Published in final edited form as:

Am J Surg. 2013 March ; 205(3): 343–348. doi:10.1016/j.amjsurg.2012.10.028.

Preoperative Risk Factors for Postoperative *Clostridium difficile* Infection in Colectomy Patients

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Abstract

OBJECTIVE—Wide variation between hospitals in the rate of *Clostridium difficile* infection (CDI) after surgery was hypothesized to be related to different prophylactic antibiotic practices.

METHODS—Between March 2008 and March 2010, 30-day confirmed postoperative CDI rates were prospectively collected for patients undergoing colectomy surgery in 23 hospitals participating in a collaborative quality improvement program. Preoperative variables significantly associated with CDI ($p \leq 0.10$) in a bivariate analysis were incorporated into a logistic regression model to test for independent associations.

RESULTS—Amongst 4936 patients, the overall rate of CDI was 1.6% (range by hospital 0–9%). After adjusting for patient comorbidities and hospital site, type of preoperative antibiotics used for prophylaxis was not significantly associated with CDI. Emergency surgery, low albumin, neurological and renal comorbidities emerged as independent preoperative predictors of CDI.

CONCLUSIONS—Perioperative antibiotic practices did not prove to be independently associated with CDI after colectomy surgery.

INTRODUCTION

Clostridium difficile, a gram-positive, spore-forming, anaerobic bacillus that produces intestinal disease, is now the most common organism to cause healthcare associated infection in the United States. [1] Compounding the rising incidence of *Clostridium difficile* infection (CDI) is an increase in both severity and mortality of the disease. [2] Despite increased attention to hygiene measures, the incidence of CDI has continued to escalate due in part to the rise the NAP1/BI/027 toxinotype III strain of *Clostridium difficile*, which has demonstrated resistance to common antimicrobial therapy and unique microbiological properties.[3-4]

Epidemiologic data suggest that the burden of CDI is increasing among surgical patients, especially among patients having digestive tract surgery; in fact, colectomy patients are almost twice as likely to acquire CDI as patients having other surgical procedures. [5] Antimicrobial use almost always precedes CDI, [3] and therefore routine prophylaxis with broad-spectrum antibiotics may explain in part the risk of CDI after colectomy. However, it is unclear whether particular antibiotic choices predispose to CDI in surgical patients.

In this context, the objective of the present study was two-fold: (1) to identify the preoperative risk factors for CDI in a cohort of surgical patients; and (2) to determine if the use of particular prophylactic antibiotics was associated with a higher (or lower) risk of CDI. The results of this study can inform practice by helping to identify high- risk patients, determine “best practices” associated with lower CDI risk, and improve patient outcomes for colectomy patients in the state of Michigan.

METHODS

This study was performed using a limited data set from the Michigan Surgical Quality Collaborative (MSQC). This is a regional coalition of 52 teaching and community hospitals across the state of Michigan that uses an audit and feedback system as well as regular meetings and site visits for quality improvement.[6] The program is funded by the Blue Cross and Blue Shield of Michigan/Blue Care Network. Trained data abstractors prospectively collect patient characteristics, intraoperative processes of care and 30-day postoperative outcomes from general and vascular surgery patients in accordance with established policies and procedures. The core data available for the present study were based on the American College of Surgeons’ National Surgical Quality Improvement Program (ACS NSQIP).[7] The colectomy-specific data were collected via the MSQC’s Colectomy Project, a subset of the larger MSQC initiative, that was started in 2007 to measure colectomy-specific processes and outcomes.[8] Institutional Review Board approval was obtained from the University of Michigan Institutional Review Board-Medical (HUM00052591).

All patients 18 years and older enrolled into the MSQC Colectomy Project between March 1, 2008 and March 10, 2011 were eligible to be included in the study. This sample included both emergent and nonemergent colectomy patients with the following four Current Procedural Terminology (CPT) codes: (1) 44140 - open colectomy, partial with

anastomosis; (2) 44160 - open colectomy, partial with removal of terminal ileum with ileocolostomy; (3) 44204- laparoscopic colectomy, partial with anastomosis, and (4) 44205- laparoscopic colectomy with removal of terminal ileum with ileocolostomy. The outcome variable was CDI, identified by laboratory detection of the toxin in the stool or by a positive stool culture up to 30-days after surgical procedure. Patient characteristics, preoperative risk factors and surgical considerations associated with CDI risk in the literature were selected as the independent variables in addition to the patient's preoperative intravenous antibiotic regimen.

