Clostridioides difficile infection among maintenance hemodialysis patients

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Abstract (Revised)

Background: Patients on maintenance hemodialysis (MHD) are 2-2.5 times more likely to develop *Clostridioides difficile* infection (CDI) with mortality rates 2-fold higher compared to the general population. The goal of this study was to determine factors and outcomes associated with severe/fulminant CDI among MHD patients.

Methods: A retrospective cohort study was performed among MHD patients admitted to 2 tertiary care hospitals, with first episodes of CDI between January 2015 and December 2018. MHD patients who had CDI at admission were identified through Theradoc®(Premier Inc., Charlotte, NC) and confirmed by electronic medical records review. Using the Infectious Diseases Society of America (IDSA) criteria, non-severe (NS) CDI was defined as a white blood cell count ≤ 15,000 cells/mL and severe/fulminant (S/F) CDI was defined as a white blood cell (WBC) count of ≥ 15,000 cells/mL, hypotension, shock, megacolon and/or ileus. Creatinine values were not included. Patient demographics, comorbidities, antimicrobial exposure and 60-day mortality were collected on all patients.

Results: A total of 129 MHD patients were identified with CDI during the study period, of whom 103 (80%) patients were presenting with the first episode of CDI. All patients were admitted with a diagnosis of diarrhea +/- abdominal pain. A subset of patients had a second admitting diagnosis (N[%]): another infection, including blood stream, skin or soft tissue, or lung (26 [25.2%]), altered mental status (9 [8.7]), diabetic ketoacidosis (5 [4.9]), congestive heart failure (5 [4.9]), mechanical fall (1 [0.01]). 68 (66%) had non-severe CDI and 35 (34%) had severe/fulminant CDI. The average age at admission was 65.3 years, 48.5% were female, and 59.2% were Caucasian. The average albumin level was 3.1 g/dL, and the average Charlson comorbidity index was 6.8. On univariable analyses, factors associated with severe/fulminant CDI as compared to non-severe CDI were older age at admission, exposure to extended-spectrum penicillins in the previous 90 days, and 60-day mortality after the first CDI (p-value ≤0.05). On multivariable logistic regression analysis, three factors remained significantly associated with severe/fulminant CDI (adjusted odds ratio [aOR], 95% confidence interval): 1] age ≥65 years (aOR=6.3 [2.25-17.45]), 2] extended-spectrum penicillins (aOR=2.7 [1.05-6.85], and 3] 60-day mortality after the first CDI (aOR=3.6 [1.11-11.74]). On univariable analyses, severe/fulminant CDI and low serum albumin level were significantly associated with 60-day mortality. On multivariable logistic regression analysis, severe/fulminant CDI (aOR=4.0 [1.28-12.79]) and low serum albumin (aOR=3.0 [1.14-7.91]) remained significantly associated with 60-day mortality.

Conclusion: A substantial proportion of patients requiring MHD with CDI present with severe/fulminant disease and are at increased risk of death. Reducing exposure to extended-spectrum penicillins may prevent severe/fulminant CDI in this patient population. Improving albumin levels via enhanced nutrition may decrease mortality among MHD patients who contract CDI.

Background

- Patients on maintenance hemodialysis (MHD) are 2-2.5 times more likely to develop *Clostridioides difficile* infection (CDI) (1) with mortality rates 2-fold higher compared to the general population (2).
- The factors associated with non-severe (NS) versus severe/fulminant (S/F) CDI and outcomes among the MHD population are not well-defined.

Aims

- Determine factors associated with NS versus S/F CDI among MHD patients with CDI
- Determine factors associated with 60-day mortality among MHD patients with CDI

Methods

- The study is a retrospective cohort study among MHD patients admitted to a 700- and a 255-bed tertiary care hospitals in Providence, Rhode Island.
- MHD patients with first episode of CDI between January 2015 and December 2018 were identified through Theradoc® and confirmed using electronic medical records. CDI was defined as a positive test using the GeneXpert® assay and documentation of diarrhea.
- Infectious Diseases Society of America (IDSA) definitions for NS and S/F CDI were used. NS CDI was defined as a white blood cell count ≤ 15,000 cells/mL. S/F CDI was defined as a white blood cell count of ≥ 15,000 cells/mL, hypotension, shock, megacolon and/or ileus. Creatinine values were not included in this study.
- The chi-squared or Fisher's exact tests were used to compare categorical data and the Student's t-test, Mann-Whitney U test, or Kruskal-Wallis test for continuous data. Logistic regression analysis was performed to identify independent variables associated with NS vs S/F CDI, and Cox regression was used for variables associated with mortality. Variables with a P value ≤ 0.05 on univariable analyses were included in the multivariable model to control for confounding.

