HHS Public Access

Author manuscript

*Infect Control Hosp Epidemiol*. Author manuscript; available in PMC 2016 January 01.

Published in final edited form as:

*Infect Control Hosp Epidemiol*. 2015 January ; 36(1): 40–46. doi:10.1017/ice.2014.8.

# The Postoperative Burden of Hospital Acquired *Clostridium Difficile* Infection

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## Abstract

**Objective—***Clostridium difficile* infection (CDI) is a common hospital-acquired infection. Previous reports on CDI's incidence, risk factors and impact on resources in the surgical population are limited. In this context, we study CDI across diverse surgical settings.

**Methods—**We prospectively identified patients with laboratory-confirmed postoperative CDI after 40 different general, vascular, or gynecologic surgeries at 52 academic & community hospitals between 7/2012-9/2013. We used multivariable regression models to identify CDI risk factors and its impact on resource utilization.

**Results—**Of 35,363 patients, 179 (0.51%) developed postoperative CDI. The highest rates of CDI were after lower-extremity amputation (2.6%), followed by bowel resection or repair (0.9%) and gastric or esophageal operations (0.7%). Gynecologic and endocrine operations had the lowest rates (0.1 & 0%, respectively). On multivariable analyses, older age, chronic immunosuppression, hypoalbuminemia (≤3.5 g/dL) and preoperative sepsis were associated with CDI. Use of prophylactic antibiotics was not independently associated with CDI, neither was sex, BMI, surgical priority, weight loss or comorbid conditions. Three procedure groups had higher odds of postoperative CDI: Lower-extremity amputations (aOR=3.5, p=0.03), gastric or esophageal operations (aOR=2.1, p=0.04) and bowel resection or repair (aOR=2, p=0.04). Postoperative CDI

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Disclosures: The authors have no disclosures to make.

Author Contributions: Dr. Hendren had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Data Acquisition: Abdelsattar, Krapohl, Krell
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Drafting the manuscript: Abdelsattar, Alrahmani, Aronoff, Krapohl
Critical revision: All authors
Final Approval: All authors

Conflict of Interest Disclosure: None to disclose.

Previous Presentation: This work was presented in part at the American Society of Colon and Rectal Surgeons' Annual Meeting in Hollywood, FL on May 19th 2014.

was independently associated with increased length of stay (mean 13.7 vs 4.5 days), emergency department presentations (18.9 vs 9.1%) and readmissions (38.9 vs 7.2%, all p<0.001).

**Conclusions—**Incidence of postoperative CDI varies by surgical procedure. Postoperative CDI is also associated with higher rates of extended length of stay, emergency room presentations & readmissions, which places a potentially preventable burden on hospital resources.

### Keywords

Postoperative; Clostridium difficile; hospital-acquired; resource utilization

## Introduction

*Clostridium difficile* Infection (CDI) is now the most common organism to cause healthcare-associated infection in the United States and is regarded as one of the serious, expensive, and potentially avoidable consequences of hospitalization.[1,2] The emergence of the virulent NAP1/B1/027 strain and the concern over resistance to traditional antibiotic regimens have elevated *C. difficile* prevention to a high priority on a national level.[3] Despite the national attention, the incidence of CDI continues to grow and the financial and human costs of CDI continue to mount.[4–6] The US government's decision to withhold Medicare reimbursement for hospitals due to CDI in 2017 underscores the gravity of the problem and the severe financial penalties it is willing to levy to address this problem.[7,8]

Epidemiological data suggest surgical patients have twice the burden of health care-associated infection (HAI) when compared to their medical counterparts and that the burden of CDI is increasing among surgical patients.[9] This is concerning given the fact that surgical care comprises approximately 40%-50% of all hospital stays and healthcare dollars.[10] However, prior studies devoted to the investigation of CDI and its impact on the surgical patient population are limited by the use of administrative data, failure to capture cases diagnosed after discharge, or reports from single centers. Surgical patients, although usually younger and healthier than their medical counterparts, frequently receive prophylactic antibiotics and have long inpatient hospital exposure. Large scale, multicenter studies that focus on the burden of surgical patients gauge the effects of CDI and understand the current epidemiological challenges of the disease are lacking.

