Midwest Surgical Association

Preoperative risk factors for postoperative Clostridium difficile infection in colectomy patients

Greta L. Krapohl, Ph.D., R.N.*, Arden M. Morris, M.D., M.P.H., Shijie Cai, M.S., Michael J. Englesbe, M.D., David M. Aronoff, M.D., Darrell A. Campbell, Jr., M.D., Samantha Hendren, M.D., M.P.H.

Michigan Surgical Quality Collaborative, University of Michigan, 2800 Plymouth Road, Building 16, Room 124, Ann Arbor, MI 48109, USA

KEYWORDS:
Clostridium difficile infection; Colectomy; Prophylactic antibiotics; Risk factors

Abstract

BACKGROUND: Wide variation among 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 at 23 hospitals participating in a collaborative quality improvement program. Preoperative variables significantly associated with CDI ($P < .10$) in a bivariate analysis were incorporated into a logistic regression model to test for independent associations.

RESULTS: Among 4,936 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, and neurologic 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.

© 2013 Elsevier Inc. All rights reserved.

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. Compounding the rising incidence of C difficile infection (CDI) is an increase in both the severity and the mortality of the disease. Despite increased attention to hygiene measures, the incidence of CDI has continued to escalate, in part because of the rise of the NAP1/BI/027 toxinotype III strain of C difficile, which has demonstrated resistance to common antimicrobial therapy and unique microbiologic properties.

Epidemiologic data suggest that the burden of CDI is increasing among surgical patients, especially among patients with digestive tract surgery; in fact, colectomy patients are almost twice as likely to acquire CDI as patients undergoing other surgical procedures. Antimicrobial use almost always precedes CDI, and therefore routine prophylaxis with broad-spectrum antibiotics may explain in part the risk for 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 2-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 for CDI. The results of this study can inform practice by helping 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 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.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 aged ≥18 years enrolled in 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 4 Current Procedural Terminology 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 the incidence of CDI were estimated using \( \chi^2 \) tests or Fisher’s exact tests for categorical variables and 2-sample \( t \) tests for the continuous measures of age, body mass index, 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, nonmechanical preparation, or no preparation). For the intravenous antibiotic analysis, each subject was placed into a mutually exclusive category on the basis of the combination of intravenous antibiotics given perioperatively for prophylaxis (excluding patients who were exempt from receiving prophylactic preoperative antibiotics for various reasons that might include: antibiotic therapy for a preexisting infection or emergency admission with antibiotics given at admission rather than preoperatively). Each category of patients was then compared with the rest of the group in the univariate analysis.

Variables significant at \( \alpha \leq 0.10 \) 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 \( P \) value \( \leq .05 \) was the criterion established for statistical significance. All statistical analysis was performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

The final cohort included 4,936 patients who underwent colectomy between March 1, 2008, and March 10, 2011, representing 23 hospital sites that were actively engaged in the MSQC Colectomy Project and had >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 patients with CDI and without CDI are shown in Table 1. Patients with CDI had a higher rate of serious disease such as sepsis (\( P = .001 \)), dialysis (\( P < .0001 \)), and ventilator use (\( P = .012 \)). Additionally, patients with CDI represented a higher rate of emergent surgery (23% vs 10%) and open surgical approach (71% vs 58%).

Only 2 intravenous antibiotics had statistically significant associations 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 multivariate analysis (Table 2). Although 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 for CDI, but they did not (data not shown). Likewise, an analysis of 392 patients who were exempt from preoperative antibiotic prophylaxis because of therapeutic antibiotic use (or other reasons) did not demonstrate a statistically significant association with CDI (\( P = .128 \)).

When bowel preparation was analyzed as a categorical variable with the patients receiving therapeutic antibiotics excluded, there was no significant association with CDI (\( P = .071 \)), and 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 2, dialysis (odds ratio [OR], 6.049; 95% confidence interval [CI], 2.104–17.394), low
albumin level (OR, 0.572; 95% CI, 0.393–0.833), history of transient ischemic attack (TIA) (OR, 2.549; 95% CI, 1.134–5.728), and emergent surgery (OR, 1.862; 95% CI, 1.045–3.317) were the strongest independent predictors of CDI in this cohort.

**Comments**

This study represents one of the largest studies of risk factors for CDI in surgical patients using a prospective clinical (not administrative) data set. Consistent with previous research, low albumin and neurologic and renal comorbidities emerged as significant preoperative predictors of CDI risk. Although 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.

Because antibiotic use almost always precedes CDI, the standard use of preoperative prophylactic antibiotics in surgical patients has been implicated as a risk factor for CDI. There is evidence to suggest that antibiotic classes including lincosamides, broad-spectrum penicillin,
significant risk factors for CDI.3

exposure to both antibiotics and health care facilities, also

rates our findings. 10 The association is attributed to a pos-

association between renal disease and CDI that corrobo-

infection in the surgical population.

and healthier than their medical counterparts. Therefore,

research conducted for CDI risk factors is in the hospital-

with CDI. A potential explanation may be that most

analyses were conducted on age as a dichotomous and

independently associated with CDI in the multivariate

univariate analysis. However, only a few factors were

with an increased risk for CDI. Additional post hoc

analysis: low albumin, dialysis, cerebrovascular disease,

was eliminated when adjusted for other comorbidities and

hospital sites. The results of this analysis suggest that no

particular prophylactic antibiotic regimen confers an in-

creased risk for 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 multivariate