Univariate associations between independent variables and incidence of CDI were estimated using chi-square tests or the Fisher's exact test for categorical variables, and a two-sample t-test for the continuous measures of age, body mass index (BMI), duration of operation and laboratory values. Bowel preparation was tested as a categorical variable for association with CDI (mechanical with oral antibiotics, mechanical without oral antibiotics, non-mechanical prep, or no prep). For the intravenous antibiotic analysis, each subject was placed into a mutually exclusive category based on the combination of IV antibiotics given perioperatively for prophylaxis (excluding patients who were exempt from receiving prophylactic preoperative antibiotics for various reasons. These might include: antibiotic therapy of a pre-existing infection, or emergency admission with antibiotics given at admission rather than preoperatively). Each category of patients was then compared to the rest of the group in the univariate analysis.

Variables significant at $\alpha = 0.10$ in the univariate analysis were entered into a logistic regression model. The logistic regression stratified by site effect, was used to examine the covariate-adjusted effect of antibiotics used on CDI, and backward selection was used to select a subset of adjustment covariates. A level of $p = 0.05$ was the criterion established for statistical significance. All statistical analysis was performed using SAS v9.2 (SAS Institute; Cary, NC).

RESULTS

The final cohort included 4936 patients who underwent colectomy between March 1, 2008 and March 10, 2011, representing twenty-three hospital sites that were actively engaged in the MSQC colectomy project and had greater than 10 patients in the project. Overall, 80 patients (1.6%) were diagnosed with CDI postoperatively (within 30 days). The rate of CDI varied by hospital site from 0% to 9%.

Significant bivariate associations between the independent variables and of patients with CDI and without CDI are shown in Table I. Patients with CDI had a higher exhibited a higher rate of serious disease such as sepsis ($p=0.001$), dialysis ($p<0.0001$) and ventilator use ($p=0.012$). Additionally, CDI patients represented a higher rate of emergent surgery (23% vs. 10%) and open surgical approach (71% vs. 58%).

Only two intravenous antibiotics had a statistically-significant association with CDI in univariate analysis; cefoxitin had a higher rate of CDI (27%), and ertapenem had a lower rate of CDI (7%). However, these did not remain significant in the multivariable analysis

(Table II). While fluoroquinolone antibiotics are used infrequently for colectomy prophylaxis, we examined those patients who received this class of antibiotics to see if they had a higher risk of CDI, but they did not (data not shown). Likewise, an analysis of 392 patients who were exempt from preoperative antibiotic prophylaxis due to therapeutic antibiotic use (or other reasons) did not demonstrate a statistically significant association with CDI ($p=0.128$).

The bowel preparation analysis showed that when the bowel prep was analyzed as a categorical variable with the patients on therapeutic antibiotics excluded, there was not a significant association with CDI ($p=0.070$), and that the group receiving oral antibiotics had a lower, not higher, rate of CDI. Therefore, this variable was not moved forward to the logistic regression model.

As demonstrated in Table II, dialysis (OR [6.049]; CI 2.104-17.394), low albumin level (OR [0.572]; CI 0.393-0.833) a history of transient ischemic attack (OR [2.549]; CI 1.134-5.728), and emergent surgery (OR [1.862]; CI 1.045-3.317), were the strongest independent predictors of CDI in this cohort.

DISCUSSION

This study represents one of the largest studies of risk factors for CDI in surgical patients using a prospective clinical (not administrative) dataset. Consistent with previous research, low albumin, neurological and renal comorbidities emerged as significant preoperative predictors of CDI risk. While this is important to validate in the surgical patient population, one of the most valuable findings of this study was not what was found significant, but what was found insignificant; preoperative prophylactic antibiotic practices did not have any independent association with CDI after adjusting for patient comorbidities and hospital site.

Since antibiotic use almost always precedes CDI, the standard use of preoperative prophylactic antibiotic use in surgical patients has been implicated as a risk factor for CDI. [9] There is evidence to suggest that antibiotics classes including lincosamides, broad spectrum penicillins, cephalosporins and fluoroquinolones may contribute to this risk.[3] Although one study suggested a higher rate of CDI with the use of preoperative prophylaxis with cefoxitin (cephalosporin class) it was unclear whether or not the association was due to the higher risk of the colon surgery itself, or the antibiotic choice. [9] Our investigation found the same association with cefoxitin in univariate analysis; however, this effect was eliminated when adjusted for other comorbidities and hospital sites. The results of this analysis suggest no particular prophylactic antibiotic regimen confers an increased risk of CDI postoperatively.

