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Post-Surgical *Clostridium difficile*-Associated Diarrhea

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Abstract

Background—Abdominal surgery is thought to be a risk factor for *Clostridium difficile*-associated diarrhea (CDAD). The aims of this study were to discern pre-operative factors associated with post-surgical CDAD, examine outcomes after post-surgical CDAD, and compare outcomes of post-surgical vs. medical CDAD.

Methods—Data from 3904 patients who had abdominal surgery at Montefiore Medical Center were extracted from Montefiore's clinical information system. Cases of 30-day post-surgical CDAD were identified. Pre-operative factors associated with developing post-surgical CDAD were identified using logistic regression. Medical patients and surgical patients with post-surgical CDAD were compared for demographic and clinical characteristics, CDAD recurrence and 90-day post-infection mortality.

Results—The rate of 30-day post-surgical CDAD was 1.2%. After adjustment for age and co-morbidities, factors significantly associated with post-surgical CDAD were: antibiotic use (OR: 1.94), proton pump inhibitor (PPI) use (OR: 2.32), prior hospitalization (OR: 2.27), and low serum albumin (OR: 2.05). In comparison with medical patients with CDAD, post-surgical patients with CDAD were significantly more likely to have received antibiotics (98.0% vs. 85.2%), less likely to have received a PPI (38.8% vs. 58.3%), or have had a prior hospitalization (42.9% vs. 67.1%). Post-surgical patients with CDAD had decreased risk of mortality when compared with medical patients with CDAD (HR 0.36).

Conclusions—CDAD is an infrequent complication after abdominal surgery. Several avoidable pre-operative exposures (e.g., antibiotic and PPI use) were identified that increase the risk of post-surgical CDAD. Post-surgical CDAD is associated with decreased risk of mortality when compared with CDAD on the medical service.

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Introduction

Clostridium difficile is the most common nosocomial pathogen and the cause of 10-20% of cases of antibiotic-associated diarrhea and most cases of antibiotic-associated colitis.[1] Both the incidence[2] and the severity[3] of *C. difficile*-associated diarrhea (CDAD) are increasing in the United States.[4-6] Abdominal surgery is thought to be a risk factor for CDAD,[7] and post-surgical CDAD has been well described. The reported rates of post-surgical CDAD range from 0.2% to 8.4% depending on the surgical population studied and types of operations performed.[7-13] No study has been reported, however, that compares post-surgical CDAD and medical CDAD with respect to risk factors and outcomes.

In the general medical inpatient population, established risk factors for CDAD include: antibiotic exposure,[14, 15] advanced age,[16, 17] and hospitalization, especially in the intensive care unit.[18] Other implicated risk factors include: overall severity of disease,[19] use of proton-pump-inhibitors,[20-22] previous hospitalizations,[23] gastric and post-pyloric tube feedings,[24] and chemotherapy.[25] Whether some or all of these exposures also are associated with post-surgical CDAD is not known, although prolonged antibiotic prophylaxis[8] and the addition of oral preoperative antibiotics[9] have been associated with increased risk of post-surgical CDAD.

Developing CDAD has been said to worsen outcomes in the non-surgical inpatient setting[26] and in the general population,[3] however, no study has reported the outcomes of post-surgical CDAD or made a comparison with the outcomes of CDAD in the non-surgical setting.

The aims of this analysis were to determine pre-operative factors associated with post-surgical CDAD, to examine outcomes of post-surgical CDAD, and to compare the outcomes of patients who had post-surgical CDAD with those who had non-surgical CDAD. We hypothesized that pre-operative factors associated with the development of post-surgical CDAD would include: pre-operative antibiotics, proton-pump inhibitors (PPIs), increased length of hospital stay, and previous hospitalization. In addition, we hypothesized that outcomes for patients with post-surgical CDAD would be worse than for post-surgical patients without CDAD.

Methods

Study setting and data collection

Montefiore Medical Center consists of The Moses Division Hospital, a 706-bed tertiary care center, and The Weiler Division Hospital, a 381-bed teaching hospital, both of which are associated with Albert Einstein College of Medicine. The patient populations served by these two hospitals differ with respect to demographic and clinical characteristics, but both hospitals adhere to the same infection control policies and practices administered by a common infection control department, patient safety officer, and antibiotic steward.

