Incidence, predictors, and 30-day outcomes of *Clostridioides difficile* infection in patients undergoing cystectomy: A national database analysis

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Abstract

Clostridioides difficile infection (CDI) is the second most common health care acquired infection (HAI) and the most common gastrointestinal HAI, with an estimated 365,200 cases reported by the center for disease control in 2017. CDI continues to remain a major cause of inpatient admission and utilization of health care resources. This study aimed to determine the true incidence, risk factors, and outcomes of CDI in patients undergoing cystectomy. We conducted an analysis of patients undergoing cystectomy between 2015 and 2017 using the American college of surgeon National Surgical Quality Improvement Program to study the incidence, risk factors, and 30 day postsurgical outcomes associated with CDI following cystectomy. Developed by the American College of Surgery, this is a nationally validated, risk adjusted, and outcomes based program designed to determine and improve the quality of surgical and postsurgical care. The incidence of CDI following cystectomy was 3.6% in our patient cohort. About 18.8% of patients developed CDI following hospital discharge. None elective surgeries and complete cystectomy procedures had a higher rate of CDI. About 48.4% of patients with CDI had a preceding postoperative infection. Postoperative organ space infections, postoperative renal failure, postoperative sepsis, and septic shock were independently associated with the development of CDI, (all $P < 0.05$). Patients who developed postoperative CDI during hospitalization had lengthier hospital admissions than those who did not develop a CDI and had a higher risk of deep venous thrombosis formation. A sizable number of patients experience CDIs after cystectomy procedures in the USA, and CDI development is associated with an increase in length of stay and unplanned readmissions. Interventions and initiatives are needed to reduce this burden of disease.

Keywords: *Clostridioides difficile*, cystectomy, incidence, National Surgical Quality Improvement Program, outcome

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INTRODUCTION

Clostridioides difficile is a Gram-positive anaerobic organism typically found as part of normal gut flora. Colonization with *C. difficile* is usually asymptomatic; however, an alteration in the intestinal microbiome and resulting

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overgrowth can result in *C. difficile* infection (CDI).[1] While antibiotic exposure is the most common culprit for CDI, gastrointestinal surgery is also a well-described risk factor.[2,3] CDI is the second most common health-care-acquired infection (HAI) and the most common gastrointestinal HAI, with an estimated 365,200 cases reported by the CDC in 2017.[4] While the incidence of CDI has seen a steady decline since 2011, it continues to remain a major cause of inpatient admission and utilization of health-care resources.[5]

The exact incidence of periprocedural CDI with cystectomy is unknown, and the reported incidence of CDI in the literature varies widely.[6,7] Furthermore, nationwide database studies investigating CDI in cystectomy are lacking. One study utilizing the Nationwide Inpatient Sample (NIS) reported an incidence of 1.4%; however, due to a lack of follow-up data, this number is likely underreported.[8] Given the significant impact of CDI on patients undergoing cystectomy, it is imperative to determine the true incidence of CDI in this patient population, as well as risk factors and outcomes.

We conducted an analysis of patients undergoing cystectomy using the ACS National Surgical Quality Improvement Program (NSQIP) to study the incidence, risk factors, and postsurgical outcomes associated with CDI following cystectomy. Developed by the American College of Surgery, this is a nationally validated, risk-adjusted, outcomes-based program designed to determine and improve the quality of surgical and postsurgical care.[9]

Objectives

The objective of the study was to determine the true incidence, risk factors, and outcomes of CDI in patients after cystectomy.

METHODS

Data source

We conducted a retrospective study utilizing data from the NSQIP database. The NSQIP database includes perioperative variables from more than 500 institutions in the United States and is collected and maintained by trained surgical reviewers.[10] Variables are included up to day 30 of admission, along with 30-day postdischarge readmission data. All reported cases are anonymous and de-identified.

CDI was included as a variable in the database for the years 2015, 2016, and 2017 only. Data from NSQIP from these 3 years were thus included in our study.