This study provides additional validation that patients with a higher severity of illness are at a higher risk for CDI, and many comorbid illnesses were associated with CDI on univariate analysis. However, only a few factors were independently associated with CDI in the multivariable analysis: low albumin, dialysis, cerebrovascular disease, and emergency (rather than elective) surgery. Contrary to the evidence in the literature, patient age was not associated with an increased risk of CDI. Additional post hoc analyses were conducted on

age as a dichotomous and categorical variable without any detectable association with CDI. A potential explanation may be that most research conducted for CDI risk factors are in the hospitalized medical population; surgical patients may be younger and healthier than their medical counterparts. Therefore, chronological age may not be as strong of a predictor of CDI infection in the surgical population.

There is evidence from the literature demonstrating an association between renal disease and CDI that corroborates our findings. [10] The association is attributed to a possible decrease or absence of gastric acid (achlorhydria or hypochlorhydria), the dose or exposure to dialysis and/or a higher *C. difficile* pathogen load in the stool due to decreased motility. [10] It is also reasonable to assume that patients with renal disease or dialysis have had higher exposure to both antibiotics and health care facilities, also significant risk factors for CDI.[3]

Puzzling as it may be, a history of transient ischemic attacks had a significant association in both univariate and multiple variable analysis with postoperative CDI. The strong association between TIA and CDI does not appear to have any precedence in the literature and no additional variables in the central nervous system category were found to be independently associated with CDI. This finding may be due to the small number of stroke patients in the cohort giving this variable inadequate power to demonstrate a significant association in comparison with TIA. It is notable that anecdotal reports have linked ischemic colitis to the development of CDI without prior antimicrobial exposure. If intestinal ischemia is a risk factor for CDI then the presence of cerebrovascular ischemia might have been a surrogate marker for that condition in our study. Another possible reason for our findings could be that the variable of TIA could be a proxy for current or past cigarette smoking. Patients who currently smoke cigarettes were recently reported to have nearly twice the odds of developing CDI than their non-smoking counterparts. [11] Although a patients past smoking status was collected for this study, whether or not a patient was a current smoker was not specifically ascertained and may have contributed to the lack of association with CDI.

The limitations of this study are consistent with those inherent in conducting a retrospective analysis and in those operating within the constraints of the ACS NSQIP dataset. The most important of these is that this study was unable to account for several important preoperative variables such as use of proton pump inhibitors, tube feeding, fecal incontinence and the type and duration of therapeutic antibiotic use. Thus, we might have missed important potential associations. Also, the sample size of just under 5000 patients may have limited the power to detect differences between antibiotic groups, particularly given the large number of different choices currently in practice in the state.

The definition we used for this study also has potential shortfalls. The first is the reliance on only confirmed lab values since it is likely that some patients were treated empirically without laboratory confirmation, and this would have missed some cases. Secondly, this study could not account for those patients that were only colonized with *C. difficile* (tested positive) but did not exhibit diarrheal symptoms; these would represent false positive cases, but would be few because testing for CDI would be infrequently done in absence of symptoms. Finally, the definition of CDI in this study included any diagnoses

from the day of surgery to 30 days after surgery. This is important since patients with less than a 48 hour window of CDI diagnosis may be patients with a community-associated CDI rather than a true health care associated infection.

Along the same lines, a widespread limitation of studying both CDI and albumin levels in multiple inpatient locations is the failure to account for the different diagnostic testing techniques used within each hospital or contracted testing laboratory. Because diagnostic detection techniques were not standardized at the 23 hospital sites, underestimation or overestimation of CDI could be a confounding variable for this study. A survey of the hospital sites in 2009 revealed that only one hospital site had switched to the more specific and sensitive polymerase chain reaction (PCR) methodology. The majority of the sites reported using the enzyme immunoassay (EIA) toxin A and B diagnostic technique with a sensitivity that is lower (higher propensity for false positive results). As the demand for more rapid and sensitive testing of *C. difficile* grows and the adoption of PCR testing increases, the challenges of multi-center comparisons for CDI will be easier and more accurate.

Although this study focused only on the preoperative risk factors of CDI, future research could evaluate the intraoperative and postoperative processes of care that are also critical factors for understanding the precise contributions of CDI risk. This subject is especially important given that patients with CDI in our study had nearly four times the risk of mortality than patients without CDI (9 patients, 11%, with CDI vs. 167 patients, 3%, without CDI). Also, future analysis of the day of CDI diagnosis in relation to the surgery could yield important clues as to where the burden of infection is greatest. For example, if the majority of the patients in this study had contracted their infection during the later portion of their 30-day data collection window, precursors to infection could be attributed to use of postoperative antibiotic dispensing or other therapeutic antibiotic regimens.