To generate the post-surgical *C. difficile* cohort, we extracted data on all patients who underwent an inpatient abdominal surgical procedure within 30 days of admission to either hospital from January1, 2006 through February 28, 2008. Qualifying abdominal procedures included surgery involving the stomach, small bowel, colon, appendix, anorectum, gallbladder and biliary tract, pancreas, hernia repair or non-otherwise specified abdominal surgery (A full list of procedures and V-codes can be found in appendix 1.)

To generate the comparison cohort of *C. difficile* on the medical service we extracted data on all inpatients on the medical service from both hospitals who had a positive *C. difficile* toxin test from January 1, 2007 through February 28, 2008.

Subjects were deemed as having post-surgical *C. difficile*-associated diarrhea (CDAD) if they had a positive *C. difficile* toxin within 30 days after the surgical procedure and the presence of diarrhea documented in the inpatient chart. Subjects on the medical service were deemed as having CDAD if they had a positive *C. difficile* toxin and the presence of diarrhea documented in the inpatient chart. Diarrhea was recorded as present if physician or nursing notes documented diarrhea within 2 days of the positive toxin result. CDAD was deemed as community acquired if the positive toxin occurred within 48 hours of admission, as has been done previously.[27]

For both cohorts, data on patient age, race-ethnicity, gender, prior medication use, laboratory values, ICD-9 codes, prior admissions, re-admissions, and in-hospital mortality were extracted from a replicate of Montefiore's clinical information system using Clinical Looking Glass™ a quality improvement health care surveillance software (Emerging Health Information Technology, Yonkers, NY). The Charlson co-morbidity score, a risk adjustment tool used for research, that measures overall co-morbidity using ICD-9 diagnosis codes,[28, 29] was calculated using information derived from Clinical Looking Glass. The data replicate is merged with the social security death registry each month, which allowed extraction of 30-day mortality rates after discharge. The Institutional Review Board of Montefiore Medical Center approved the study.

Outcome Variables

For the descriptive analysis of post-surgical CDAD, the main outcome variables were: presence of CDAD, and 90-day post-operative mortality. CDAD was analyzed as a dichotomous variable defined by the presence of a positive *C. difficile* toxin assay in the electronic medical record and diarrhea documented in the inpatient chart within 2 days of the positive toxin result and 30 days of surgery. Subjects with community acquired CDAD were excluded. 90-day post-operative mortality was analyzed as a time-to-event variable using the social security death registry to obtain the date of death.

For the analysis comparing post-surgical CDAD with medical CDAD, the main outcome variables were recurrence of CDAD and 90-day post-infection mortality. Recurrence was analyzed as a time-to-event variable defined by recurrence of symptoms and a second positive *C. difficile* toxin at least 15 days, but not more than 90 days, after the first positive toxin. 90-day post-infection mortality was analyzed as a time-to-event variable using the social security death registry to obtain the date of mortality.

Independent Variables

Independent covariates examined for each subject included: demographic characteristics (age, gender, race-ethnicity), albumin and white blood cell count at the time of CDAD diagnosis, the Charlson co-morbidity score, prior admissions to Montefiore Medical Center within 180 days, and prior use of antibiotics and proton-pump inhibitors (PPIs).

Prior exposure to antibiotics was analyzed as a dichotomous variable; a subject was coded as having been exposed to antibiotics if a dose of any systemic antibacterial agent was given during the 30 days prior to the surgical procedure (excluding antibiotics given as prophylaxis within two hours of surgery). Prior exposure to PPIs was analyzed as a dichotomous variable and coded as having been exposed if a dose of PPI (omeprazole, lansoprazole, pantoprazole, rabeprazole, or esomeprazole) was given during the 10 days prior to the surgical procedure.

The Charlson co-morbidity score was treated as a continuous variable and was used as a risk-adjustment covariate.

Statistical analysis

All patients with a qualifying abdominal procedure and those who had a positive *C. difficile* toxin assay and diarrhea were characterized using descriptive statistics of demographic data. Factors thought potentially associated with post-surgical CDAD were tested using bivariate logistic regression. Factors found to significantly associated with post-surgical CDAD were tested using multivariate logistic regression, after adjustment for patient age and Charlson co-morbidity score. To test whether there was heterogeneity in the associations between risk factors and CDAD across the two hospitals, regression models were constructed to test for interactions between factors, hospital and the development of CDAD.

