RESEARCH LETTER

Clostridioides difficile Infection Among Patients Requiring Maintenance Hemodialysis

To the Editor:

Clostridioides difficile is the most common cause of gastroenteritis-related death in the United States.[1] Rates of *C difficile* infection (CDI) are increasing in the maintenance hemodialysis (HD) population.[2] These patients are 2.5 times more likely to develop CDI and have 2-fold higher mortality rates compared with the general population.[3,4] Hospital costs and lengths of stay are also longer.[5] There is a paucity of data pertaining to the clinical epidemiology of CDI among patients requiring maintenance HD. To improve the management and outcomes of CDI in this patient population, we characterized clinical factors associated with severe or fulminant CDI, compared with nonsevere CDI, and identified the subset of maintenance HD patients with CDI at highest risk for mortality.

From January 2015 through December 2018, a retrospective cohort study among patients requiring maintenance HD with a diagnosis of CDI at admission to a 700- and 255-bed tertiary-care hospital in Rhode Island was conducted. Approval from the ethics board was obtained (#1327710). Informed consent was waived because the study was retrospective. Only the first episode per patient was included. CDI was defined as a positive test result using the GeneXpert assay (Cepheid) and documentation of diarrhea. Infectious Diseases Society of America (IDSA) criteria were used to classify CDI severity.[6] Nonsevere and severe CDI were defined as a white blood cell (WBC) count ≤ 15,000 cells/mL and WBC count ≥ 15,000 cells/mL, respectively. Fulminant CDI required the presence of hypotension or shock, megacolon, or ileus. IDSA criteria also include serum creatinine values but these were excluded in the study definitions.

IDSA guidelines were used to determine the appropriateness of CDI treatment.[6] Clinical data and requirement for maintenance HD were collected using Theradoc (Premier, Inc), a clinical surveillance software used nationwide by infection preventionists to monitor infections within hospitals, and review of electronic medical records. Variables with $P \leq 0.05$ on univariable analyses were included in a stepwise logistic and Cox regression model to identify independent variables associated with baseline characteristics and 60-day mortality, respectively.

A total of 129 patients requiring maintenance HD were admitted with a primary diagnosis of CDI during the study period, of which 26 (20.2%) were recurrences and 103 (80%) were a first CDI episode. All patients had diarrhea and a positive GeneXpert assay result. A subset of patients had a second admitting diagnosis, including another infection, including bloodstream, skin or soft tissue, or lung (N = 26 [25.2%]); altered mental status (N = 9 [8.7%]); diabetic ketoacidosis (N = 5 [4.9%]); congestive heart failure (N = 5 [4.9%]); and mechanical fall (N = 1 [1.0%]).

A total of 68 (66%) study patients had nonsevere CDI, 23 (22%) had severe CDI, and 12 (12%) had fulminant CDI. Among those with fulminant CDI, all had either hypotension or shock and 1 had evidence of ileus. The average WBC count for nonsevere and severe or fulminant CDI was 7.4 (range, 2.3-13.1) cells/mL and 17.2 (range, 2.9-33.0) cells/mL, respectively. All patients were treated appropriately as per IDSA guidelines. A total of 19 patients (18.4%) died within 60 days. Among these, cause of death was as follows: unknown (patient died at home; N = 8 [42.1%]), septic shock (N = 4 [21.1%]), and cardiogenic shock (N = 7 [36.8%]). Analyses of factors associated with nonsevere compared with severe or fulminant CDI at admission and factors associated with 60-day mortality are shown in Tables 1 and 2.

In this study, patients requiring maintenance HD who presented to the hospital with severe or fulminant CDI, compared with nonsevere CDI, were more likely to be older and have had exposure to extended-spectrum penicillins in the previous 90 days, with 3.6-fold higher risk for death within 60 days after CDI diagnosis. Among patients who died, peripheral vascular disease, lower albumin level, and presenting with severe or fulminant CDI were associated with 60-day mortality.

