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Clinical Predictors of Recurrent *Clostridium difficile* Infection in Outpatients

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Summary

Background & Aim—*Clostridium difficile* infection (CDI) recurs in 20-30% of patients. Our aim is to describe the predictors of recurrence in outpatients with CDI.

Methods—Outpatient cases of CDI in Olmsted County, MN residents diagnosed between June 28, 2007 and June 25, 2010 were identified. Recurrent CDI was defined as recurrence of diarrhea with a positive *C. difficile* PCR test from 15-56 days after the initial diagnosis with interim resolution of symptoms. Patients who had two positive tests within 14 days were excluded. Cox-proportional hazard models were used to assess the association of clinical variables with time to recurrence of CDI.

Results—The cohort included 520 outpatients; 104 had recurrent CDI (cumulative incidence of 17.5% by 30 days). Univariate analysis identified increasing age and antibiotic use to be associated with recurrent CDI. Severe CDI, peripheral leukocyte count, and change in serum creatinine >1.5-fold were not. In a multiple variable model, concomitant antibiotic use was associated with risk of recurrent CDI (HR=5.4, 95% CI 1.6-17.5, p=0.005), while age (HR per 10 year increase =1.1, 95% CI 0.9-1.3, p=0.22); peripheral leukocyte count > 15×10^9/L (HR =1.0, 95% CI 0.5-2.1, p=0.92); and change in serum creatinine greater than 1.5-fold (HR=0.8 , 95% CI 0.4 -1.5, p=0.44) were not.

Conclusion—Antibiotic use was independently associated with a dramatic risk of recurrent CDI in an outpatient cohort. It is important to avoid unnecessary systemic antibiotics in patients with CDI, and patients with ongoing antibiotic use should be monitored closely for recurrent infection.

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Keywords

Clostridium difficile; recurrent infection; clinical predictors

Introduction

Clostridium difficile infection (CDI) causes significant morbidity and mortality, and the incidence of CDI in the hospital setting has increased significantly over the past 15 years [1]. Recurrent infection occurs in about 20% of patients with CDI [2-6]. The risk of recurrence increases with multiple episodes, and there is an approximate 65% risk of additional recurrence in those with 2 or more episodes of CDI [7].

Recurrent CDI is defined by the Infectious Disease Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) as the presence of diarrhea and a positive *Clostridium difficile* stool aspsay within 2-8 weeks from the initial episode [8]. Early recurrences generally occur within the first 2-3 weeks after the initial infection, however late infections can occur up to 8 weeks [2, 5].

Predicting the risk of recurrence of CDI is important for several reasons, including the necessity to closely monitor those identified to be at higher risk. Management of recurrent CDI, especially multiple recurrences, poses a clinical dilemma as there is a lack of strong evidence for a specific treatment strategy [7]. Longer courses of metronidazole and vancomycin, pulse-dosed or tapering regimens of vancomycin, probiotics, rifaximin, fidaxomicin, immunotherapy, and fecal microbial transplantation have been used to treat recurrent CDI [7-9].

Studies have assessed predictors of recurrent CDI, including gender, older age, illness severity, ongoing antibiotic use, serum concentrations of immunoglobulin G (IgG) against toxin A, vancomycin resistant enterococcus (VRE) colonization, anemia, use of proton pump inhibitors (PPI), renal insufficiency, underlying immunosuppression, history of diabetes, elevated leukocyte count, presence of a nasogastric tube, nursing home residence, history of recurrent CDI, presence of cramps on initial presentation, and diverticulosis [2, 10-14]. However, the existing data on predictors of recurrent CDI comes from inpatient cohorts, with relatively little known about risk factors for recurrent infection in outpatients. Furthermore, some of these variables such as anti-toxinA IgG are not routinely available. Testing for VRE may not be routinely performed in outpatients. In this study, we aimed to identify predictors of the risk of recurrent CDI in outpatients.