In this context, we designed a prospective, population-based study of hospital acquired, postoperative CDI within the context of a statewide surgical quality collaborative. Our research questions were: 1) which surgical procedures are associated with the highest risk for CDI; 2) which patient characteristics are associated with CDI risk; and 3) is perioperative antibiotic use independently associated with CDI? Finally, we assessed the burden of CDI on resource utilization at the hospital level (extended length of stay, 30-day emergency department presentations, hospital readmission and reoperation). With new reimbursement legislation and penalties on the horizon, the results from this study can help inform clinicians and administrators about timely and practical strategies to target certain surgical patient populations at high-risk for CDI.

## Methods

### Data sources

The Michigan Surgical Quality Collaborative (MSQC) is a 52-hospital consortium representing diverse practice settings throughout the state. MSQC data abstraction and data quality assurance details have been described elsewhere.[11,12] In brief, specially trained data abstractors prospectively collect patient characteristics, intraoperative processes of care, and 30-day postoperative outcomes for patients undergoing specified surgical operations utilizing a sampling algorithm that minimizes selection bias. Regular data audits ensure registry data validity. Data collection for MSQC is Institutional Review Board (IRB) exempt at participating hospitals, and the current study was reviewed and deemed “non-regulated” by the University of Michigan's IRB.

### Patient Population

Patients aged 18 years and older undergoing selected general, vascular or gynecologic operations from 7/2012 to 9/2013 at any of 52 MSQC community or academic hospitals were included in this study. Forty different procedure types were identified based on Current Procedural Terminology (CPT) codes and grouped into 8 clinically relevant categories (Table 1) to limit degrees of freedom.

### Independent Variables

Registry based clinical and demographic data analyzed included age, sex, race, ASA class, functional status, and body mass index (BMI). Comorbidities included preoperative cardiac, pulmonary, gastrointestinal, renal, neurological, hematological, infectious and endocrine diagnoses. Patients were categorized as having no comorbidities; 1 comorbid condition; or ≥2 comorbidities. Hypoalbuminemia was defined as a preoperative albumin blood level ≤3.5 g/dL. Patients who did not have an albumin level were categorized in a separate category within this variable.

Antibiotic prophylaxis processes were categorized into the following mutually exclusive 3 categories: patients who received intravenous antibiotics within 1 hour of incision for prophylaxis; patients who were exempt from receiving prophylactic preoperative antibiotics due to use of therapeutic antibiotic therapy for a preexisting infection; and patients who did not receive prophylactic antibiotics.

### Main Exposure Variable and Outcome Measures

The development of hospital-acquired postoperative CDI was the main outcome measure in this study. The MSQC piloted the abstraction of CDI as an outcome for colectomy surgery between 2008-2012, and then began prospectively measuring this outcome for all eligible cases in 2012. This is the first study using this unique data source. CDI was defined as a laboratory confirmed positive toxin assay by polymerase chain reaction (PCR), positive enzyme linked immunosorbent assay (ELISA) or stool culture up to 30 days postoperatively. Post-discharge complications, including CDI, are identified using a 30-day follow-up procedure that includes some combination of medical record review, a patient letter, and/or a patient phone call. Patients who had a positive result within 72 hours of admission were

excluded to reduce inclusion of community-acquired CDI cases.[13] CDI was also analyzed as an exposure variable to assess its impact on the following resource utilization metrics, which were the secondary outcome measures in this study: 1) extended length of stay (LOS) defined as LOS which extended beyond the 75$^{th}$ percentile; 2) any emergency department (ED) presentation within 30 days of index operation; 3) any 30 day hospital readmission; and 4) any reoperation within 30 days regardless of indication.

### Statistical Analyses

Patients' clinical and demographic variables were analyzed using chi-square tests for categorical and 2-sided t-tests for continuous variables, with significance set at a p-value $<0.05$.

Multivariable logistic regression was used to identify risk factors for CDI. To account for clustering within the 52 included hospitals, robust standard errors were calculated. The model was evaluated for discrimination using the c-statistic. The c-statistic evaluates model discrimination and represents the area under the receiver-operator-characteristic curve. A value of 0.5 indicates that the model is equivalent to chance while a value of 1.0 indicates perfect discrimination. To assess the association of CDI with resource utilization measures, four multiple logistic regression models with robust standard errors were constructed with CDI as an exposure variable, along with other independent variables.

### Post-hoc Analysis

To assess the robustness of the results given the low event rate, *post-hoc* power calculations were performed, and the sample size was deemed adequate to answer the research questions. For example, in assessing the association between prophylactic antibiotics and postoperative CDI the study had a statistical power of 96%.

All statistical analyses were conducted using STATA special edition (version 13, StataCorp, College Station, TX).

