Identification of Factors Impacting Recurrent *Clostridium difficile* Infection and Development of a Risk Evaluation Tool

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Received, June 10, 2016; Revised, August 18, 2016; Accepted, August 22, 2016; Published, September 12, 2016

ABSTRACT - Purpose. Recurrent *Clostridium difficile* infection (RCDI) is a growing concern, yet limited data exists to clarify which patients are at highest risk. Identification of these patients may better inform decisions of those who may benefit from prophylactic intervention. The purpose of this study was to determine which factors are associated with the recurrence of *Clostridium difficile* infection (CDI) and to develop a risk stratification tool. **Methods.** Patients readmitted within 10 weeks of positive *C. difficile* polymerase chain reaction (PCR) with symptoms were included in this retrospective case control study. The primary outcome was analyzed via univariate regression analyses of the independent factors including age, gender, number of CDI episodes, administration of acid blocking agents, antibiotics or chemotherapy, Charlson Comorbidity Index, gastrointestinal conditions, and exposure to healthcare facilities. **Results.** Recurrent CDI was identified in 44 of 220 included patients. In the univariate analysis, factors associated with development of RCDI included antibiotic exposure (OR 2.51, 95% CI 1.14-5.54; p 0.02) and inflammatory bowel disease (OR 5.77, 95% CI 1.24-26.79; p 0.03). An evaluation tool was created from a well-fit model. Additional factors included in the tool were chosen based on evaluation of findings from existing literature. **Conclusions.** Antibiotic therapy and inflammatory bowel disease were found to be associated with RCDI. Although a statistically significant association with RCDI was not found for other factors, this is likely related to small sample size. The creation of an evaluation tool using specific patient factors can help determine the risk of RCDI, while future studies may validate this tool.

INTRODUCTION

Clostridium difficile is a gram-positive, spore-forming anaerobe which accounts for 15-30% of nosocomial antibiotic-associated diarrhea. *Clostridium difficile* infection (CDI) occurs when *Clostridium difficile* overpopulates the gastrointestinal tract and produces toxins leading to colitis which presents commonly as diarrhea and sometimes more severely as toxic megacolon (1-2). Onset of symptoms are reported to occur frequently after several days to months of antibiotic administration or healthcare exposure. While treatment is effective in improving systemic symptoms within a few days, diarrhea may persist for several weeks or infection can recur shortly after treatment ends (2-3).

The incidence of recurrent *Clostridium difficile* infection (RCDI) is consistently cited in literature at 5-30% (mean 20%) of patients within the first eight weeks when risk is highest. Up to 40-65% of patients will have another episode of CDI when that time period is extended to several years in the presence of multiple risk factors such as repeated exposure to healthcare and broad spectrum antibiotics (1, 3-7). The majority of epidemiology literature defines recurrence as CDI within the first two months of the initial episode (4-5, 7-8).

With the high burden of recurrence and association with healthcare observed with CDI, current guidelines by the Infectious Disease Society of America (IDSA) and the Society of Healthcare Epidemiology of America (SHEA) support the use

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of preventative techniques such as handwashing, environmental cleaning and antimicrobial stewardship to prevent the spread of *C. difficile* and the development of CDI. There is scarce literature, however, addressing the question of using chemical prophylaxis for the prevention of CDI (2, 9). Chemical prophylaxis is not common practice, but some hospital facilities have begun to use prophylaxis for patients at high risk for CDI or recurrent infection. In a retrospective study by Rodriguez, et al. metronidazole was associated with a decreased rate of CDI in patients who were hospitalized and received broad spectrum antibiotics (10). Collecting data on 12,000 high-risk individuals, the authors found that patients who received metronidazole 1-3 days prior to starting piperacillin/tazobactam or ciprofloxacin had a statistically significant reduction in the incidence of CDI by 80% in comparison to patients who did not receive metronidazole (OR 0.21; 95% CI 0.11-0.38; p <0.001). Oral vancomycin has been used for prophylaxis as well. A recent retrospective study performed at Mercy Hospital St. Louis by Van Hise, et al. showed an association between the use of twice daily oral vancomycin prophylaxis and a reduction in the incidence of RCDI (11). Of 203 high risk patients, 3/71 (4.2%) patients who received vancomycin prophylaxis versus 35/132 (26.5%) who did not receive vancomycin prophylaxis developed RCDI (OR 0.12; 95% CI 0.04-0.4; p <0.001). With new literature suggesting the potential efficacy of prophylaxis, the risk of developing CDI and recurrent infection compared to these benefits must be considered.