Methods

The microbiology laboratory database and patient medical records were queried to identify all outpatient cases (community-onset) of CDI at our institution between June 28, 2007 and June 25, 2010. Cases were based on *C. difficile* polymerase chain reaction (PCR) assay positivity and compatible clinical symptoms. The microbiology laboratory had transitioned to a PCR based assay for the detection of *C. difficile* in June 2007 [15].

Recurrent CDI was defined as recurrence of diarrhea with a positive *C. difficile* PCR test from 15-56 days after the initial diagnosis with interim resolution of symptoms. Patients who had two positive tests within 14 days or less were excluded from analysis. The electronic medical records were abstracted for patient demographics, weighted Charlson Comorbidity index [16], maximum peripheral leukocyte count (WBC), serum albumin, change in serum creatinine (compared to baseline over the past year), and serum lactate, all measured within 7 days of CDI diagnosis. We also abstracted information on medication use, which included antibiotics (divided into two periods, 90 days before diagnosis and within 30 days after diagnosis), narcotics (opiate derivatives), histamine-2 receptor blockers, PPI, and antimotility drugs (all recorded between 7 days before and 30 days after diagnosis). Histamine-2 (H2) blockers and PPIs were analyzed together as gastric acid suppression medications. Peripheral leukocytosis was dichotomized as greater than or less than 15×10^9/L. Antimotility agents included loperamide, prochlorperazine, diphenoxylate/atropine, and bismuth subsalicylate. Vancomycin and metronidazole were excluded from the list of antibacterials that were analyzed as risk factors.

Statistical analysis

Descriptive statistics for demographics and outcomes are reported as median (range) or frequency (percent). The Kaplan-Meier method was used to estimate the cumulative probability (%) of recurrent CDI. Univariate and multiple variable proportional hazards regression models were used to assess the association of clinical and demographic variables with time to recurrent CDI. These variables were chosen based on previous assessments in the literature.

Multiple variable models were formulated and variables were obtained based on clinical judgment and formal statistical assessment (at a univariate alpha level of 0.05). Only patients with complete data on the candidate variables were included in the multiple variable models.

Results

A total of 520 outpatients were diagnosed with CDI over the study period. The cohort included 213 females (41%) and had a median age of 56.4 years (range 0.1-101.6). A total of 104 patients had a recurrent infection, with a cumulative probability of recurrence by 30 days of 17.5% (95% CI=14.1, 20.8) and by 7 weeks of 20.5% (95% CI=16.9, 24.0).

Older age and antibiotic use within 30 days after the first CDI diagnosis were associated with recurrent CDI on univariate analysis (Table 1). A total of 331 patients (63.7%) had concomitant antibiotic use after their initial episode of CDI. WBC, creatinine ratio, and the use of acid suppressors (H2 blockers and PPIs), narcotics, and antimotility agents were not associated with the risk of recurrent CDI on univariate analysis. Severe-complicated CDI, which was diagnosed in 62 patients (11.9%) during their initial episode, was not associated with the risk of recurrent CDI.

There were a total of 264 patients with missing baseline creatinine values and 153 patients with missing peripheral leukocyte counts; these patients were excluded from the multiple

variable analysis, resulting in 248 (47.6%) out of 520 patients being included in the final multiple variable model. Recurrent disease occurred in 43 out of 248 of these included patients (cumulative probability of recurrence by 30 days of 15.4% (95% CI=10.7, 19.8), and by 7 weeks of 17.9% (95% CI= 12.9, 22.7). The following factors were significantly associated with the likelihood that baseline serum creatinine and peripheral leukocyte count were recorded: older age, male gender, severe first episode of CDI, and higher weighted Charlson comorbidity index.

In the multiple variable analysis, only concomitant antibiotic use was associated with risk of recurrent CDI. Gender, older age, comorbidities, and medication use (including acid suppressors, narcotics, and antimotility agents) were not associated with the risk of recurrent CDI (Table 2).