Surgical patients with and without post-surgical CDAD were compared with respect to 90-day mortality using Kaplan-Meier methods. The independent association between post-surgical CDAD and mortality was assessed using a Cox proportional hazards model. To test whether there was heterogeneity in the association between CDAD and mortality risk across the two hospitals, a Cox proportional hazards model was constructed to test for interaction between CDAD, hospital and mortality.

Medical and surgical patients with post-surgical CDAD were compared using chi-squared, t-tests, or Wilcoxon rank-sum tests as appropriate for demographic and clinical characteristics, and using the Kaplan-Meier method for outcomes recurrence and 90-day post-infection mortality. Propensity score methods were used to match each surgical case of CDAD with 5 controls from the pool of medical CDAD using a non-parsimonious logistic regression model.[30, 31] Variables included in the propensity score model were: age, sex, Charlson co-morbidity score, and community vs. hospital acquired infection. Then, for each post-surgical CDAD case, 5 propensity score matched controls were selected using a nearest neighbor greedy match protocol without replacement.[32] To minimize matching bias, data were randomly sorted prior to matching.

Cases of post-surgical CDAD and matched controls with medical CDAD were compared with respect to 90-day recurrence and 90-day mortality using the method of Kaplan and Meier and log rank tests.

STATA software, version 10.0, (StataCorp, College Station, TX) was used for all statistical analyses.

Results

Study population

From January 1, 2006 through February 28, 2008, there were 3904 patients at Montefiore Medical Center who underwent a qualifying surgical procedure (Table 1). 805 (20.6%) of the patients had had a prior hospitalization within the previous six months. 1042 (26.8%) patients had been exposed to pre-operative antibiotics and 391 (10.0%) had been exposed to pre-operative PPIs.

Post-surgical CDAD

46 patients (1.2%) had CDAD within 30 days after their operative procedure. Compared with all patients undergoing abdominal surgery, patients with post-surgical CDAD were older (mean 65.5 vs. 52.9 years, $p < 0.001$), more likely to have been given pre-operative antibiotics (47.8% vs. 26.8%, $p < 0.001$) and PPIs (28.3% vs. 10.0%, $p < 0.001$), and more likely to have had a prior hospitalization (41.3% vs. 20.6%, $p < 0.001$), and to have a lower mean albumin (3.05 vs. 3.69 g/dl, $p < 0.001$).

Pre-operative risk factors for post-surgical CDAD—Data on pre-operative factors associated with post-surgical CDAD are presented in Table 2. Significant pre-operative risk factors were age (OR: 1.46 for each 10-year increment in age; 95% CI: 1.24-1.73), antibiotic use within 30 days prior to surgery (OR: 2.54; 95% CI: 1.42-4.55), high-risk antibiotic use within 30 days prior to surgery (OR: 4.80; 95% CI: 2.57-8.98), proton-pump inhibitor (PPI) use within 10 days prior to surgery (OR: 3.62; 95% CI: 1.89-6.95), prior hospitalization (OR: 2.75; 95% CI: 1.52-4.97), and low serum albumin level on admission (OR: 2.51 for each loss of 1 g/dl, 95% CI: 1.70-3.71).

After adjustment for age and Charlson co-morbidity score, factors significantly associated with post-surgical CDAD were: antibiotic use (OR: 1.94; 95% CI: 1.07-3.52), high-risk antibiotic use (OR: 3.42; 95% CI: 1.80-6.50), PPI use (OR: 2.32; 95% CI: 1.18-4.58), prior hospitalization (OR: 2.27; 95% CI: 1.30-3.96), and low serum albumin (OR: 2.05; 95% CI: 1.29-3.25). Hospital site did not significantly affect the association between pre-operative risk factors and the development of post-operative CDAD (all p-values for interaction = ns).

Post-operative Mortality—Post-surgical patients with CDAD had a significantly increased 90-day mortality ($p < 0.0001$, Figure 1.) on bivariate analysis, compared with post-surgical patients without CDAD; after adjustment for age, albumin value, creatinine value, Charlson comorbidity score, and prior hospitalizations, however, post-surgical CDAD was not associated with increased risk of mortality (HR: 1.30; 95% CI: 0.64-2.66), compared with post-surgical patients without CDAD. Hospital site did not significantly affect the association between CDAD and mortality (p for interaction = 0.99).