Results

- 129 MHD patients were identified with CDI during the study period, of whom 103 (80%) patients were presenting with the first episode of CDI. All patients were admitted with a diagnosis of diarrhea +/- abdominal pain.
- A subset of patients had a second admitting diagnosis (N[%]): another infection, including blood stream, skin or soft tissue, or lung (26 [25.2%]), altered mental status (9 [8.7]), diabetic ketoacidosis (5 [4.9]), congestive heart failure (5 [4.9]), mechanical fall (1 [0.01]).
- 68 (66%) had non-severe CDI, 23 (22%) had severe CDI, and 12 (12%) had fulminant CDI. All patients were treated appropriately as per IDSA guidelines (3).
- 19 patients (18%) died at 60 days. Among the patients who died within 60 days of CDI, cause of death was as follows (N[%]): unknown (patient died at home) (8 [42.1]), septic shock (4 [21.2]), cardiogenic shock (7 [36.8]).
- Univariable and multivariable analyses of factors associated with S/F CDI and 60-day mortality are shown in Tables 1 and 2.

Table 1

Characteristics and Clinical Data of Patients with Severe/Fulminant and Non-severe *Clostridioides difficile* Infection

Variable	Non-severe CDI (n=68, 66.0%)	Severe /Fulminant CDI (n=35, 34.0%)	Univariable OR (95% CI)	Univariable P value	Multivariable aOR (95% CI)	Multivariable P value
Age ≥ 65	27 (39.7)	28 (80.0)	6.1 (2.33 - 15.9)	<0.01	6.3 (2.25-17.45)	<0.01
Gender (female)	34 (50.0)	16 (45.7)	0.8 (0.37 - 1.91)	0.68		
Race						
Hispanic/Latinx	18 (26.5)	6 (17.1)	0.6 (0.21-1.61)	0.29		
White/Caucasian	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, mean (SD)	6.7 (3.9)	7.0 (3.5)	0.98 (0.88-1.09)	0.68		
Comorbidities						
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 (2.96)	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		
Previous hospitalizations						
None	32 (47.1)	14 (40.0)	1.32 (0.50 - 3.50)	0.57		
One	17 (25.0)	10 (28.6)	0.98 (0.34 - 2.89)	0.98		
More than one	19 (27.9)	11 (31.4)	Reference	-		
Albumin (g/dL), mean (SD)	3.2 (0.6)	3.0 (0.6)	1.4 (0.73-2.88)	0.29		
Hemoglobin (g/dL), mean (SD)	10.0 (1.8)	9.4 (1.5)	1.3 (0.99-1.66)	0.06		
Antibiotics in previous 90 days						
All	52 (76.5)	28 (80.0)	1.2 (0.45-3.35)	0.68		
1st generation cephalosporins	42 (38.2)	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-day mortality	8 (11.8)	11 (31.4)	3.44 (1.23 - 9.59)	0.02	3.62 (1.12 - 11.74)	0.03

CDI, *Clostridioides difficile* Infection; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; COPD, chronic obstructive pulmonary disease; AVF, arteriovenous fistula; CVC, central venous catheter; TDC, tunneled dialysis catheter; SD, standard deviation; extended-spectrum penicillins, piperacillin-tazobactam; TMP-SMX, trimethoprim-sulfamethoxazole; CI, confidence interval; aOR, adjusted odds ratio

Table 2

Analysis of 60-day Mortality in Patients with *Clostridioides difficile* Infection

