

Research Report

Prevalence of *Clostridium Difficile* Infection in Patients After Radical Cystectomy and Neoadjuvant Chemotherapy

Katherine J. Cotter*, Yunhua Fan, Gretchen K. Sieger, Christopher J. Weight and Badrinath R. Konety

University of Minnesota Department of Urology, Minneapolis, MN, USA

Abstract.

Background and Objectives: *Clostridium Difficile* is the most common cause of nosocomial infectious diarrhea. This study evaluates the prevalence and predictors of *Clostridium Difficile* infections in patients undergoing radical cystectomy with or without neoadjuvant chemotherapy.

Methods: Retrospective chart review was performed of all patients undergoing cystectomy and urinary diversion at a single institution from 2011–2017. Infection was documented in all cases with testing for *Clostridium Difficile* polymerase chain reaction toxin B. Patient and disease related factors were compared for those who received neoadjuvant chemotherapy vs. those who did not in order to identify potential risk factors associated with *C. Difficile* infections. Chi squared test and logistic regression analysis were used to determine statistical significance.

Results: Of 350 patients who underwent cystectomy, 41 (11.7%) developed *Clostridium Difficile* in the 30 day post-operative period. The prevalence of *C. Difficile* infection was higher amongst the patients undergoing cystectomy compared to the non-cystectomy admissions at our hospital (11.7 vs. 2.9%). Incidence was not significantly different among those who underwent cystectomy for bladder cancer versus those who underwent the procedure for other reasons. Median time to diagnosis was 6 days (range 3–28 days). The prevalence of *C. Diff* infections was not significantly different among those who received neoadjuvant chemotherapy vs. those who did not (11% vs. 10.4% $p=0.72$). A significant association between *C. Difficile* infection was not seen with proton pump inhibitor use ($p=0.48$), patient BMI ($p=0.67$), chemotherapeutic regimen ($p=0.94$), individual surgeon ($p=0.54$), type of urinary diversion (0.41), or peri-operative antibiotic redosing ($p=0.26$).

Conclusions: *Clostridium Difficile* infection has a higher prevalence in patients undergoing cystectomy. No significant association between prevalence and exposure to neoadjuvant chemotherapy was seen.

Keywords: Bladder cancer, neoadjuvant chemotherapy, *Clostridium Difficile*, radical cystectomy

INTRODUCTION

Clostridium Difficile infection (CDI) is the most common cause of nosocomial infectious diarrhea, with a recent prevalence rate of 1.4–2.3% described

in the post-radical cystectomy and urinary diversion population. Most recently, a prevalence of 8.8% in the post-cystectomy population was reported in a cohort of 552 patients with bladder cancer [1], which is a greater rate than previously described [2, 3]. In a study assessing the outcomes of hospital-acquired adverse events in patients undergoing radical cystectomy (RC), Kim et al. [2] found that patients with CDI had a longer median hospital stay by 9 days

*Correspondence to: Katherine J. Cotter, M.D., 420 Delaware St SE, MMC 394, Minneapolis, MN 55455, USA. Tel.: +1 612 625 8364; Fax: +1 612 625 0428; E-mail: cotte029@umn.edu.

and an increase in the total hospitalization cost by \$21,000 per patient when compared with those without adverse events. In addition, the cost of CDI within the United States is approaching \$10 billion, and the cost of preventable hospital adverse events has led to policy changes regarding reimbursement for such events [4]. Therefore, CDI generates both a significant clinical and financial burden and is being viewed as a quality metric.

Prior studies demonstrate an independent association between CDI and age, chronic antacid use, and perioperative antibiotic use greater than seven days [1]. Receipt of neoadjuvant chemotherapy does not appear to be associated with the rates of CDI. Krapohl and colleagues evaluated other risk factors for CDI in the general surgery population, and found that low pre-operative albumin and renal or neurologic comorbidities were significant risk factors [5]. However, to our knowledge, prior studies have not evaluated all of these factors specifically in a single study or evaluated the specific type of antibiotic(s) and antineoplastic agent(s) used. In the current study we evaluated the relative prevalence of CDI in patients undergoing cystectomy for bladder cancer, as well as for non-oncologic indications, and assessed potential predictive factors associated with such infection.