## Results

In the 15-month period 35,363 patients undergoing surgery at 52 MSQC community and academic hospitals were studied. Of those, 179 (0.51%) developed a hospital-acquired postoperative CDI. On univariate analyses, patients developing CDI were older, had lower BMI's, higher ASA scores, more comorbid conditions, and were more likely to have undergone urgent or emergent surgery, as shown in Table 2. Patients developing CDI were also more likely to have been exposed to preoperative therapeutic antibiotics for other indications.

Postoperative CDI incidence rates varied significantly between the 8 procedure groups (Figure 1). Lower extremity amputations had the highest incidence of CDI at 2.6%, followed by bowel resection and/or repair operations at 0.9%. Endocrine and gynecologic operations had the lowest incidence rates (0% & 0.1%, respectively).

On multivariable analysis, increasing age (aOR = 1.03, 95% confidence interval [CI]: 1.01-1.04), hypoalbuminemia (aOR = 1.76, CI: 1.12-2.77), preoperative sepsis (aOR = 1.65, CI: 1.09-2.51) and chronic immunosuppression (aOR = 1.56, CI: 1.01-2.41) were independently associated with CDI, but not prophylactic antibiotics, ASA class, surgical priority, comorbidity index, or weight loss. Obese patients were less likely to develop CDI (aOR =0.62, CI: 0.42-0.93). In addition, 3 procedure groups had higher adjusted odds of postoperative CDI, namely: Lower extremity amputations (aOR = 3.5, CI: 1.59-7.9), gastric or esophageal operations (aOR = 2.14, CI: 1.05-4.35) and bowel resection or repair (aOR = 2.01, CI: 1.06-3.8).

When examining the resource utilization metrics as the outcome, significant associations with CDI were evident as shown in Table 3. Postoperative CDI was independently associated with increased length of stay (mean 13.7 days vs 4.5 days), higher risk-adjusted ED presentation rates (18.9% vs 9.1%) and risk-adjusted readmission rates (38.9% vs 7.2%) within 30 days of operation (all $p<0.001$).

## Discussion

This study of 35,363 surgical patients at 52 different hospitals in the state of Michigan showed that 1) the incidence of postoperative CDI, although uncommon overall, was greater in lower extremity amputations, gastric or esophageal operations and bowel resection or repair, 2) the use of intravenous prophylactic antibiotics was not associated with CDI, and 3) CDI was significantly associated with organizational resource utilization metrics, as risk adjusted readmission rates and LOS were more than double in patients with CDI.

The overall incidence rate of CDI of 0.51% is comparable to other published incidence rates.[14–17] However, the recent time frame, diverse surgical population, and prospective data collection with 30-day follow-up are unique to this report. In the year the data were collected (2012-2013), the majority of Michigan hospitals had adopted PCR diagnostic testing methodology, which is more sensitive and specific and therefore has fewer false positive results. Furthermore, our study reflects the contemporary nature of the CDI epidemic in this cohort of surgical patients, most likely involving a substantial number of cases caused by epidemic strains of *C. difficile*, including the NAP1/BI/027 strains. Nonetheless, directly comparing CDI rates to other surgical populations and reports is difficult since the incidence and consequence of CDI are not uniformly defined, reported nor calculated, especially from administrative databases.[14,17]

The present study demonstrates that CDI incidence rates vary significantly between procedures. Similar to the work by Zerey and colleagues,[17] patients undergoing gastric, small bowel, or colonic resection were more at risk for CDI. The highest incidence, however, was in patients undergoing a lower extremity amputation, (2.6%, aOR: 3.5). These patients tend to be in and out of the hospital very frequently before ultimately undergoing an amputation or have frequent courses of therapeutic antibiotics, thereby increasing their likelihood developing this infection. On the other hand, the low incidence of CDI among patients who underwent endocrine operations or hysterectomy is not surprising, given that most of them have a short and limited exposure to the healthcare setting. Although the

majority (95%) of patients developing CDI had some form of exposure to antibiotics, prophylactic antibiotics per se were not associated with CDI in this report, confirming the findings from a prior study limited to colectomy patients.[18] While there was a trend for patients who were receiving therapeutic antibiotics for other indications to develop CDI, this did not reach statistical significance on multivariable analysis. It is important to note, however, that patients undergoing higher risk surgical operations are also more likely to be exposed to preoperative antibiotics depending on their indication (e.g., colectomy for diverticulitis), thereby contributing to the overall risk.