Antimicrobial exposure is a well-defined risk factor for CDI.[6] Antimicrobial stewardship programs have been shown to be effective in reducing inappropriate antimicrobial prescribing within outpatient dialysis facilities.[7] Implementation of these programs should consider targeting extended-spectrum penicillins to minimize the occurrence of severe or fulminant CDI among the maintenance HD population. Other interventions to improve CDI outcomes should include a focus on optimizing albumin levels because low albumin levels have been associated with greater risk for CDI among patients requiring maintenance HD and, in this study, were associated with greater risk for mortality.[8]

Limitations of this study are lack of generalizability because only 2 hospitals were included and that antimicrobials administered in outpatient dialysis units were not captured. In addition, the study used the IDSA criteria for CDI severity, which require validation in the maintenance HD population.[9]

Improving outcomes of CDI entails accurate recognition of factors associated with CDI and poor outcomes to optimize treatment and management decisions. This study identifies a subset of patients at higher risk for severe or fulminant CDI and modifiable risk factors associated with the severity of CDI and mortality.

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Table 1. Characteristics and Clinical Data of Patients Requiring Maintenance Hemodialysis With CDI at Hospital Admission

Variable	Nonsevere CDI[a] (n = 68; 66.0%)	Severe/Fulminant CDI[a] (n = 35; 34.0%)	Univariable OR (95% CI)	*P*	Multivariable aOR (95% CI)	*P*
Age ≥ 65 y	27 (39.7%)	28 (80.0%)	6.1 (2.33-15.9)	<0.01	6.3 (2.25-17.45)	<0.01
Female sex	34 (50.0%)	16 (45.7%)	0.8 (0.37-1.91)	0.68		
Race						
Hispanic/Latino	18 (26.5%)	6 (17.1%)	0.6 (0.21-1.61)	0.29		
White	39 (57.4%)	22 (62.9%)	Reference	-		
Black/African American	14 (20.6%)	8 (22.9%)	1.0 (0.36-2.72)	0.98		
Other	15 (22.1%)	5 (14.3%)	1.7 (0.54-5.29)	0.37		
Charlson Comorbidity Index score	6.7±3.9	7.0±3.5	0.98 (0.88-1.09)	0.68		
Comorbid conditions						
Peripheral vascular disease	18 (26.5%)	13 (37.1%)	1.6 (0.69-3.93)	0.27		
COPD	27 (39.7%)	13 (37.1%)	0.9 (0.39-2.08)	0.80		
Rheumatic disease	3 (4.4%)	1 (2.9%)	0.6 (0.0-6.362)	0.70		
Diabetes with chronic complications	40 (58.8%)	21 (60.0%)	1.1 (0.46-2.41)	0.91		
Moderate severe liver disease	3 (4.4%)	3 (8.6%)	2.0 (0.39-10.6)	0.40		
HIV/AIDS	4 (5.9%)	2 (5.7%)	1.0 (0.17-5.57)	0.97		
Any malignancy	9 (13.2%)	2 (5.7%)	0.4 (0.08-1.95)	0.26		
Type of vascular access						
AVF	60 (88.2%)	29 (82.9%)	Reference	—		
CVC/TDC	8 (11.8%)	6 (17.1%)	1.6 (0.49-4.89)	0.45		
Hospitalizations in previous 6 mo						
0	32 (47.1%)	14 (40.0%)	1.32 (0.50-3.50)	0.57		
1	17 (25.0%)	10 (28.6%)	0.98 (0.34-2.89)	0.98		
>1	19 (27.9%)	11 (31.4%)	Reference	—		
Albumin, g/dL[b]	3.2±0.6	3.0±0.6	1.4 (0.73-2.88)	0.29		
Hemoglobin, g/dL[b]	10.0±1.8	9.4±1.5	1.3 (0.99-1.66	0.06		
Antibiotics in previous 90 d						
All	52 (76.5%)	28 (80.0%)	1.2 (0.45-3.35)	0.68		
1st-generation cephalosporins	42 (61.8%)	10 (28.6%)	0.6 (0.26-1.56)	0.33		
2nd-generation cephalosporins	1 (1.5%)	0 (0.0%)	NA	—		
3rd-generation cephalosporins	17 (25.0%)	14 (40.0%)	2.0 (0.84-4.78)	0.12		
Macrolides	5 (7.4%)	2 (5.7%)	0.8 (0.14-4.15)	0.75		
Clindamycin	4 (5.9%)	2 (5.7%)	1.0 (0.17-5.57)	0.97		
Fluoroquinolones	11 (16.2%)	9 (25.7%)	1.8 (0.66-4.85)	0.25		
Simple penicillins	3 (4.4%)	6 (17.1%)	4.5 (1.05-19.2)	0.04		
Extended-spectrum penicillins	24 (35.3%)	22 (62.9%)	3.1 (1.33-7.24)	<0.01	2.69 (1.05-6.85)	0.04
Aminoglycoside	4 (5.9%)	0 (0.0%)	NA	—		
Carbapenems	3 (4.4%)	0 (0.0%)	NA	—		
TMP-SMX	6 (8.8%)	3 (8.6%)	1.0 (0.23-4.13)	0.97		
60-d mortality	8 (11.8%)	11 (31.4%)	3.44 (1.23-9.59)	0.02	3.62 (1.12-11.74)	0.03