In conclusion, CDI has grown into an increasingly deadly and prevalent infection. Since surgical patients now carry more than twice the burden of healthcare-associated infections (HAI) than their medical counterparts,[12] strategies to identify the intrinsic and extrinsic risk factors contributing to avoidable infections are important. This study demonstrated that particular preoperative prophylactic antibiotics were not independently associated with CDI after colectomy surgery. However, patients that underwent emergency surgery or had renal, cerebrovascular, and nutritional comorbidities were significant predictors of CDI in this cohort. As the findings of this study suggest, the burden of risk for CDI may be influenced more by individual patient comorbidities than other device-related HAIs such as urinary tract and central line-associated infections. Therefore, surgical patients at high risk for CDI may benefit from early intervention strategies such as allocation of a private room, preemptive isolation, cohorting nursing staff and/or patients, reinforced education to patients and visitors and nurse-driven protocols for initiating timely stool specimen collection and processing. The ability to identify and recognize the risk factors of CDI in this vulnerable patient population is an opportunity to intervene before, not in response to, the threat of a deadly and more virulent CDI.

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Table IBivariate Analysis of Preoperative Variables and CDI^{*}

Patient Characteristics			
	No CDI (4856)	Yes CDI (80)	P Value
Race			
White	3843 (79%)	53 (66%)	0.005
Nonwhite	1013 (21%)	27 (34%)	
Preoperative Risk Factors			
Acute renal failure	23 (0.50%)	3 (4%)	0.008
Dialysis	42 (0.90%)	6 (8%)	<0.0001
Functional Status	4523 (93%)	65 (81%)	<0.000
Congestive heart failure	60 (1%)	3 (4%)	0.082
CVA (neurological deficit)	129 (3%)	5 (6%)	0.065
TIA	192 (4%)	8 (10%)	0.015
Hemiplegia	47 (0.97%)	3 (4%)	0.047
Hypertension	2742 (56%)	55 (69%)	0.028
Myocardial infarction	40 (0.82%)	3 (4%)	0.032
Sepsis	452 (9%)	16 (20%)	0.001
Ventilator Dependent	27 (0.60%)	3 (4%)	0.012
Weight loss >10%	191 (4%)	7 (9%)	0.040
Albumin	3.7±0.7	3.4±0.8	0.003
Hematocrit	37.6±5.9	35.8±6.5	0.006
Surgical Factors			
Laparoscopic	2016 (42%)	23 (29%)	0.021
Open	2840 (58%)	57 (71%)	
Prior Operation	60(1%)	3 (4%)	0.085
Emergent	499 (10%)	18 (23%)	0.0001
Bowel Prep ^{**}			
	No CDI (3794)	Yes CDI (51)	0.071
No prep	116 (3%)	4 (8%)	
NonMechanical Prep	871 (23%)	14 (27%)	
Mechanical Prep(no oral antibiotics)	1472 (39%)	22 (43%)	
Mechanical Prep (oral antibiotics)	1335 (35%)	11 (22%)	
Preoperative Intravenous Prophylactic Antibiotics			
Ertapenum (Invanz)	893(20%)	5(7%)	0.008
Cefoxitin (Mefoxin)	833 (19%)	19 (27%)	0.070

CVA=cerebrovascular accident, TIA= transient ischemic attack.

* Variables analyzed but not achieve a level of significance >.1 are not listed in this table. Insignificant variables included Patient Characteristics: Age, BMI, Gender; Perioperative Risk Factors: Hx of Smoking, ETOH, Diabetes, Dyspnea; COPD, Pneumonia, CHF, CVA without neurological

deficit, Chemotherapy, Radiation, Cancer, Steroids; Surgical Factors: Duration of Operation; Laboratory values: WB C; Preoperative intravenous prophylactic antibiotics: Surgical Care Improvement Project approved antibiotics and other combinations.

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Not carried forward to logistic regression model.;

Table II Logistical Regression Model to Assess the Effect of Variables on CDI Stratified by Hospital Site (backward selection at level 0.1)

Variable	OR	95% CI	
		Lower	Upper
Albumin	0.0036	0.572	0.393
Dialysis	0.0008	6.049	2.104
Hemiplegia	0.0649	3.378	0.927
Emergent Surgery	0.0349	1.862	1.045
Acute Renal Failure	0.0846	3.598	0.840
Transient ischemic attack	0.0235	2.549	1.134

OR= Odds ratio; CI=confidence interval.

CDI=80; Total =4856