Study population

We included all adult patients from NSQIP in our study if: (a) they underwent a complete or partial cystectomy; as defined by the Current Procedural Terminology codes 51550, 51570, 51580, 51555, 51565, 51590, 51575, 51596, 51585, 51595, and 51597a, and (b) had data available for the postoperative CDI variable. As the variable was added in the latter half of 2015 in the database, some patients from 2015 have missing data for this variable; however, the risk of bias resulting from this is negligible as no specific subpopulation is at risk for missing data.

Covariates

For all patients included in our study, patient age at the time of surgery, gender, race, body mass index (BMI), smoking status, preoperative comorbidities, hematocrit, albumin, creatinine, white blood cell count, source of admission, type of procedure (partial vs. radical cystectomy), American Society of Anesthesiologists classification, days from admission to procedure, and duration of procedure were included.

Study outcomes

The incidence of CDI was the primary endpoint of the study. Secondary outcomes included independent predictors of CDI deduced by multivariable logistic regression analysis and the effect of CDI development on length of stay, readmission, and mortality.

Postoperative CDI data were included up to the 30th postoperative day in the NSQIP database. NSQIP notes the postoperative day of development of each complication. CDI was divided into predischarge and postdischarge categories by comparing the day of development of infection with the length of stay.

Statistical analysis

All statistical analyses were conducted using SPSS statistical software v. 23 (IBM, Armonk, New York, United States). Multivariable logistic regression analyses were conducted to assess independent associations. The final covariates were selected using backward stepwise logistic regression analyses; all variables noted in Table 1 were initially entered into the model, and the variables with the least significant association with CDI were successively eliminated to arrive at the final model. These final variables included in the model had significant independent associations with CDI.

Albumin was the only variable included in our analysis that had more than 10% missing values. The patients with missing albumin values were treated using the missing indicator method as described in previous studies on

Table 1: Patient population included in the study

Characteristic	*n* (%)
Total	100
Age (years), mean: SD	10.4
18-59	1302 (20.9)
60-69	1993 (32.0)
70-79	2178 (34.9)
≥80	764 (12.2)
Gender	
Male	4946 (79.3)
Female	1291 (20.7)
Race	
Caucasian	4596 (73.7)
African American	307 (4.9)
Asian	95 (1.5)
Others/unknown	1312 (19.9)
Body mass index (kg/m^2, mean: SD)	
18-24	91 (1.5)
25-29	1620 (26.0)
30-34	2337 (37.5)
35-40	1877 (30.1)
≥40	283 (4.5)
Functional status before surgery	
Independent	6041 (96.9)
Dependent	173 (2.8)
Unknown	23 (0.4)
American Society of Anesthesiologists classification	
1-2	1401 (22.5)
3	4406 (70.6)
≥4	419 (6.7)
Smoking history	
No	4863 (78.0)
Yes	1374 (22.0)
Anemia (hematocrit<39 for men, hematocrit<36 for women)	
No	2951 (47.3)
Yes	3136 (50.3)
Missing	150 (2.4)
White blood cell count	
<15,000 (cells/m^3)	5845 (93.7)
≥15,000 (cells/m^3)	166 (2.7)
Missing	150 (2.4)
Hypoalbuminemia (<3.5 mg/dL)	
No	3824 (61.3)
Yes	245 (3.9)
Missing	2168 (34.8)
Diabetes mellitus	
No diabetes mellitus	5002 (80.2)
Noninsulin-dependent diabetes mellitus	788 (12.6)
Insulin-dependent diabetes mellitus	447 (7.2)
Chronic steroid use	
No	6013 (96.4)
Yes	224 (3.6)
Hypertension	
No	2561 (41.1)
Yes	3676 (58.9)
Dyspnea on exertion	
No	5748 (92.2)
Yes	489 (7.8)
Chronic obstructive pulmonary disease	
No	5780 (92.7)
Yes	457 (7.3)
Ascites	
No	6234 (100.0)
Yes	3 (0.0)
History of myocardial infarction	
No	6128 (98.3)
Yes	109 (1.7)
Days from admission to procedure	
Same day	5696 (91.3)
One day	257 (4.1)
Two days	70 (1.1)
Three or more	214 (3.4)
History of >10% weight loss	
No	6071 (97.3)
Yes	166 (2.7)
Operative duration (min)	
0-60	27 (0.4)
61-120	124 (2.0)
120-180	435 (7.0)
180+	5651 (90.6)
Source of admission	
Home	6100 (97.8)
Other facility	136 (2.2)
Procedure	
Partial cystectomy	489 (7.8)
Total cystectomy	5748 (92.2)