METHODS

Our Institutional Review Board approved database was searched for all patients undergoing cystectomy at our institution between 1/1/2011–7/2017. Retrospective chart review was performed of all identified patients. In order to thoroughly identify all cases and to identify the background prevalence of CDI in all inpatient hospital admissions at our institution, we also searched the institutional electronic health record derived dataset maintained by our bioinformatics center for the same. Cases were identified from the institutional dataset using claims data. ICD9 diagnosis codes for cystectomy were used (ICD9 57.71, 57.79, 57.6 and ICD10 0TTB0ZZ, 0TTB4ZZ, 0TTB7ZZ, 0TTB8ZZ, and CPT codes 51550–51597) and the code 008.45 was used to identify CDI in this administrative dataset. Documentation of neoadjuvant chemotherapy history was evaluated and categorized as either positive (had chemotherapy) or negative (did not have chemotherapy), and the specific chemotherapy regimen was recorded. Patients undergoing cystectomy without

the presence of bladder cancer did so for complications associated with neurogenic bladder, including recurrent urinary tract infections, intractable urinary incontinence, or urodynamic findings suggestive of a hostile bladder, such as reduced compliance. We excluded patients with active colorectal malignancy, inflammatory bowel disease, and chronic preoperative antibiotic use, including patients with a positive urine culture within 30 days of surgery treated with antibiotics. 3 patients were excluded for active colorectal malignancy, 1 for irritable bowel syndrome, and 20 for chronic pre-operative antibiotic use. All patients undergoing cystectomy were maintained on a clear liquid diet for the day prior to surgery, and until 2014, routine mechanical bowel preparation with magnesium citrate and Fleets enema was administered to all patients the day prior to surgery. Since 1/2015, we have adopted the Enhanced Recovery After Surgery (ERAS) protocol for all cystectomy patients, and hence they do not receive any mechanical or antibiotic bowel preparation pre-operatively.

Standard dosing of intravenous antibiotic within 30–60 minutes of incision was performed. If baseline renal dysfunction ($\text{CrCl} \leq 30 \text{ mL/minute/1.73 m}^2$) was present, antibiotic dosing was modified accordingly. The standard pre-operative antibiotic used was one gram of intravenous ertapenem, which was modified for patient allergies according to the American Urological Association Best Practice Statement on antimicrobial prophylaxis [6]. If administered, antibiotic re-dosing intra-operatively and within the 24 hour peri-operative period was recorded and the additional doses quantified. All patients underwent open or robotic-assisted laparoscopic radical cystectomy and urinary diversion with either conduit or neobladder creation. For those patients undergoing cystectomy for malignancy, bilateral pelvic lymphadenectomy was performed.

Post-operatively, *Clostridium Difficile* infection diagnosis was triggered by one of the following: diarrhea, unexplained elevation of white blood cell count, or unexplained fever. Standard testing with polymerase chain reaction toxin B from patient stool samples was used for detection. Additional patient information obtained from medical charts included factors that have been reportedly associated with CDI, such as a history of cerebrovascular accident, proton pump inhibitor use, pre-existing renal dysfunction, operative time, length of hospital stay, discharge disposition, and basic laboratory values, including albumin, complete blood count, and basic metabolic panel.

A chi-squared test was used to compare patients who had received neoadjuvant chemotherapy with those who underwent radical cystectomy only and to evaluate which patients developed infection. Logistic regression was used to determine association of patient and disease related factors with CDI occurrence. Multiple logistic regression models were applied, and we found the last model had the best fit (c statistic=0.661). The Hosmer and Lemeshow Goodness-of-Fit Test for this model showed $p=0.4225$, indicating that model fit was appropriate.

RESULTS

Of the 297 patients who were identified through our database, 212 (75%) had a diagnosis of bladder cancer. 80/212 (38%) patients received NAC for bladder cancer prior to cystectomy with either Gemcitabine and Cisplatin or Methotrexate, Vinblastine, Adriamycin and Cisplatin. Among those 212 patients with a bladder cancer diagnosis, 26 (12.3%) developed *Clostridium Difficile* infection within the first 30 days after surgery. 9/80 (11%) who received NAC developed CDI vs. 17/132 (13%) who did not receive NAC but underwent cystectomy for bladder cancer. Patients without a diagnosis of bladder cancer who underwent cystectomy had a CDI prevalence rate of 20% (14 patients total); however, this was not statistically significant when compared with CDI rates in bladder cancer patient ($p=0.19$). The incidence rate of CDI among all inpatient admissions to our hospital during the corresponding time period (1/1/2011–12/31/2015) was 1,692 cases out of 58,740 patients, with an incidence rate of 2.9%. Therefore, the incidence of CDI was higher amongst the population undergoing cystectomy compared to the background rate for all inpatient admissions at

our institution (10.6 versus 2.9%). We also compared patients undergoing radical cystectomy for bladder cancer versus those without bladder cancer.