While these prophylaxis studies used exposure to broad-spectrum antibiotics in their definitions of high risk, other factors such as age and use of acid-suppression were studied as well. There is currently no accepted systematic method to determine or stratify the risk of development of RCDI, but there is an abundance of retrospective and surveillance literature citing several factors associated with the development of both an initial episode of CDI and RCDI. Factors shown to repeatedly correlate with RCDI were increasing age (≥ 65 years old), antibiotic therapy, and concomitant use of acid-suppressing medications (proton-pump inhibitors most frequently studied) (5-7, 12-16). While these factors were the most commonly cited, there are many other factors individually studied and found to be independently associated with CDI/RCDI including obesity, intra-abdominal or gastrointestinal surgery, tube feedings or nasogastric tubes, inflammatory bowel disease (IBD), and immunocompromising disease states or medications (1, 4, 17-21). The purpose of this study was to identify factors associated with RCDI and develop an evaluation tool to stratify the risk of developing recurrent infection.

METHODS

The study was a single-center, retrospective case control conducted at a 979 bed community-teaching hospital. Institutional Review Board approval was obtained prior to commencement. Patients 18 years of age or older with a history of positive *Clostridium difficile* PCR who were admitted to the hospital within 10 weeks of the positive result were included. Patients were excluded if they were pregnant, had received oral vancomycin during the admission, or had a subsequent PCR performed less than 10 days after the initial positive PCR.

Outcomes

The primary outcomes were the odds ratios associated with the following factors in relation to the development of RCDI: demographics such as age, gender, and body mass index (BMI); number of CDI episodes prior to admission; length of stay of current admission; concomitant administration of the pharmacologic agents including acid blocking agents, antibiotics stratified by class, and chemotherapy; Charlson Comorbidity Index; Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome(HIV/AIDS); gastrointestinal diseases including IBD (such as ulcerative colitis and Crohn's disease) and irritable bowel syndrome (IBS); gastrointestinal bowel resection within the past four weeks; requirement of tube feeding or total parenteral nutrition during admission; and recent exposure to healthcare facilities within 30 days.

Statistical Analysis

Differences in baseline characteristics between continuous variables were tested via Student's t-test or the nonparametric Mann-Whitney U test. Categorical data were summarized as proportions, and the Chi-square test or Fisher's exact test for small samples was used to examine differences between groups. Factors were each independently

analyzed via univariate regression analysis. A subset of factors was then selected for multiregression analysis if a p-value of <0.2 was yielded in the univariate analysis or if strongly supported as a risk factor in previous literature. The model's calibration was assessed with the Hosmer-Lemeshow goodness-of-fit test. The risk evaluation tool was determined based on the odds ratios generated from the univariate regression analysis. Statistical analyses were performed using SPSS® Software.

RESULTS

In the designated time frame, there were 3044 positive PCR events screened; of which 220 events were included in the study. There were 44 occurrences of RCDI and the remaining 176 initial positive PCR events which were not followed by a recurrence of CDI (Figure 1). Table 1 outlines the results of the primary outcome with univariate binary regression analyses. The mean age of patients who developed RCDI was five years older (70 ± 18 years vs. 65 ± 18 years) and an increased percentage of RCDI patients were greater than 75 years of age (50.0% vs. 34.1%). Additionally, there was a greater percentage of females (70.5% vs. 55.7%) and a slightly longer mean length of stay (7.5 days vs. 5.8 days) in patients with recurrence compared to patients without recurrence. BMI and number of CDI occurrences per patient were equal between groups. None of these differences between groups reached statistical significance.

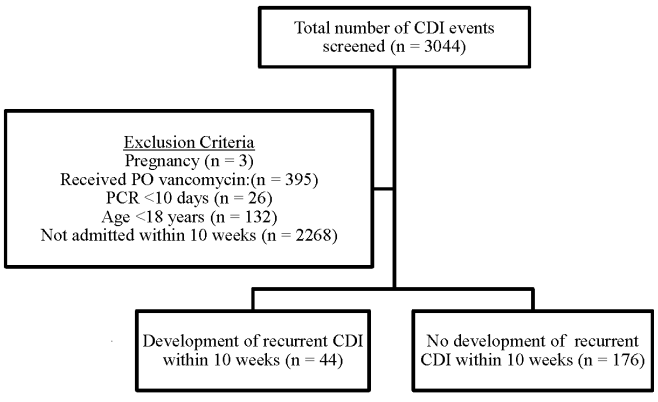

Figure 1. Study Flow Diagram

There was a correlation between exposure to any antibiotic and RCDI as indicated via univariate analysis (OR 2.51, 95% CI 1.14-5.54; p 0.02). The number of antibiotics prescribed per patient was higher in the group with RCDI (OR 1.37, 95% CI 1.11-1.68; p 0.01). The antibiotics prescribed most frequently in both groups were beta-lactam/beta-lactamase inhibitors, 3rd and 4th generation cephalosporins, fluoroquinolones, metronidazole, and intravenous vancomycin. Most of these, with the exception of fluoroquinolones, had a higher percentage prescribed in the RCDI group. Table 2 outlines the results of the univariate analyses of the primary outcome stratified by antibiotic class.