Note: Values expressed as mean ± standard deviation or number (percent).

Abbreviations: aOR, adjusted odds ratio; AVF, arteriovenous fistula; CVC, central venous catheter; CDI, *Clostridioides difficile infection*; COPD, chronic obstructive pulmonary disease; extended-spectrum penicillins, piperacillin-tazobactam; OR, odds ratio; TDC, tunneled dialysis catheter; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]A total of 12 (11.7%) patients with CDI had a recurrence within 8 weeks of the initial episode. Treatment regimens for the initial episode were as follows: oral metronidazole, vancomycin, or fidaxomicin for nonsevere CDI; oral vancomycin or oral vancomycin plus metronidazole for severe CDI; and high-dose vancomycin ± intravenous metronidazole or rectal vancomycin for fulminant CDI.

[b]Values were obtained within 48 hours of hospital admission.

Table 2. Analysis of Factors Associated With 60-Day Mortality Among Patients Requiring Maintenance Hemodialysis With CDI at Hospital Admission

Variable[a]	Alive (N = 84; 81.6%)	Dead (N = 19; 18.4%)	Univariable HR (95% CI)	P	Multivariable aHR (95% CI)	*P*
Age ≥ 65 y	44 (52.4%)	11 (57.9%)	0.78 (0.31-1.93%)	0.59	1.23 (0.43-3.51)	0.70
Female sex	44 (52.4%)	6 (31.6%)	0.47 (0.18-1.23%)	0.12	0.36 (0.12-1.09)	0.07
Race						
Hispanic/Latino	19 (22.6%)	5 (26.3%)	1.19 (0.43-3.29)	0.74	1.21 (0.41-3.53)	0.73
White/Caucasian	51 (60.7%)	10 (52.6%)	Reference	—	Reference	—
Black/African American	18 (21.4%)	4 (21.1%)	1.14 (0.36-3.63)	0.83	1.49 (0.45-4.99)	0.51
Other	15 (17.9%)	5 (26.3%)	1.59 (0.54-4.64)	0.40	2.42 (0.78-7.52)	0.13
Charlson Comorbidity Index score	6.6±3.6	7.7±4.5	1.07 (0.96-1.20)	0.23	1.08 (0.95-1.24)	0.25
Comorbid conditions						
Peripheral vascular disease	22 (26.2%)	9 (47.4%)	2.32 (0.94-5.72)	0.07	3.09 (1.19-8.06)	0.02
COPD	31 (36.9%)	9 (47.4%)	1.51 (0.61-3.70)	0.37	1.80 (0.69-4.68)	0.23
Rheumatic disease	4 (4.76%)	0 (0.00%)	NA	—	NA	—
Diabetes with chronic complications	49 (58.3%)	12 (63.1%)	1.22 (0.48-3.10)	0.68	1.53 (0.53-4.39)	0.43
Moderate severe liver disease	5 (5.95%)	1 (5.26%)	0.90 (0.12-6.73)	0.90	0.57 (0.07-4.33)	0.58
HIV/AIDS	3 (3.57%)	3 (15.8%)	3.03 (0.88-10.40	0.08	1.65 (0.37-7.36)	0.51
Any malignancy	9 (10.7%)	2 (10.5%)	0.95 (0.22-4.09)	0.94	1.62 (0.37-7.16)	0.53
Type of vascular access						
AVF	73 (86.9%)	16 (84.2%)	Reference	—	Reference	—
CVC/TDC	11 (13.1%)	3 (15.8%)	1.33 (0.39-4.56)	0.65	1.10 (0.31-3.92)	0.89
Hospitalizations in previous 6 mo						
0	40 (47.6%)	6 (31.6%)	0.64 (0.21-1.97)	0.43	0.55 (0.15-2.01)	0.36