From a human and financial perspective, CDI is a costly infection. The financial costs of a CDI episode for a hospital are estimated to be about $10,000.[5,6] The human cost, is more difficult to quantify but no less important. Together these costs create a preventable burden that could be a rich target for quality improvement and patient care outcomes. Our data confirm that CDI has significant downstream strains on resource utilization. The readmission rate was more than double compared with those patients without CDI. This is not surprising given the deconditioning, dehydration and overall fatigue that accompany CDI in patients already debilitated by recent surgery. With the continued rise in CDI and stricter financial penalties in 2017, there is a strong business case for making an investment in strategy and resources for CDI prevention.[4]

Since surgical patients already carry twice the burden of HAI than their medical counterparts, administrators may want to consider pathogen- directed or vertical interventions to target specific surgical patients undergoing high-risk procedures. Pathogen-directed or vertical interventions are designed to prevent transmission of specific pathogens causing the infection, and are developed to combat the unique epidemiological characteristics of the organism. In contrast, the non-pathogen directed, or the horizontal intervention approach, attempts to reduce the rates of all infections, from all pathogens, simultaneously.[19] An example of a pathogen-directed approach is the success of the rapid screening and decolonizing of nasal carriers of *Staphylococcus aureus* upon admission, in order to reduce surgical site infections.[20] Proponents of the non-pathogen directed approaches report similar success rates using horizontal interventions with similar success rates at a significant cost savings.[21] Although effective horizontal successes have been reported in relation to CDI infection, the severe financial penalties for CDI may drive the more aggressive and focused preventative interventions strategies pathogen-directed interventions deliver (i.e. preemptive isolation, private rooms, etc.).[22]

This study has several limitations. Primary among them are the shortfalls in the definition and interpretation of CDI. Our CDI diagnosis included only the results of confirmed laboratory diagnosis of *C. difficile* toxin assay or culture. It did not detect those patients who may have had received empiric treatment, which may lead to underestimation of CDI in this cohort. Additionally, this study did not account for those patients who were colonized with *C. difficile* (tested positive) but did not exhibit symptoms (not infected). The overall influence of these patients that are colonized but not infected are believed to be minimal since they would not qualify for testing without the requisite diarrhea episodes. In addition, because diagnostic detection techniques were different at each of the 52 locations, underestimation or overestimation of CDI could confound the results. However, because the

data collection occurred during 2012, it is likely most hospitals have updated their diagnostic testing to the more specific and sensitive PCR methodology. On the other hand, we captured all patients who had a positive result within 30 days of their index operation, which is unique to this report, and is one of the major limitations of other studies using discharge-data. Finally, we excluded patients who had a positive result within 72 hours, thereby truly capturing the incidence of a hospital acquired infection.

In conclusion, the present study shows that 1) postoperative CDI rates vary between procedures with up to a 5 time increased risk in lower extremity amputations, 2) the use of intravenous prophylactic antibiotics was not significantly associated with CDI, and that 3) CDI was significantly associated with resource utilization metrics, as risk adjusted readmission rates and LOS were more than double in patients with CDI. With new reimbursement legislation and penalties on the horizon, the results from this study can help inform clinicians and administrators with timely and practical implications to target surgical patient populations at high-risk for CDI and downstream resource utilization.

## Acknowledgments

Funding/Support: This work was supported by the Agency for Healthcare Research and Quality [T32 HS000053-22 to ZMA]; the National Cancer Institute at the National Institute of Health [1K07 CA163665-22 to SH]; and the National Institute of Allergy and Infectious Diseases [5U19AI090871 to DMA].

