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Original Article

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Risk Factors Associated With Recurrent *Clostridium difficile* Infection

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Abstract

Background: Recurrence of *Clostridium difficile* infection (CDI) is a problem that can cost up to $20,000 each year in the United States. Studies have reported risk factors that may be associated with a higher incidence of recurrent CDI. We studied additional risk factors, including history of partial colectomy, chemotherapy use and hospitalization in the intensive care unit (ICU).

Methods: We conducted a retrospective chart review of all outpatients and inpatients at our institution to determine risk factors associated with recurrent CDI. Frequencies were compared using Fisher's exact test and continuous data were compared using Wilcoxon ranks sums test. Recurrent CDI was determined for all patients and risk factors were analyzed using single and multiple logistic regression. A $P < 0.05$ was used to determine significance.

Results: This study included 435 patients and found that advanced age significantly increased the odds of recurrent CDI by 2.3% per year (OR = 1.023, 95% CI = 1.009 - 1.037, $P < 0.05$). Patients with prior partial colectomy were found to have 3.2 times increased odds of recurrence compared to those without history of partial colectomy (OR = 3.168, 95% CI = 1.324 - 7.579, $P < 0.05$). Patients receiving chemotherapy or hospitalized in the ICU were not found to have a significantly higher rate of recurrent CDI ($P > 0.05$).

Conclusions: Advanced age and history of partial colectomy were associated with a significantly higher recurrence rate of CDI. Contrary to prior studies, chemotherapy use or hospitalization in the ICU were not found to be associated with a higher rate of recurrent CDI.

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Introduction

Recurrence of *Clostridium difficile* infection (CDI) is a problem that can cost up to $20,000 each year in the United States [1-3]. Several studies have been done to investigate different risk factors that may be correlated to recurrent CDI. Fekety et al found five risk factors associated with recurrence of CDI: number of previous infections with *C. difficile*, onset of initial disease in the spring, exposure to additional antibiotics to treat other infections, infection with immunoblot type 1 or 2 strains, and female gender [4]. Similarly, Kim et al showed that advanced age, low serum albumin, and proton pump inhibitor use were associated with a higher risk of recurrent CDI [5]. Our objective was to determine if additional characteristics that are not as well studied, such as concomitant chemotherapy use and history of partial colectomy, are associated with a higher rate of recurrent CDI.

Materials and Methods

Study selection

This study was a retrospective cohort review that observed the relationship between recurrent CDI and different risk factors. All data were gathered from the electronic patient medical record at Cooper University Hospital. Patients above the age of 9 years who were diagnosed with CDI through laboratory testing (either by polymerase chain reaction or glutamate dehydrogenase in conjunction with enzyme immunoassay) in the inpatient and outpatient settings at our institution between October 1, 2010 and December 31, 2017 were included. Recurrent CDI was defined as relapse of infection within 2 months after resolution of symptoms from the first episode of CDI. The exclusion criterion was patients without laboratory evidence of CDI on the electronic medical record. The study was reviewed and approved by the Institutional Review Board (IRB) of our institution and the procedures followed were in accordance with the Board's ethical standards. The certificate number given by

Table 1. Baseline Characteristics

Variable	Frequency	Recurrence	P value
Age (mean (standard deviation))	59 (18.0)		
Sex			0.058
Female (n, %)	266 (61.3)	67 (25.1)	
Male (n, %)	168 (38.7)	29 (17.3)	
Race			0.840
Caucasian (n, %)	217 (63.5)	50 (14.6)	
African American (n, %)	68 (19.9)	17 (5.0)	
Hispanic (n, %)	44 (12.9)	9 (2.6)	
Asian (n, %)	5 (1.5)	1 (0.3)	
Other (n, %)	8 (2.3)	3 (0.9)	
Setting			0.555
Inpatient (n, %)	263 (60.6)	61 (23.2)	
Outpatient (n, %)	171 (39.4)	35 (20.5)	

the IRB is 1814333.