1	20 (23.8%)	7 (36.8%)	1.35 (0.46-4.03)	0.59	1.15 (0.37-3.57)	0.81
>1	24 (28.6%)	6 (31.6%)	Reference	—	Reference	—
Severe/fulminant CDI	24 (28.6%)	11 (57.9%)	3.19 (1.28-7.95)	0.01	3.45 (1.28-9.45)	0.01
Albumin, g/dL	3.21±0.66	2.79±0.3	0.42 (0.20-0.88)	0.02	0.45 (0.21-0.94)	0.03
Hemoglobin, g/dL	9.9±1.8	9.46±1.7	0.87 (0.66-1.16)	0.35	0.96 (0.70-1.32)	0.80
Antibiotics in previous 90 d						
All	64 (76.1%)	16 (84.2%)	1.59 (0.46-5.45)	0.46	1.10 (0.22-5.46)	0.91
1st-generation cephalosporins	28 (33.3%)	8 (42.1%)	1.38 (0.55-3.43)	0.49	1.73 (0.66-4.53)	0.26
2nd-generation cephalosporins	1 (1.2%)	0 (0.00%)	NA	—	NA	—
3rd-generation cephalosporins	26 (31.0%)	5 (26.3%)	0.82 (0.30-2.28)	0.71	0.45 (0.14-1.45)	0.18
Macrolides	5 (5.95%)	2 (10.5%)	1.58 (0.36-6.83)	0.54	1.63 (0.37-7.13)	0.52
Clindamycin	5 (5.95%)	1 (5.26%)	0.91 (0.12-6.79)	0.92	1.36 (0.18-10.32)	0.77
Fluoroquinolones	17 (20.2%)	3 (15.8%)	0.73 (0.21-2.51)	0.62	0.76 (0.22-2.68)	0.67
Simple penicillins	7 (8.33%)	2 (10.5%)	1.29 (0.30-5.58)	0.73	0.80 (0.18-3.54)	0.77
Extended-spectrum penicillins	35 (41.7%)	11 (57.9%)	1.82 (0.73-4.53)	0.20	1.21 (0.42-3.53)	0.72
Aminoglycosides	4 (4.76%)	0 (0.00%)	NA	—	NA	—
Carbapenems	3 (3.57%)	0 (0.00%)	NA	—	NA	—
TMP-SMX	8 (9.52%)	1 (5.26%)	0.52 (0.07-3.395)	0.53	0.48 (0.06-3.64)	0.48

Note: Values expressed as mean ± standard deviation or number (percent).
Abbreviations: aHR, adjusted hazard ratio; AVF, arteriovenous fistula; CDI, *Clostridioides difficile infection*; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; extended-spectrum penicillins, piperacillin-tazobactam; HR, hazard ratio; NA, not applicable; TDC, tunneled dialysis catheter; TMP-SMX, trimethoprim-sulfamethoxazole; WBC, white blood cell count.
[a]Variables were obtained within 48 hours of CDI diagnosis from hospital admission. End of follow-up period was 60 days.

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Support: This work was supported by National Institutes of Health grant K24 AI119158 and Agency for Healthcare Research and Quality grant R01HS026895 (Dr D'Agata).

Financial Disclosure: None.

Peer Review: Received November 9, 2020. Evaluated by 1 external peer reviewer, with direct editorial input from the Statistical Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form February 9, 2021.

Publication Information: © 2021 The Authors. Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). Published online March 23, 2021 with doi 10.1016/j.xkme.2021.02.005

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