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 for 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 is in the hospital-

ized medical population; surgical patients may be younger

and healthier than their medical counterparts. Therefore,

chronologic 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 corrobo-

rates our findings.10 The association is attributed to a pos-

sible 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 de-

c eased motility.10 It is also reasonable to assume that pa-

tients 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 TIA had a significant

association in both univariate and multivariate analysis with

postoperative CDI. The strong association between TIA and

CDI does not appear to have any precedent 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 patients with stroke 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 cerebrovas-

cular 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 nonsmoking

counterparts.11 Although patients’ smoking status within

the year preceding surgery was collected for this study,

whether a patient was currently smoking or had a history

of smoking 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 those

operating within the constraints of the National Surgical

Quality Improvement Program data set. The most important

of these is that we were unable to account for several

important preoperative variables, such as the 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 5,000 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, because it is likely that some patients were treated

empirically without laboratory confirmation, and this would

have missed some cases. Second, this study could not

account for those patients who were only colonized with C
difficile (tested positive) but did not exhibit diarrheal symp-

toms; these would represent false-positive cases but would

be few because testing for CDI would be infrequently done

in the absence of symptoms. Finally, the definition of CDI

in this study included any diagnoses from the day of sur-
ge ry to 30 days after surgery. This is important because pa-

tients with less than a 48-hour window of CDI diagnosis

may be those with community-associated CDI rather than

true health care–associated infection.

Along the same lines, a widespread limitation of study-

ing both CDI and albumin levels in multiple inpatient

locations is the failure to account for the different diag-
nostic 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 1 hospital site had switched

Table 2 Logistical regression model to assess the effect of

variables on CDI stratified by hospital site (backward selection

at level 0.10)

<table>
<thead>
<tr>
<th>Variable</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>.0036</td>
<td>0.572</td>
<td>.393–.833</td>
</tr>
<tr>
<td>Dialysis</td>
<td>.0008</td>
<td>6.049</td>
<td>2.104–17.394</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>.0649</td>
<td>3.378</td>
<td>.927–12.303</td>
</tr>
<tr>
<td>Emergent surgery</td>
<td>.0349</td>
<td>1.862</td>
<td>1.045–3.317</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>.0846</td>
<td>3.598</td>
<td>.840–15.413</td>
</tr>
<tr>
<td>TIA</td>
<td>.0235</td>
<td>2.549</td>
<td>1.134–5.728</td>
</tr>
</tbody>
</table>

Of the total sample of 4,856 patients, 80 had CDI.

CDI = Clostridium difficile infection; CI = confidence interval;

OR = odds ratio; TIA = transient ischemic attack.
to the more specific and sensitive polymerase chain reaction methodology. The majority of the sites reported using the enzyme immunoassay toxin A and B diagnostic technique, with 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 polymerase chain reaction testing increases, multicenter comparisons for CDI will be easier and more accurate.

Although we focused only on the preoperative risk factors for 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 4 times the risk for 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 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 infections during the later portion of their 30-day data collection windows, 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. Because surgical patients now carry more than twice the burden of health care–associated infections compared with their medical counterparts, 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, emergency surgery and 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 health care–associated infections 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 the allocation of a private room, preemptive isolation, cohorting nursing staff members 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 for 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.

**References**


**Discussion**

Dr Donald Fry (Chicago, IL): I would like to congratulate Dr Krapohl on a very nice presentation and on the Michigan Surgical Quality Collaborative for this latest iteration of excellent work demonstrating what can happen when hospitals work together and when you have an excellent surveillance mechanism that allows you to identify adverse outcomes so you can make meaningful changes. I was surprised to see that patients in the elderly age group you did not have higher rates of *C. difficile*, so I would ask about whether that is a potential shortcoming in this study? The issue of previous *C. diff* needs to be included, I think, in future analyses as a risk factor for patients having acute *C. diff* following a colectomy or any other operation. The accuracy of the diagnosis of *C. difficile* in the postoperative patient is a problem. And about one-third of the hospitals now in the country have gone to PCR measurement of the actual genetic sequence of the *C. difficile* organism. So I’m curious whether MSQC is going down the road of recommending PCR as a meaningful diagnostic method?

Were there deaths associated with *C. difficile*. I think the attributable death issue is always important and a lot of patients have *C. difficile*, but they really don’t have necessarily catastrophic morbidity from it. Finally, how do you deal at MSQC with outlier hospitals in terms of performance? You had 0 percent to 9 percent in terms of incidence. Is reporting and feedback enough, or is there a more active method?
that needs to be employed in trying to improve the apparent suboptimal outcomes in selected facilities?

Greta Krapohl, Ph.D., R.N. (Ann Arbor, MI): The first one about age I think is really great, because the number one risk factor for \textit{C diff} is always age, but those studies rarely take out the surgical patients. They usually look at these patients collectively, and the patient, the surgical patients are usually younger and healthier than their medical counterparts. The average age in this population was 65. Possibly may not be as great of a risk factor or predictor for \textit{C diff} in this population. But for the future, I definitely want to, and I did touch on it, look at maybe that 80 and over age range in the future. Second, you talked about the testing, which is a great topic that affects all \textit{Clostridium difficile} nationally when we look at any multicenter studies. And I can tell you that the \textit{C diff} rate has gone up to 2008, but what we found in our collaborative is that it has gone down. There are less false positives with PCR, the sensitivity is 93 percent as opposed to the EIA, which is 75 percent, and the specificity is high in the 90s, too.

Three, you mentioned about the mortality. So the patients that had \textit{C diff} compared to the patients that did not had four times the rate of mortality. So I think this underscores the potential for us to be even more proactive in some of these patient that are high risk, especially the colectomy patients. And then, finally, you touched on how do we deal with the outlying hospitals those that are at 9 percent versus the 0 percent, and I think in the MSQC how we would like to do that in the future, is change the paradigm, maybe not look at the ones that are the worst, but look at the ones that are the best that had the 0 percent and translate those best practices to the other hospitals that aren’t in the collaborative.