Median time to CDI diagnosis was 6 days (range 3–28 days) in all patients, with 5.5 days in the post-chemotherapy group and 7.0 in the cystectomy only group. A total of 80 patients received neoadjuvant chemotherapy, and 9/80 (11%) developed *C. Difficile* infection within 30 days after surgery. Amongst who did not receive NAC, the prevalence of CDI was 21/202 (10.4%) ($p=0.72$). 70 patients had intraoperative redosing of antibiotics, and 10 (14%) of those patients developed CDI. Median length of hospital stay was 12 days in patients who received a diagnosis of CDI and 9 days in patients who were not diagnosed with CDI ($p=0.35$). Median patient BMI was 26.8 kg/m² in patients with CDI and 27.0 kg/m² in patients without CDI ($p=0.67$). A total of 64 patients (22.7%) were readmitted to the hospital within 30 days post-operatively. Pre-operative proton pump inhibitor use, chemotherapeutic regimen, individual surgeon, type of urinary diversion, or perioperative antibiotic redosing were not predictive of occurrence of CDI (Table 1). Logistic regression (Table 2) showed no statistically significant difference in the rates of CDI with any of the proposed risk factors for infection. Five patients were readmitted to the hospital within 30 days of surgery specifically for CDI-related diarrhea and dehydration. There was no known endoscopic intervention required within 30 days due to CDI.

DISCUSSION

Clostridium Difficile is a gram-positive, spore-forming anaerobic bacillus that produces two major cytotoxins, which confer the organism's virulence. Infection may lead to clinical manifestations ranging

Table 1
Clostridium Difficile infection rates and potential risk factors

Potential Risk Factors	C. Diff +	C. Diff –	N (%n)	p-value
All Patients	30 (11)	252 (89)	282 (100)	
Any Chemotherapy	9 (11)	71 (89)	80 (28)	
• Gemcitabine/cisplatin	11 (20)	44 (80)	55 (20)	0.72
• MVAC	2 (17)	10 (83)	12 (4)	
• Other	1 (11)	8 (89)	9 (3)	
Pre-op PPI use	4 (8)	44 (92)	48 (17)	0.48
Personal history of CVA	3 (16)	16 (84)	19 (7)	0.50
Perioperative antibiotic redosing	10 (14)	60 (86)	70 (25)	0.26
Non-continent urinary diversion	25 (11)	198 (89)	223 (79)	0.41
Continent urinary diversion	5 (8)	54 (92)	59 (21)	

Percentages may not add up to 100 due to rounding.

Table 2
Association with patient risk factors and CDI (logistic regression)

Effect	Odds Ratio	95% Wald Confidence Limits		<i>p</i> -value
Any Chemotherapy				
No	1			
Yes	1.033	0.429	2.489	0.9418
Personal history of CVA				
No	1			
Yes	2.735	0.786	9.521	0.1139
Pre-op PPI				
No	1			
Yes	0.384	0.108	1.371	0.1406
Continent Urinary Diversion				
No	1			
Yes	0.532	0.169	1.676	0.281
Perioperative antibiotic redosing				
No	1			
Yes	1.193	0.523	2.722	0.6749

from severe diarrhea to colonic perforation and even death. In our study, we found that the prevalence of CDI in patients undergoing cystectomy for benign or malignant conditions was much higher than that amongst inpatient admissions at our hospital. We also found that there was no difference in the rates among those undergoing the procedure for benign or malignant conditions. These data, while confirming earlier observations, expand on them by examining potential associated risk factors and also examining the presence of a cancer diagnosis itself as a risk factor. Further, the risk conferred by receipt of NAC in patients with bladder cancer was not significant in this particular study.

The prevalence of *Clostridium Difficile* infection in the general population has been reported to be under 1% [7]. Kraphol et al. evaluated 4,936 adult general surgery patients prospectively and found a CDI rate of 1.6% within the first 30 days post-operatively [5]. This rate is roughly equivalent to the 1.7% incidence rate described by Calvert et al. [3] in patients with bladder cancer who underwent radical cystectomy. Both studies reporting rates — years ago, demonstrate a higher rate of infection than in the general population.