Data collection

The following data were collected for each patient: age, gender, race (Caucasian, African American, Hispanic, Asian, or other), weight, height, comorbidities, such as inflammatory bowel disease, cancer, gastroesophageal reflux disorder (GERD), hypertension, diabetes, history of organ transplant, chronic obstructive pulmonary disease, coronary artery disease, chronic kidney disease, liver disease, HIV and other rheumatologic diseases. Additional data collected included: vital signs at time of symptom onset, including temperature, heart rate, systolic and diastolic blood pressure, white blood cell count, albumin level, creatinine and baseline creatinine; if patients were on active chemotherapy (received chemotherapy within the last 6 months); if patients were hospitalized in the intensive care unit (ICU) at time of diagnosis; if patients were receiving antibiotics for treatment of a different infection at time of diagnosis; if patients were receiving antisecretory or stool softener medications at time of diagnosis; if they were receiving enteral tube feeding or mechanically ventilated; the severity of CDI based on the Infectious Diseases Society of America guidelines; the treatment regimen given for their CDI; and if patients had a history of partial colectomy prior to CDI.

Statistical analysis

Data were collected and entered into a Microsoft Excel (2013, Redmond, Washington, USA) spreadsheet. The dependent variable was recurrent CDI and independent variables were the different risk factors being included in this study. Categorical data were analyzed as frequencies with percentages and continuous data were analyzed as means with standard deviations. Frequencies were compared using Fisher's exact test and continuous data were compared using Wilcoxon ranks sums test. Recurrent CDI was determined for all patients and risk factors were analyzed using single and multiple logistic regression. A P value of < 0.05 was used to determine the statistical significance. Statistical analysis was carried out using SAS v9.4 software (SAS Institute, Cary, North Carolina, USA).

Results

A total of 435 patients were included in this study. Recurrent CDI was observed in 22.1% patients. The mean age of patients with CDI was 59 ± 18 years and the majority of them were female (61.5%) (Table 1). Sixty-seven females (25%) and 29 males (17.3%) had recurrent CDI. The difference was not statistically significant (P = 0.058). Most patients in this study were Caucasian (63.5%), followed by African American (19.9%), Hispanic (12.9%), Asian (1.5%), or another race (2.3%). No differences in recurrent CDI were seen among races (Table 1). Patients were mostly treated for their CDI in the inpatient setting (60.6%) and a fraction of them were hospitalized in the ICU (8%). Sixty-one patients (23.2%) in the inpatient setting were found to have recurrent CDI compared to 35 (20.5%) patients in the outpatient setting. These differences were not statistically significant (P = 0.555). Similarly, seven patients hospitalized in the ICU were found to have recurrent CDI (20.6%) compared to 89 patients in the non-ICU setting (22.3%), which was not significantly different (P = 1.000) (Table 1). We found that advancing age significantly increased the odds of recurrent CDI by 2.3% per year (OR = 1.023, 95% CI = 1.009, 1.037; P = 0.0012).

The vast majority of the patients in our study were neither on tube feeding (nasogastric or percutaneous endoscopic gastrostomy) (93.9%) nor on mechanical ventilation (97.3%). Three patients on tube feeding had recurrent CDI (11.5%) compared to 93 patients who were not receiving tube feeding but who had recurrent CDI (22.7%). There was no significant

Table 2. Recurrence Rates Based on Risk Factors

Variable	Frequency (n, %)	Recurrence (n, %)	P value
Inpatients			1.000
ICU	34 (7.8)	7 (20.6)	
Non-ICU medical unit	400 (92.2)	89 (22.3)	
Method of nutrition			0.228
Artificial tube feeds	26 (6.0)	3 (11.5)	
Non-tube feeds	409 (94.0)	93 (22.7)	
Ventilation			1.000
Mechanical ventilation	11 (2.5)	2 (18.2)	
Non-mechanical ventilation	424 (97.5)	94 (22.2)	
Severity			0.260
Mild/moderate	338 (78.4)	71 (21.0)	
Severe	93 (21.6)	25 (26.9)	
Treatment			0.919
Metronidazole	216 (51.2)	47 (21.8)	
Vancomycin	152 (36.0)	34 (22.4)	
Combination	54 (12.8)	13 (24.1)	
Antisecretory use			1.000
On antisecretory Meds	221 (51.8)	50 (22.6)	
Not on antisecretory Meds	206 (48.2)	46 (22.3)	
Prior antibiotic use			0.727
On antibiotics	191 (43.9)	44 (23.0)	
Not on antibiotics	244 (56.1)	52 (21.3)	
Chemotherapy Use			1.000
On chemotherapy	57 (13.1)	12 (21.1)	
Not on chemotherapy	378 (86.9)	84 (22.2)	
Stool softener use			0.359
On stool softeners	53 (15.2)	8 (15.1)	
Not on stool softeners	296 (84.8)	65 (22.0)	
Presence of colectomy			0.014*
Prior partial colectomy	22 (5.1)	10 (45.5)	
No prior partial colectomy	413 (94.9)	86 (20.8)	