Acid blocking therapy with either a PPI or histamine$_2$-receptor antagonist (H_2RA) was recorded if initiated during the admission with no history of chronic use. There were a higher proportion of patients started on PPIs who developed RCDI compared to those who did not, but the correlation with RCDI was not statistically significant (OR 2.37, 95% CI 0.89-6.36; p 0.09). The proportion of patients in each group receiving H_2RA therapy was similar and was not correlated with an increased recurrence (OR 0.79, 95% CI 0.17-3.75; p 0.77). There was no correlation found for patients receiving chemotherapy during the time of the admission (OR 0.70, 95% CI 0.23-2.15; p 0.53).

Comorbidities were evaluated by comparison of the mean Charlson Comorbidity Index scores between groups. The mean scores did not vary significantly between groups with a score of 7.1 for the RCDI group and 6.3 in the group without recurrence. There were differences seen when looking specifically at gastrointestinal comorbid conditions. Although only four patients in the RCDI group and three patients in the group without recurrence were diagnosed with IBD, the condition was statistically correlated with RCDI (OR 5.77, 95% CI 1.24-26.79; p 0.03). IBS also had a higher percentage in the RCDI group compared to no RCDI, but the difference was not significant via univariate analysis (OR 2.37, 95% CI 0.82-6.80; p 0.11). Overall, a small percentage of patients included in this study had documented gastrointestinal disease.

The incidence of exposure to any healthcare (both hospital and other associated facilities) was higher in the RCDI group, but not statistically correlated with RCDI (OR 2.37, 95% CI 0.88-6.40;

p 0.09). The incidence of hospitalization within 30 days was similar between the groups (61.4% vs. 60.8%). Although not correlated with RCDI via univariate analysis, there was a higher percentage of patients exposed to healthcare facilities, excluding hospitals (skilled nursing facilities, infusion centers, rehabilitation), within 30 days in the RCDI group (61.4% vs. 48.3%).

When all independent variables meeting the pre-specified p value criteria were analyzed via multiregression analysis, none of the variables retained a statistically significant association with RCDI. Backward regression revealed the same two statistically significant variables: IBD and number of antibiotics. Factors which were used in the risk evaluation tool include: age > 65 years, systemic antibiotic exposure, inflammatory bowel disease and any healthcare exposure in the past 30 days. Assignment of points was relatively based on the odds ratios associated with these variables from the univariate analyses.

Table 1. Univariate Analysis of Primary Endpoint[a]

Characteristic	Recurrence (n = 44)	No Recurrence (n = 176)	Univariate Analysis		
			Odds Ratio	95% CI	p-value
Age >65 years, n (%)	29 (65.9)	98 (55.7)	1.54	0.77-3.07	0.22
Age >75 years, n (%)	22 (50.0)	60 (34.1)	1.93	0.99-3.77	0.05
Female, n (%)	31 (70.5)	98 (55.7)	1.90	0.93-3.87	0.08
BMI (kg/m^2), mean ± SD	28.2 ± 7.8	28.5 ± 8.2	1.00	0.95-1.04	0.80
Length of stay (days), mean ± SD	7.5 ± 5.6	5.8 ± 6.8	1.00	0.98-1.08	0.69
Number of CDI occurrences, mean	1.2	1.3	0.90	0.52-1.57	0.71
Antibiotic exposure, n (%)	35 (79.5)	107 (60.8)	2.51	1.14-5.54	0.02
Number of antibiotics, mean	2.1	1.4	1.37	1.11-1.68	0.01
Acid blocking therapy initiated in hospital					
Proton pump inhibitor, n (%)	7 (15.9)	13 (7.4)	2.37	0.89-6.36	0.09
$Histamine_2$ receptor antagonist, n (%)	2 (4.5)	10 (5.7)	0.79	0.17-3.75	0.77
Received chemotherapy concomitantly, n (%)	4 (9.1)	22 (12.5)	0.70	0.23-2.15	0.53
Charlson Comorbidity Index, mean	7.1	6.3	1.07	0.97-1.19	0.16
HIV/AIDS, n (%)	0	0	-	-	1.00
Gastrointestinal diseases, n (%)	10 (22.7)	14 (8.0)	3.40	1.40-8.30	0.01
Inflammatory bowel diseases, n (%)	4 (9.1)	3 (1.7)	5.77	1.24-26.79	0.03
Irritable bowel syndrome, n (%)	6 (13.6)	11 (6.3)	2.37	0.82-6.80	0.11
Bowel resection, n (%)	5 (11.4)	19 (10.8)	1.06	0.37-3.01	0.91
Tube feeds or total parenteral nutrition, n (%)	5 (11.4)	16 (9.1)	1.28	0.44-3.71	0.65
Exposure to any healthcare, n (%)	39 (88.6)	135 (76.7)	2.37	0.88-6.40	0.09
Hospitalization, n (%)	27 (61.4)	107 (60.8)	1.02	0.52-2.02	0.94
Healthcare-associated facility, n (%)	27 (61.4)	85 (48.3)	1.70	0.87-3.34	0.12
Exposure to multiple healthcare facilities, n (%)	18 (40.9)	58 (33.0)	1.41	0.71-2.78	0.32