Discussion

Older age and antibiotic use were associated with risk of recurrent infection in univariate analyses in the present study. Concomitant systemic antibiotic use was the only independent predictor of recurrent CDI in outpatients. [2, 11, 20]. None of the other variables studied (including older age, severity of CDI, acid suppression, antimotility agents, elevated WBC, and rise in serum creatinine) were independent predictors of recurrent CDI. Our findings are in contrast to other studies that have found several of these variables predictive of recurrent CDI in inpatients [2, 14].

A recent meta-analysis found older age to be associated with recurrent CDI [11]. However, this meta-analysis involved only 12 studies, several of which were small, and included case-control studies [11], and 3 studies included in the meta-analysis did not find age to be a significant predictor of recurrence [17-19]. Also, robust sensitivity analyses could not be performed due to the small number of studies [11].

Our group of outpatients is younger than previous studies in which inpatient cohorts were studied (56 years versus 63-69 years)[2, 10]. Of note, there were 36 children under the age of 2 included in this study. Patients with community-acquired infection have been shown to be younger than those with hospital-acquired infections[6]. Differences in age may explain some differences between risk factors for recurrent CDI in outpatients compared to inpatients.

Hu, *et al*., showed older age, additional antibiotic use, disease severity and serum antitoxin A IgG levels were predictive of recurrent CDI [2]. Whereas our study was an outpatient cohort, theirs was a smaller inpatient cohort (n=63) [2]. Also, their study used the Horn index to measure the severity of disease while we used the current expert guideline definition for severe-complicated CDI (8). While the Horn index is a subjective index of disease severity, markers such as peripheral leukocyte count and serum creatinine are surrogate markers of disease severity.

About 63% of outpatients in this study had ongoing antibiotic use in the 30 days after initial CDI diagnosis. In our previously studied cohort of community acquired CDI, 78% of patients had antibiotic use in the 90 days prior to CDI diagnosis[6]. It is therefore not surprising that a number of these patients had ongoing need for antibiotics to complete a

treatment course after their initial CDI diagnosis; therefore this may explain the high rate of patients with ongoing antibiotics 30 days after CDI diagnosis.

Acid suppression has been associated with the risk of CDI, especially in the hospital setting[20]. The association between CDI and acid suppression is thought to be due to lack of killing of the vegetative form of *C. difficile* in patients with decreased gastric acid[21]. However, the role of acid suppression in recurrent CDI is controversial [10, 11, 14, 21]. Kim, *et al*., reported that PPI use, along with recent gastrointestinal surgeries and additional antibiotic use, were associated with recurrent CDI in a matched case-control study [14]. However, this was a relatively small study with only 28 patients (14%) having recurrent CDI. Conversely, Choi, et al., did not find acid suppressive medications to be a significant predictor of recurrent CDI[10]. Our finding that acid suppression is not associated with recurrent CDI in outpatients is similar to what was found in a population-based cohort of Olmsted County patients with CDI[21].

There have been other recent studies that assessed risk factors associated with the development of recurrent CDI [10, 11, 22]. Choi, *et al*., found that only colonization with vancomycin-resistant enterococci independently predicted risk of recurrent CDI in hospitalized patients. They too did not find disease severity, WBC count, or acute kidney injury to be predictive [10], in keeping with our results. However, this was also a small study (n=84) with only 11 patients (13%) having recurrent disease, and age was not included in the multiple variable analysis because it was not significant on univariate analysis [10]. Also, similar to our study, Tal, et al., did not find WBC or elevated creatinine to be associated with recurrent CDI [22].