*Indicates statistical significance. Meds: medications.

difference in these rates (P = 0.228) (Table 2). Two patients on mechanical ventilation had recurrent CDI (18.2%), whereas 94 patients who were not on mechanical ventilation were found to have recurrent CDI (22.2%). The differences in these rates were not statistically significant (P = 1.000) (Table 2).

Severe CDI occurred in about 93 patients (21.3%), while the remainder had mild to moderate CDI. Seventy-one of the mild to moderate CDI patients had recurrent CDI (21%) compared to 25 of the severe CDI patients with recurrence of infection (26.9%). No significant difference was found between these groups (P = 0.260) (Table 2).

The majority of the patients (216) were treated with metronidazole (50.2%), while 157 were treated with vancomycin (36.5%), and 54 were treated with combination metronidazole and vancomycin (12.6%). Of the patients treated with metronidazole, 47 were found to have recurrent CDI (21.8%); 34 of the patients treated with vancomycin had recurrence of infection (22.4%), and 13 patients in the combination vancomycin and metronidazole group had recurrent CDI (24.1%). None of these differences were statistically significant (P = 0.919) (Table 2).

About half of all subjects with CDI were taking gastric antisecretory medication (51.8%) in this study. Fifty of these patients were found to have recurrent CDI (22.6%), whereas 46 patients who were not on gastric antisecretory therapy had recurrence of infection (22.3%), which was not significantly

different (P = 1.000). Likewise, 193 patients were taking antibiotics for a prior unrelated infection at the time of CDI diagnosis (43.86%). Recurrence of CDI was observed in 44 of these patients (23%) compared to 52 patients who were not on antibiotics but who had recurrent CDI (21.3%). The difference in these percentages was also not statistically significant (P = 0.727) (Table 2).

Fifty-seven patients included in this study were on chemotherapy (13%). Twelve of these patients had recurrent CDI (21.1%), whereas 84 patients who were not on chemotherapy had recurrent CDI (22.2%). No significant difference was found between these two groups (P = 1.00). Moreover, about 54 subjects were taking stool softeners (15.3%) and eight of them had recurrent CDI (15.1%), whereas 65 patients who were not on stool softeners had recurrent CDI (22%), which was not significantly different (P = 0.359) (Table 2).

A total of 22 subjects in this study had a partial colectomy prior to infection (5%). Ten of these patients had recurrent CDI (45.5%) compared to 86 patients without history of partial colectomy (20.8%). The difference in these rates was statistically significant (P = 0.014) (Table 2). Patients with a prior partial colectomy were found to have 3.2 times increased odds of recurrence compared to those without history of partial colectomy (OR = 3.168, 95% CI = 1.324 - 7.579, P = 0.010).

Discussion

Clostridium difficile is an anaerobic gram-positive bacillus that forms spores and produces a toxin that can cause intestinal disease varying from mild diarrhea to severe colitis [6-9]. Infection with this organism is the leading identifiable cause of antibiotic-associated diarrhea that has increased in incidence and severity over the years and is associated with considerable morbidity and mortality, as well as increased hospitalization duration and costs [6, 10-13]. *C. difficile* infection (CDI) has also recently emerged in the community, thus increasing its impact on the health care system.

Recurrence of CDI particularly has been found to be an increasing problem. About 15% to 35% of patients develop recurrent CDI after initial response to treatment [1, 14-16]. This can occur up to several months following initial therapy, but most relapses occur within the first 2 weeks after treatment completion.