[a] BMI = Body Mass Index; SD = Standard Deviation; CDI = *Clostridium difficile* Infection; PCR = Polymerase Chain Reaction; HIV = Human Immunodeficiency Virus; AIDS = Acquired Immunodeficiency Syndrome; CI = Confidence Interval

Table 2. Univariate Analysis of Antibiotics Stratified by Class[a]

Antibiotic class	Recurrence, n (%) n = 44	No Recurrence, n (%) n = 176	Odds Ratio	95% CI	p-value
Penicillin	1 (2)	2 (1)	2.02	0.18-22.83	0.57
Beta-lactam/Beta-lactamase inhibitor	14 (32)	33 (19)	2.02	0.97-4.23	0.06
1st or 2nd generation cephalosporin	4 (9)	9 (5)	1.86	0.54-6.33	0.32
3rd or 4th generation cephalosporin	11 (25)	26 (15)	1.92	0.87-4.28	0.11
Carbapenem	2 (5)	5 (3)	1.63	0.31-8.69	0.57
Aztreonam	6 (14)	10 (6)	2.62	0.90-7.66	0.08
Macrolide	2 (5)	3 (2)	2.75	0.44-16.96	0.28
Aminoglycoside	1 (2)	4 (2)	1.00	0.11-9.18	1.00
Fluoroquinolone	10 (23)	42 (24)	0.94	0.43-2.06	0.87
Sulfamethoxazole/trimethoprim	0	0	-	-	1.00
Tetracycline	1 (2)	2 (1)	2.02	0.18-22.83	0.57
Clindamycin	1 (2)	3 (2)	1.34	0.14-13.21	0.80
Metronidazole	17 (39)	40 (23)	2.14	1.06-4.32	0.03
Vancomycin (intravenous only)	14 (32)	36 (20)	1.82	0.87-3.78	0.11
Linezolid	4 (9)	10 (6)	1.66	0.50-5.57	0.41
Daptomycin	0	2 (1)	-	-	1.00

[a] CI = Confidence Interval

DISCUSSION

Consistently, antibiotic exposure and age show association with RCDI in literature. The results of this study were no exception to correlation of RCDI with antibiotic exposure. In regards to age, previous literature cites an association in patients greater than 65 years (6, 12, 13). It is likely this study population was too small to detect correlations in many of the factors found to be associated with RCDI in previous literature.

Comorbidities examined in this study were chosen based on their inclusion in the Charlson Comorbidity Index. Several of these comorbidities had very low incidence in both groups, likely too small to demonstrate an association. When GI comorbidities were specifically examined, IBD showed an independent correlation with RCDI, but this was a very low incidence in both groups. Prior literature noted 3-fold higher incidences of CDI in ulcerative colitis than the general population and 2-fold higher in Crohn's disease; recurrence has not been studied. There are also documented higher rates of mortality due to CDI in patients with IBD, which may warrant prophylactic measures in this population (19). The risk of developing recurrence may depend on severity of GI disease, as well as treatment of the disease with immunosuppressive agents, but there is currently insufficient evidence to conclude which may have greater impact.