SD: Standard deviation

NSQIP database.[11,12] This approach to account for missing values has been supported over alternative approaches to account and adjust for missing values in this database by a study on missing data in NSQIP.[13]

Finally, a multivariable linear regression model was applied to assess the length of stay between patients who developed postoperative CDI during index hospitalization and those who did not. Multivariable logistic regression analysis incorporating the same covariates was also conducted for 30-day mortality, unplanned readmission, and pulmonary embolism, to assess the impact of CDI on these outcomes.

Two-sided significance level of 0.05 was set for all analyses conducted for the purposes of this study.

RESULTS

Study population

A total of 7422 patients underwent cystectomy procedures during the period studied. Of these patients, 1185 patients were excluded due to missing data on CDI. Among the included patients, 489 (7.8%) patients underwent partial cystectomies with or without ureteral reimplantation, while 5748 patients (92.2%) underwent radical cystectomies with or without conduit or lymphadenectomy performed.

The mean age of participants was 67.45 years (standard deviation [SD]: 11.43), and 20.7% % of participants (1291 patients) were female. The mean BMI of the population was 28.68 (SD: 6.01), and 22% % of participants had a history of smoking within 1 year before the procedure.

Incidence of *Clostridioides difficile* infection

A total of 223 were diagnosed with CDI during the 30-day postsurgical period, which translated into an incidence of 3.6%. Of the patients with CDI, 42 patients (18.8%) developed infections after discharge from the hospital.

Predictors of *Clostridioides difficile* infection

Multivariable logistic regression was applied to deduce independent associations of preoperative, procedural, and postoperative factors with the development of CDI. Among preoperative factors, preoperative anemia (odds ratio [OR]: 1.397 and confidence interval [CI]: 1.021–1.912) and male gender (OR: 1.8 and CI: 1.282–2.528) were associated with the development of CDI. Table 2 shows the preoperative and procedure-related risk factors for CDI.

After adjusting for all factors mentioned above, among operative factors, nonelective nature of surgery was significantly associated with increased risk of CDI (OR: 2.56 and CI: 1.020–6.399). Complete cystectomy was associated with an increased risk of CDI when compared to partial cystectomy procedures (OR: 3.54 and CI: 1.212–10.322).

After adjusting for preoperative and procedure-related factors, postoperative organ space infections (OR: 1.95 and CI: 1.269–3.003), postoperative renal failure (OR: 2.38 and CI: 1.020–5571), postoperative sepsis (OR: 2.49 and CI: 1.621–3.828), and septic shock (OR 2.33 and CI 1.176–4.619) were independently associated with the development of CDI (all $P < 0.05$).

Among patients who developed CDI, 108 patients (48.4%) had preceding postoperative infections. The preceding infections included surgical site infections in 65 patients, pneumonia in 18 patients, and urinary tract infection in 25 patients, with 44 and 21 patients being diagnosed with sepsis and sepsis shock, respectively. Surgical site infections included superficial infections in 20 patients, deep incisional infections in 3 patients, and organ space infections in 42 patients.

Table 2: Independent preoperative and procedure-related risk factors for *Clostridioides difficile* infection

Characteristic	RR	95% CI	*Pa*
Preoperative characteristics			
Gender			
Female	Reference	-	
Male	1.800	1.282-2.528	0.001
Anemia (hematocrit<39 for men, hematocrit <36 for women)			
No	Reference	-	
Yes	1.397	1.021-1.912	0.037
Missing	0.113	0.000-0.000	
Procedure-related characteristics			
Procedure urgency			
Elective procedure	Reference	-	
Nonelective procedure	2.555	1.020-6.399	0.045
Type of procedure			
Partial cystectomy	Reference	-	
Complete cystectomy	3.537	1.212-10.322	0.q021

CI: Confidence interval, RR: Reference range

Effect of postoperative *Clostridioides difficile* infection on patient outcomes

Patients who developed postoperative CDI during hospitalization had lengthier hospital admissions than those who did not develop a CDI after adjusting for preoperative, procedure-related, and postoperative factors (OR: 2.29 and CI: 1.780–2.938). Patients with CDI were more likely to be diagnosed with deep vein thromboses (OR: 2.48 and CI: 1.351–4.565).