Role of the Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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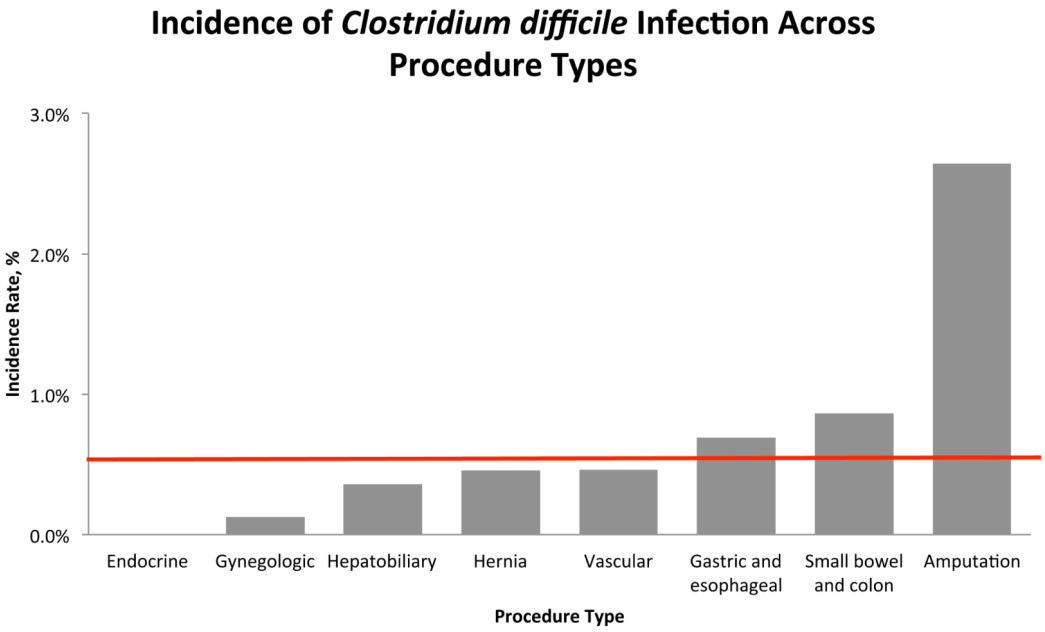


**Figure 1.**

Incidence of *Clostridium difficile* infection varies across different surgical procedure types. The horizontal line represents the overall population mean (0.51%).

## Table 1

Distribution of patients across 8 different categories.

| Procedure types (n=35,363) | Patients |
|---|---|
| **Small bowel and colon (n=8,713)** | |
| Laparoscopic appendectomy | 2,975 |
| Laparoscopic partial colectomy | 1,267 |
| Laparoscopic proctectomy | 28 |
| Laparoscopic total colectomy | 49 |
| Laparoscopic small bowel resection | 33 |
| Open appendectomy | 556 |
| Open partial colectomy | 2,292 |
| Open proctectomy | 221 |
| Open small bowel resection | 715 |
| Open total colectomy | 166 |
| Colostomy | 59 |
| Enterotomy repair | 323 |
| Ileostomy | 27 |
| Pelvic exenteration | 2 |
| **Hepatobiliary (n=8,305)** | |
| Laparoscopic cholecystectomy | 7,444 |
| Liver resection, any | 104 |
| Open cholecystectomy | 515 |
| Pancreatectomy, any | 234 |
| Pancreatic debridement | 8 |
| **Gynecologic (n=7,907)** | |
| Hysterectomy, any | 7,907 |
| **Hernia (n=4,128)** | |
| Inguinal hernia | 1,270 |
| Internal hernia and/or lysis of adhesion | 420 |
| Ventral hernia repair | 2,438 |
| **Vascular (n=3,700)** | |
| Abdominal aortic aneurysm repair | 631 |
| Aorto-femoral bypass | 53 |
| Axillary-femoral bypass | 26 |
| Carotid endarterectomy | 1,554 |
| Endovascular lower extremity revascularization | 548 |
| Lower extremity bypass | 888 |
| **Gastric and esophageal (n=1,301)** | |
| Esophagectomy | 543 |
| Gastrectomy and/or gastrotomy | 180 |
| Laparoscopic Nissen fundoplication | 499 |
| Open Nissen fundoplication | 8 |

| Procedure types (n=35,363) | Patients |
|---|---|
| Ulcer and perforation repair | 71 |
| **Endocrine (n=665)** | |
| Thyroid, parathyroid or adrenal | 614 |
| Open splenectomy | 36 |
| Laparoscopic splenectomy | 15 |
| **Amputation (n=644)** | |
| Above knee amputation | 287 |
| Below knee amputation | 357 |

**Table 2**

Clinical and Demographic Characteristics. % May not add to 100% due to rounding.

