)	15 (10.3)	1.000
Acute kidney injury	3 (11.5)	13 (9.0)	0.714
Albumin	2.95 (2.62–3.17)	2.90 (2.70–3.20)	0.791
Hemoglobin A1c	6.15 (5.80–6.60)	5.9 (5.50–6.70)	0.753
WBC count > $15 \times 10^3/\mu L$	16 (61.5)	37 (25.5)	0.001
More advanced CKD (eGFR < 30 mL/min/1.73 m^2)	9 (34.6)	23 (15.9)	0.031
Recurrence of CDI	6 (24.0)	15 (10.9)	0.099
In-hospital mortality	3 (11.5)	11 (7.6)	0.450

Values are expressed as median (confidence interval 25%–75%) or number of patients (%).
CDI, *Clostridium difficile* infection; ICU, intensive care unit; GARD, gastric acid-reducing drug; SBP, systolic blood pressure; WBC, white blood cell; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Table 5. Multivariate logistic regression analysis[a] of risk factors for treatment resistance (backward method)

Variable	Odds ratio	95% CI	*p* value
Use of two or more antibiotics	3.47	1.21–9.95	0.020
Vancomycin use	5.64	1.11–28.52	0.036
WBC count > $15 \times 10^3/\mu L$	4.11	1.61–10.50	0.003
More advanced CKD (eGFR < 30 mL/min/1.73 m^2)	2.83	1.00–7.94	0.048

CI, confidence interval; WBC, white blood cell; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
[a]Included variables: use of two or more antibiotics, carbapenem use, vancomycin use, WBC count > $15 \times 10^3/\mu L$, and more advanced CKD.

ly with poor response to initial treatment and increased in-hospital mortality. Thus, in CKD patients, careful attention should be paid to the occurrence of CDI and its management to improve the outcome of CDI. Considering the recent changes in the epidemiology and clinical severity of CDI in Korea, further long-term prospective studies with larger sample sizes based on the CKD stage will be useful to assess the clinical impact of CKD on CDI.

KEY MESSAGE

1. Advanced chronic kidney disease (CKD), with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 is a risk factor for *Clostridium difficile* infection (CDI) even in CKD patients not on dialysis.
2. Advanced CKD (eGFR < 30 mL/min/1.73 m^2) was associated with higher in-hospital mortality among patients with CDI.
3. Patients who had poor response to initial CDI treatment showed significantly higher prevalences of previous use of two or more antibiotics, previous use of vancomycin, white blood cell count > 15 × 10^3/μL, and more advanced CKD.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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