Recurrent CDI is problematic not only because of increased morbidity and mortality, but also due to its economic burden on US healthcare costs. It extends hospitalization stays, increases the rate of re-hospitalization, and increases lab and medication utilization. A systematic review by Ghantoji et al found that studies investigating cost for patients with primary CDI ranged from $2,871 to $4,846 per patient versus cost for patients with recurrent CDI ranged from $13,655 to $18,067 [1-3]. As can be seen, not only is the cost of CDI quite high, but the cost of recurrent CDI is significantly higher.

The causes of recurrent CDI are unclear. Possible causes of recurrence include infection with a more virulent strain of *C. difficile*, which is BI/NAP1/027 designated by restriction endonuclease analysis (REA), pulsed-field gel electrophoresis, and PCR ribotyping. A study by Marsh et al found that infection with this particular strain was associated with a higher rate of recurrent CDI [14].

This study had several important findings: first, the risk of recurrent CDI significantly increased with advancing age; second, patients with a history of partial colectomy are at significantly higher risk of developing recurrent CDI; and third, the risk of recurrent CDI did not significantly increase with the use of gastric antisecretory medications, chemotherapy, and hospitalization in the ICU.

Our finding that recurrent CDI significantly increases with advanced age has been supported by several studies. For instance, Kim et al conducted a study showing that age greater than 65 years was associated with a significantly higher risk of recurrent CDI [5]. Similarly, Eyre and colleagues found that advanced age significantly increased the risk of recurrent CDI [17]. A plausible explanation for this is that as patients age, their gut microbiome and immune system are not as robust, thus increasing their risk for recurrent CDI.

On the other hand, our study has refuted other reports that have shown an association with antisecretory use with recurrent CDI. Gastric acid is known to inhibit the reproductive cycle of *C. difficile* and thus the use of gastric acid suppressants likely promotes a less hostile environment for the bacteria to grow. Kim et al found that proton pump inhibitor use was associated with recurrent CDI [5]. Similarly, Tariq et al conducted a meta-analysis of observational studies that showed gastric acid suppression may increase the risk of recurrent CDI [18]. Moreover, hospitalization in the ICU was not found to be significantly associated with a higher risk of recurrent CDI in our study, contrary to a study performed by Jasiak and colleagues who found that adults hospitalized in the ICU had a significantly higher incidence of recurrent CDI compared to non-ICU patients [19].

Chung and colleagues investigated the impact of malignancy on CDI and found that patients with cancer had a higher recurrence rate of CDI compared to the general population. It is unclear if these patients were receiving chemotherapy at the time of infection but according to the article, the presence of malignancy was found to be an independent risk factor for recurrent CDI [20]. In contrast, our study found no significant difference in recurrent CDI between patients receiving chemotherapy versus the general population.

Based on our literature review, no studies have been conducted to determine if there is a relationship with recurrent CDI in patients with a history of partial colectomy. To the best of our knowledge, our study is the first to determine an association of higher risk of recurrent CDI in patients with history of partial colectomy. A possible reason for this association may be that patients who have had a portion of their colon removed have likely had alterations to their gut microbiome, making them more susceptible to recurrent CDI compared to patients without a history of partial or total colectomy.

It is important to note that infection with *C. difficile* can still occur after total colectomy. Several cases have been reported of CDI in patients with total colectomy [21-29]. Despite the relatively high frequency of *C. difficile* colitis, the rate of small bowel *C. difficile* enteritis is rare [21]. Regardless, the

recurrence of *C. difficile* enteritis was beyond the scope of our study.

The main strength of our study was the large sample size of more than 400 patients. However, this was an observational study that included patients limited to a specific geographic region in southern New Jersey, USA. Therefore, its generalizability is somewhat limited. More studies will need to be done that span across multiple centers to either confirm or refute our findings.

Conclusions

Recurrent CDI has been found to be associated with several different factors. Our study has found a significant relationship in patients with advanced age and history of partial colectomy, but not those who take antisecretory medications, are on chemotherapy, or hospitalized in the ICU. More prospective studies need to be conducted in the future.

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