The strength of our study is its novel focus on outpatients as well as the large sample size that provided statistical power to assess multiple variables for their association with recurrent CDI. We chose to focus our study on outpatients with CDI rather than hospitalized patients since several recent studies had assessed inpatients, and since we have more complete data on concomitant antibiotic use through 30 days and comorbidities for outpatients. In addition, in our practice, inpatients tend to represent more of a referral population from surrounding states and therefore follow-up to assess true recurrences and post-hospital use of additional antibiotics is limited. The emerging recognition of the important entity of community acquired CDI highlights the need to find risk factors for CDI recurrence in outpatients [6]. A potential limitation of our study is the fact that the diagnosis of CDI was made by a highly sensitive PCR- test. Even though inclusion criteria required diarrhea in addition to a positive test, it is possible that colonized individuals who had diarrhea for another reason were included in the study since PCR-based CDI diagnosis does not differentiate between symptomatic infection and colonized individuals.

In conclusion, while older age and ongoing antibiotic use were predictive of recurrent CDI on univariate analysis, only ongoing antibiotic use was independently predictive of recurrent CDI in this outpatient cohort. Future studies should assess novel risk factors, such as the intestinal microbiome, that might also play a role in recurrence in outpatients.

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Table 1

Results from univariate Cox proportional hazards analysis for selected predictors of recurrent *Clostridium difficile* infection in outpatients.

Variable	Hazard Ratio	95% Confidence Interval	p-value
Male	0.9	0.6-1.4	0.65
Age[1]	1.1	1.0-1.2	0.01
Weighted Charlson Comorbidity index			
=0	1.0 (reference)		
=1	0.8	0.3-1.80	0.55
>1	1.5	96-2.5	0.07
Peripheral WBC count > 15×10^9/L [2]	1.3	0.8 -2.2	0.31
Serum creatinine increase [3]	0.8	0.4-1.5	0.44
First episode of CDI was severe-complicated	1.5	0.9-2.6	0.16
Antibiotic use[4]	2.0	1.2-3.1	0.003
Narcotic use[5]	1.1	0.7-1.6	0.76
H2 blockers or PPI use[5]	1.3	0.9-2.0	0.14
Antimotility use[5]	1.4	0.8-2.5	0.22

[1] Age was treated as a continuous variable and HR is per 10 years.

[2] Peripheral white blood cell count was dichotomized as $\geq15\times10^9$/L or $<15\times10^9$/L

[3] Increase in serum creatinine was dichotomized as ≥1.5 fold or <1.5 fold compared to baseline

[4] Antibiotic use 30 days after first CDI diagnosis

[5] Medication use was examined from 7 days prior to, to 30 days after initial CDI diagnosis

Table 2

Results of the multiple variable Cox proportional hazards analysis for selected predictors of recurrent *Clostridium difficile* infection in outpatients.

Variable	Hazard Ratio	95% Confidence Interval	p-value
Male	0.9	0.5 -1.7	0.77
Age[1]	1.1	0.9-1.3	0.22
Weighted Charlson Comorbidity index			
=0	1.0 (reference)		
=1	0.7	0.1-3.1	0.59
>1	0.9	0.3 -2.9	0.87
Peripheral WBC count > 15×10^9/L [2]	1.0	0.5-2.1	0.92
Serum creatinine increase [3]	0.8	0.4 -1.5	0.44
First episode of CDI was severe-complicated	0.8	0.3-2.1	0.70
Antibiotic use[4]	5.4	1.6-17.5	0.005
Narcotic use[5]	1.0	0.5-1.8	0.93
H2 blockers or PPI use[5]	0.9	0.5 -1.6	0.65
Antimotility use[5]	1.1	0.5-2.5	0.74

[1] Age was treated as a continuous variable and studied in 10 year intervals

[2] Peripheral white blood cell count was dichotomized as $\geq 15 \times 10^9$/L or $<15 \times 10^9$/L

[3] Increase in serum creatinine was dichotomized as ≥1.5 fold or <1.5 fold compared to baseline

[4] Antibiotic use 30 days after first CDI diagnosis

[5] Medication use was examined from 7 days prior to, to 30 days after, initial CDI diagnosis