There was no difference in the risk of 30-day mortality between patients who developed CDI and patients who did not. Development of CDI after hospital discharge was significantly associated with the risk of unplanned readmission (OR: 7.8; 95% CI: 3.4–17.9).

DISCUSSION

CDI is primarily nosocomial in nature, associated with increased morbidity in surgical practice and considered an important hospital quality and reimbursement metric.[14] It is previously known that although most urological procedures carry an inherently low risk of CDI, cystectomy procedures are associated with higher CDI rates.[15] The data on CDI after cystectomy are primarily derived from small single-center studies that reported rates as high as 7%–8.8%.[16] Large studies estimating CDI incidence and its predictors after cystectomy are lacking, and the only previous study available that estimated a rate of 1.4% was based on the NIS, a dataset that does not contain follow up data after discharge.[15] Contrary to their estimation, we found an incidence rate of 3.6%. This is likely due to the fact that the more appropriate use of NSQIP database allowed us to include 30-day follow-up data, including data after discharge, and thus more accurately captured CDI that developed in the postoperative setting, especially cases that would have been missed in a study utilizing inpatient data alone. Given that most cases of CDI are reported within 1 month of alteration of gut flora, we believe that the 30-day follow-up interval used in our study is most appropriate.[17] Our findings reaffirm the high rate of CDI in patients undergoing cystectomy and provide further insight into the incidence, risk factors, and outcomes of CDI following cystectomy.

It is worth discussing the role of antibiotics in the prevention of postoperative wound infections, as well as their impact on postoperative CDI. Antimicrobial prophylaxis is recommended by both the American Urological Association and the European Association of Urology for perioperative use in patients undergoing cystectomy and is routinely used in these patients.[18,19] In addition, when preparing patients for surgery, mechanical, antibiotic, or both kinds of bowel preparation are also employed. The effect of these antibiotic bowel preparations on CDI incidence is not yet clear, with studies showing conflicting results for noncolon surgery patients.[20] In comparison, for patients undergoing colorectal surgery, some studies have found an increased risk of CDI with antibiotic bowel preparation.[21] Interestingly, one previous retrospective study noted fewer cases of CDI after cystectomy if no bowel preparation was used in comparison to the use of mechanical bowel prep (2 vs. 11, $P = 0.08$).[16] One limitation of our study is the inability to determine a difference between CDI rates based on the type of surgical preparation utilized. While NSQIP reports bowel preparation data for colorectal surgery, such data for urological interventions are not available at present. Additional studies are needed to further identify the role of bowel preparation in patients undergoing cystectomy.

This is the first study utilizing NSQIP to study the incidence, risk factors, and outcomes of CDI in a urological procedure. We found that preoperative anemia and male gender were associated with CDI. Anemia has been associated with CDI in the past.[22,23] Similarly, male patients have been found to be at increased risk of CDI in studies on other postsurgical populations.[24] Postoperative infections have also been previously studied as risk factors for CDI in the postoperative setting. Based on our data, it appears that CDIs after cystectomy continue to remain a concern, and are associated with an increase in length of stay as well as a higher risk of readmissions. Therefore, it is imperative that quality improvement initiatives and interventions for reducing this burden continue to be tested and employed.

The main strength of our study is the high representative number of patients included in the study population, as well as the 30-day postoperative period of data accrual. One limitation to our study is the lack of bowel preparation data, as mentioned above. Second, we were not able to report the effect of CDI on inpatient cost. This is an important determinant of health-care resource use, as one previous study noted that over a 7-year period, $8.3 million in excess costs related to patients undergoing cystectomy could be attributed to postoperative CDI.[15]

CONCLUSIONS

A sizable number of patients experience CDIs after cystectomy procedures in the USA, and CDI development is associated with an increase in length of stay and unplanned readmissions. Interventions and initiatives are needed to reduce this burden of disease.

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Conflicts of interest
There are no conflicts of interest.

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