However, CDI has risen over the past several years and its distribution has become more varied. Epidemiological studies demonstrate an increasing incidence of *Clostridium Difficile* in the community given chronic antibiotic use, antibiotic resistance, and a greater percentage of asymptomatic carriers [8, 9, 10]. In our study we found that among all inpatient admissions, CDI rates were much higher than that reported in these earlier studies, and rates among those undergoing cystectomy were almost tenfold

higher. This finding represents an alarmingly high prevalence rate, which cannot all be ascribed to time-related changes in antibiotic use or sensitivity, as the study windows are fairly close. Specifically for patients with bladder cancer, Liu et al. [1] reported an incidence rate as high as 8.8% in the post-radical cystectomy patient population. The rate of CDI after radical cystectomy also appears greater in comparison to other urologic malignancies studied, including renal cell carcinoma and prostate adenocarcinoma [3]. In their analysis, extended antibiotic prophylaxis was more prevalent in patients undergoing RC versus radical prostatectomy. In our study, we also found that CDI rates are higher post cystectomy performed for non-cancer related reasons which is new data that was not included in prior studies. As most patients undergoing cystectomy for non-cancer indications were due to sequelae of neurogenic bladder, this difference may be partially explained by a greater predisposition for infectious complications. In addition, while we did exclude patients on chronic antibiotics 30 days pre-operatively, many of these patients had been on antibiotic prophylaxis in the past and are therefore at greater risk for resistant infections.

In an investigation of modifiable risk factors for infection, the study by Calvert et al. highlights the importance of antibiotic stewardship and its previously described role in reducing CDI rates. According to the American Urological Association Best Practice Statement on Antimicrobial Prophylaxis, perioperative antibiotics should not routinely be continued beyond the first 24 hours in the absence of active infection [6]. While our study did not show a significant association with CDI and antibiotic redosing in the peri-operative period (Table 2), this finding may

have also been in part due to exclusion of all patients on chronic antibiotics before the procedure, and CDI may have subsequently developed beyond the 30 day post-operative period. Prior studies of CDI in bladder cancer patients included patients on antibiotics pre-operatively. The use of mechanical bowel preparation may have a role in increasing risk of CDI. A recent study examining this specific question found a higher rate of CDI amongst those receiving a mechanical bowel preparation vs. those who did not (10% vs. 3%) though this difference was not statistically significant [11]. Our results were not statistically significant, which indicated that a bowel prep was not associated with a lower rate of CDI.

Neoadjuvant chemotherapy may also serve as a major risk factor for CDI in patients with bladder cancer. In the medical oncology literature, chemotherapy is well-described as a risk factor for CDI, with an incidence ranging from 2.3–7%, with 8.2% ultimately developing severe enterocolitis [12]. Potential mechanisms for this finding include immunosuppression from chemotherapy and a subsequent predisposition for opportunistic infections, disruption of anatomic barriers, and/or exposure to nosocomial pathogens [13]. In those with prior chemotherapy, the degree of immunosuppression may place patients at a greater baseline risk than the general population, and the effects may be additive in patients with bladder cancer given known risk factors such as advanced age and medical co-morbidities. Whether malignancy itself increases the risk for CDI has not been clearly supported and may also be an area for future research.

Therefore, in adult patients undergoing cystectomy with urinary diversion and may have also had neoadjuvant chemotherapy, there are a multitude of described risk factors that predispose to CDI [14, 15]. The current study found a prevalence rate of 10% in the cystectomy only group within the first 30 days after surgery, which is greater than the reported incident rates in this patient population [1], and an 11% prevalence rate in patients who received neoadjuvant chemotherapy prior to cystectomy. However, these results were not found to be statistically significant, perhaps in part due to the limited number of patients. Similar to earlier reports, average hospital stay was longer in patients developing CDI but the difference was not statistically significant (12 days vs 9 days, $p=0.35$).

As patient data was obtained from a tertiary referral center where patients may inherently have more complex medical and surgical histories, applicability of results outside of this setting may be limited.

Furthermore, secular trends in testing for *Clostridium Difficile* infection has become more widespread. Hence it is possible that the higher rates detected in this study are influenced by a growing shift toward early and aggressive testing, and this has to be factored in when comparing these results to that derived from studies of earlier time periods. Further studies are warranted to address these questions.

CONCLUSIONS

Clostridium Difficile infection is fairly prevalent among patients undergoing radical cystectomy for bladder cancer or other non-cancer related causes. Though previous studies have found an association between CDI and NAC, as well as other factors, we did not find them to be statistically significant in the current analysis. Judicious use of antibiotics, rapid testing, and prompt therapy can help reduce the morbidity of this infection.

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