Although several risk factors were found to be associated with the development of CDI and RCDI, very little literature evaluated the use of prediction models. A small single-centered trial looked at the impact of a clinical prediction rule for the detection of RCDI (22). The tool was derived

from previous literature and created a rule for which patients received a score on a 0-5 point scale. Factors included in the rule included age greater than 65 years, Horn's Index score of severe or fulminant CDI, and additional antibiotic use. Each factor was designated one point and detection of antitoxin A IgG less than 1.29 was designated two points. Based on 13 patients scored in a derivation cohort cited in the study, the tool yielded a sensitivity and specificity of 88.9% and 100%, respectively, in the eight patients scored high risk in the derived population. In contrast, a validation cohort of 64 patients using the clinical prediction rule in the study yielded a sensitivity and specificity of 76.5% and 53.8%, respectively (22). Although, the clinical prediction model demonstrated accurate discrimination of high risk patients in the derivation cohort, it was less accurate in the validation cohort. Unfortunately, this clinical rule may not be generalizable to practice due to some limitations. While it is reasonable to apply the Horn's index in the clinical prediction tool because it was found to be correlated with poorer outcomes of CDI, calculation of the index is interpreter-dependent and may lead to variations in calculated scores (23-25). Additionally, antitoxin A IgG is both an additional cost and not widely accepted or available. Exclusion of this variable would decrease the accuracy of the scoring tool. Ultimately, the limitations of this prediction tool restrict its widespread clinical practice application.

Another retrospective observational study was designed to validate a clinical prediction scale used to identify at risk patients for developing hospital-onset CDI. Correlation between the disease and the designated score was found, and similar risk factors were included in this study compared to previous literature (e.g. new-onset diarrhea, hospital length of stay beyond seven days, age over 65 years, long-term care facility resident, high-risk antibiotic use, and hypoalbuminemia). In this study, the prediction scale scores demonstrated high sensitivity (97%) and specificity (83%) when compared to results of PCR assay for *C. difficile* (25). Heavily weighted characteristics in this prediction scale were age and exposure to healthcare. Antibiotics were used in the 6-component scale, but were not weighted as heavily. This led to a difference between this scale and our proposed tool since antibiotic use was strongly associated with RCDI in our data.

Based on these previous studies, as well as findings from this study, several variables were chosen to create a risk evaluation tool. Scores were relatively suggested based on odds ratios, but these variables and scoring index will be modified based on future validation of this tool. The goal of this study was to develop a tool which could be used in a more generalized setting by defining easily identifiable factors. The proposed tool uses factors which have been cited with robust data in previous literature such as healthcare exposure, antibiotic use, and elderly age (greater than 65 years). Among the gastrointestinal diseases, IBD is included based on our findings, as well as literature citing higher incidence of CDI in this population compared to other gastrointestinal diseases (19). The extremely small sample size of IBD patients makes it difficult to easily use the calculated odds ratio to develop a score for this criterion. Therefore the score, while included, is slightly lower than the odds ratio would suggest. Table 3 outlines the proposed risk evaluation tool including the tentative scoring system. The tool developed is intended to provide a simple, but systematic way of determining a patients risk for RCDI which can easily be calculated by any practitioner. The proposed tool separates risk categories into low, moderate, and high to assist with stratification of patients. One suggestion is to consider initiating oral vancomycin prophylaxis for patients in the higher risk categories to reduce the likelihood of recurrence. This needs to be investigated further with larger, prospective studies.

Table 3. Proposed Tool for Determining Risk of Recurrent *Clostridium difficile* Infection

Characteristic	**Point**
Age >65 years	1
Antibiotic exposure	3
Inflammatory bowel disease	2
Healthcare exposure (hospital or healthcare facility) within 30 days	2
High risk	6-8
Moderate risk	3-5
Low risk	0-2

There were several limitations which should be considered when evaluating the results of this study. Due to the small sample size of patients with RCDI, there are many non-significant findings likely resulting from a lack of power to detect a correlation. While the small sample size does limit interpretation of these findings, the data obtained can be used to stimulate discussion and possibly initiate future studies at other institutions.

Another limitation is that additional factors that may impact risk of RCDI were not studied. For example, agents such as steroids, biologics, and other immunosuppressants were not included, leading to an underrepresentation of immunocompromised patients recorded in this study. Since immunosuppression has been considered as a risk factor for hospital-acquired infections such as CDI, this population may be unintentionally stratified with lower risk. Lastly, immunologic factors, such as detection of anti-toxin antibodies and virulence factors of *Clostridium difficile*, were not recorded in this study because these are not commonly collected at the site where this study was conducted.

CONCLUSION

Antibiotic exposure and past medical history of IBD were found to be correlated with the recurrence of *Clostridium difficile* infection. Although an association was not found with other variables evaluated, this is likely due to an insufficient sample size. The proposed tool is designed to help determine the level of risk of developing RCDI and guide the practice of prophylactic vancomycin for patients at higher risk.

ACKNOWLEDGMENTS

The authors wish to thank Scott Micek, Pharm.D., BCPS, FCCP for his assistance with study design and statistical analyses.

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