| Characteristics | *Clostridium difficile* Infection | | | | p Value |
|---|---|---|---|---|---|
| | No (n= 35,184) | | Yes (n=179) | | |
| | No. | Col % | No. | Col % | |
| **Age, y, mean ±SD** | 54 ±17.1 | | 67.0 ±15.7 | | < 0.001 |
| **Gender; Male** | 11,659 | 33.1 | 79 | 44.1 | |
| **Race; Black** | 4,820 | 13.7 | 25 | 14 | 0.917 |
| **BMI, kg/m2, mean ±SD** | 30.3 ±7.9 | | 27.6 ±7.5 | | < 0.001 |
| **ASA Class** | | | | | < 0.001 |
| **I/II** | 19,403 | 55.15 | 29 | 16.2 | |
| **III** | 13,248 | 37.7 | 108 | 60.3 | |
| **IV/V** | 2,533 | 7.2 | 42 | 23.5 | |
| **Exposure to Antibiotics** | | | | | |
| **None** | 1,460 | 4.2 | 9 | 5 | 0.557 |
| **Therapeutic antibiotics** | 4,657 | 13.2 | 43 | 24 | <0.001 |
| **Prophylactic antibiotics** | 29,067 | 82.6 | 127 | 71 | <0.001 |
| **Surgical Priority** | | | | | < 0.001 |
| **Elective** | 29,823 | 84.8 | 128 | 71.5 | |
| **Urgent/Emergent** | 5,361 | 15.2 | 51 | 28.5 | |
| **Comorbidity index** | | | | | < 0.001 |
| **0** | 11,393 | 32.4 | 25 | 14 | |
| **1** | 10,885 | 30.9 | 32 | 17.9 | |
| **≥2** | 12,906 | 36.7 | 122 | 68.2 | |
| **Cardiovascular** | | | | | |
| **Arrhythmias** | 2,661 | 7.6 | 43 | 24 | < 0.001 |
| **Congestive heart failure** | 360 | 1 | 10 | 5.6 | < 0.001 |
| **Coronary artery disease** | 5,003 | 14.2 | 62 | 34.6 | < 0.001 |
| **Deep vein thrombosis** | 1,735 | 4.9 | 14 | 7.8 | 0.075 |
| **Hypertension** | 16,162 | 45.9 | 124 | 69.3 | < 0.001 |

*Infect Control Hosp Epidemiol*. Author manuscript; available in PMC 2016 January 01.

| Characteristics | *Clostridium difficile* Infection | | | | p Value |
|---|---|---|---|---|---|
| | No (n= 35,184) | | Yes (n=179) | | |
| | No. | Col % | No. | Col % | |
| **Peripheral vascular disease** | 2,566 | 7.3 | 34 | 19 | < 0.001 |
| **Pulmonary** | | | | | |
| **Ventilator dependence** | 181 | 0.5 | 3 | 1.7 | 0.031 |
| **COPD** | 2,989 | 8.5 | 32 | 17.9 | 0.001 |
| **Pneumonia** | 170 | 0.5 | 7 | 3.9 | < 0.001 |
| **Endocrine/GI/Renal** | | | | | |
| **Ascites** | 136 | 0.4 | 1 | 0.6 | 0.712 |
| **Cirrhosis** | 188 | 0.5 | 4 | 2.2 | 0.002 |
| **Diabetes** | 5,401 | 15.4 | 44 | 24.6 | 0.001 |
| **Dialysis** | 424 | 1.2 | 6 | 3.4 | 0.009 |
| **Hematologic/Immune** | | | | | |
| **Bleeding Disorder** | 2,237 | 6.4 | 25 | 14 | < 0.001 |
| **Chronic Immunosuppression** | 1,074 | 3.05 | 16 | 8.94 | <0.001 |
| **Disseminated Cancer** | 484 | 1.4 | 7 | 3.9 | 0.004 |

## Table 3

**Impact of *Clostridium difficile* Infection (CDI) on Resource Utilization Measures**

| Resource Utilization Measure | Univariate Analysis Odds Ratio; p Value [95% Conf. Interval] | Multivariable Analysis§ Adjusted Odds Ratio; p Value [95% Conf. Interval] |
|---|---|---|
| **Extended LOS** | 14; p < 0.001 [9.5-20.7] | 4.8; p < 0.001 [2.7-8.5] |
| **ED presentation** | 2.3; p < 0.001 [1.6-3.4] | 1.6; p < 0.001 [1.1-2.4] |
| **Reoperation** | 4.5; p < 0.001 [3.1-6.5] | 1.3; p=0.23 [0.8-2.1] |
| **Readmission** | 8.1; p < 0.001 [6-11.1] | 2.8; p < 0.001 [1.9-4] |

§: After adjusting for: age, sex, race, BMI, ASA class, prophylactic antibiotics, surgical priority, preoperative sepsis, procedure type, hypoalbuminemia, weight loss, any complication (excluding CDI) and other comorbidities. All statistical models have a c-statistic >0.7. ED: Emergency department, LOS: length of stay.