Variable N (%)	Alive N=84 (81.6%)	Dead N=19 (18.4%)	Univariable OR (95% CI)	Univariable P value	Multivariable aOR(95% CI)	Multivariable P value
Age ≥ 65	44 (52.4)	11 (57.9)	1.3 (0.46-3.42)	0.66		
Gender (female)	44 (52.4)	6 (31.6)	0.4 (0.15-1.21)	0.11		
Race						
Hispanic/Latinx	19 (22.6)	5 (26.3)	1.2 (0.39-3.82)	0.73		
White/Caucasian	51 (60.7)	10 (52.6)	Reference	-		
Black/African-American	18 (21.4)	4 (21.1)	0.9 (0.25-3.17)	0.85		
Other	15 (17.9)	5 (26.3)	0.6 (0.17-2.00)	0.39		
Charlson Comorbidity Index, mean (SD)	6.6 (3.6)	7.7 (4.5)	0.9 (0.81-1.05)	0.22		
Comorbidities						
Peripheral vascular disease	22 (26.2)	9 (47.4)	2.5 (0.91-7.06)	0.07		
COPD	31 (36.9)	9 (47.4)	1.5 (0.56-4.20)	0.40		
Rheumatic disease	4 (4.76)	0 (0.00)	NA	-		
Diabetes with chronic complications	49 (58.3)	12 (63.1)	1.2 (0.44-3.42)	0.70		
Moderate severe liver disease	5 (5.95)	1 (5.26)	0.9 (0.10-7.98)	0.91		
HIV/AIDS	3 (3.57)	3 (15.8)	5.1 (0.94-27.4)	0.06		
Any malignancy	9 (10.7)	2 (10.5)	1.0 (0.19-4.96)	0.98		
Type of vascular access						
AVF	73 (86.9)	16 (84.2)	Reference	-		
CVC/TDC	11 (13.1)	3 (15.8)	1.2 (0.31-4.98)	0.76		
Previous hospitalizations, mean (SD)						
None	40 (47.6)	6 (31.6)	1.67 (0.48 - 5.76)	0.42		
One	20 (23.8)	7 (36.8)	0.71 (0.20 - 2.47)	0.60		
More than one	24 (28.6)	6 (31.6)	Reference	-		
Severe/fulminant CDI	24 (28.6)	11 (57.9)	3.4 (1.23 – 9.59)	0.02	4.0 (1.28-12.79)	0.02
Albumin (g/dL), (mean (SD)	3.21 (0.66)	2.79 (0.38)	3.1 (1.23-7.79)	0.02	3.0 (1.14-7.91)	0.03
Hemoglobin (g/dL), mean (SD)	9.9 (1.8)	9.46 (1.7)	1.2 (0.85-1.60)	0.33		
Antibiotics in previous 90 days						
All	64 (76.1)	16 (84.2)	1.7 (0.44-6.31)	0.45		
1st generation cephalosporins	28 (33.3)	8 (42.1)	1.5 (0.53-4.02)	0.47		
2nd generation cephalosporins	1 (1.2)	0 (0.00)	NA	-		
3rd generation cephalosporins	26 (31.0)	5 (26.3)	0.8 (0.26-2.44)	0.69		
Macrolides	5 (5.95)	2 (10.5)	1.9 (0.33-10.4)	0.48		
Clindamycin	5 (5.95)	1 (5.26)	0.9 (0.10-7.98)	0.91		
Fluoroquinolones	17 (20.2)	3 (15.8)	0.7 (0.19-2.83)	0.66		
Simple penicillins	7 (8.33)	2 (10.5)	1.3 (0.25-6.79)	0.76		
Extended-spectrum penicillins	35 (41.7)	11 (57.9)	1.9 (0.70-5.28)	0.20		
Aminoglycosides	4 (4.76)	0 (0.00)	NA	-		
Carbapenems	3 (3.57)	0 (0.00)	NA	-		
TMP-SMX	8 (9.52)	1 (5.26)	0.5 (0.06-4.49)	0.56		

HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; COPD, chronic obstructive pulmonary disease; AVF, arteriovenous fistula; CVC, central venous catheter; TDC, tunneled dialysis catheter; SD, standard deviation; CDI, Clostridioides difficile Infection; extended-spectrum penicillins, piperacillin-tazobactam; TMP-SMX, trimethoprim-sulfamethoxazole; CI, confidence interval; aOR, adjusted odds ratio

Conclusions

- A substantial proportion of patients requiring MHD with CDI present with severe/fulminant disease and are at increased risk of death.
- Reducing exposure to extended-spectrum penicillins may prevent severe/fulminant CDI in this patient population.
- Improving albumin levels via enhanced nutrition may decrease mortality among MHD patients who contract CDI.
- There is a need to validate the IDSA classification of the severity of CDI in MHD populations, especially since creatinine cannot be used as a marker.

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