Post-surgical vs. Medical CDAD

In comparison with medical patients with CDAD, post-surgical patients with CDAD were significantly more likely to have received antibiotics (98.0% vs. 85.2%; p=0.01), less likely to have received a PPI (38.8% vs. 58.3%; p=0.009), and less likely to have had a prior hospitalization (42.9% vs. 67.1%; p=0.001). Medical patients were more likely to have received a high-risk cephalosporin (30.3% vs. 18.4%), but the difference was not significant ($p = 0.08$). (Table 3.)

Compared with medical patients with CDAD, patients with post-surgical CDAD had a significantly lower 90-day mortality rate (19.0% vs. 36.2%; p=0.009; Figure 2A). After adjustment for age, albumin, antibiotics, and Charlson score, post-surgical CDAD was independently associated with lower mortality compared with medical CDAD (HR: 0.36; 95% CI: 0.15-0.83).

Compared with medical patients with CDAD, patients with post-surgical CDAD had a lower 90-day recurrence rate (6.2% vs. 12.6%), but the difference was not significant ($p = 0.14$, Figure 2B).

Discussion

The 30-day incidence of post-surgical CDAD in our study (1.2%) is similar to what has been reported previously. We found, however, that risk for developing post-surgical CDAD was increased with exposure to pre-operative antibiotics and PPIs, having a prior hospitalization, and having a low albumin level at the time of the procedure. The association between antibiotics and post-surgical CDAD is particularly strong for the high-risk antibiotics we examined: 3rd and 4th-generation cephalosporins, flouroquinolones, clindamycin, and imipenim/meropenim.

Given the increased risk of post-surgical CDAD associated with antibiotic use, unnecessary use of high-risk antibiotics before surgery should be avoided. In our analysis, we did not

consider antibiotics given within two hours of the procedure. This prophylactic dose given immediately before surgery is associated with dramatically reduced rates of wound infection and post-operative sepsis.[33, 34] It is likely that any increased risk of post-operative CDAD associated with such prophylactic use of antibiotics would be outweighed by benefit.

PPI use also was associated with increased risk for post-surgical CDAD, possibly by allowing *C. difficile* spores safe transit through the hypochlorhydric stomach of patients treated with these agents. Pre-operative PPIs are used for prophylaxis against stress-related mucosal damage which is common post-operatively,[35] and preventable.[36] It is likely that the benefit of pre-operative PPIs outweighs their potential risk for CDAD.

We have found an association between low albumin and increased risk of post-surgical CDAD. It is possible that low albumin, associated with chronic disease, is a marker for poor immune function. Poor anti-toxin IgA antibody response has been associated with increased risk of recurrence after an episode of CDAD,[37] and immunosuppression has been associated with the development of CDAD,[38, 39] thus low albumin may be associated with CDAD through poor immune function. Postoperative impairment of cell-mediated immunity is another potential risk factor for CDAD which may last up to days after surgery.[40]

In previous studies, the lowest reported rates of post-surgical CDAD were in patients undergoing cardiovascular procedures (0.2%-1.2%);[8, 12, 13] moderate rates were observed in populations that included general surgery procedures (2.0%-5.6%);[7, 10] and the highest rate was reported in patients undergoing aortic procedures (8.4%).[11] Our patient population all had surgical procedures that entered the abdominal cavity, and the rate of post-surgical CDAD that we observed (1.2%) is in the low range; we found no evidence that entering the abdominal cavity increases the incidence of post-surgical CDAD. We suspect that the differences in rates reported above reflect the underlying differences in patient risks and exposures, rather than variable risk associated with specific procedures.

We found that post-surgical CDAD differs from CDAD on the medical service in several respects. Post-surgical CDAD is more commonly associated with antibiotic use, and less commonly associated with PPI use and prior hospitalization. In addition, post-surgical CDAD may have a better prognosis that medical CDAD.

Despite the strengths of our study, it does have some limitations. Our definition of CDAD included only patients with diarrhea in whom a *C. difficile* toxin assay was positive. Whether there were additional patients with CDAD who were treated empirically without a positive toxin assay, or were diagnosed by the presence of toxic megacolon, or by endoscopy, is unclear, and it is possible that we have underestimated the true incidence of post-surgical CDAD. We were unable to stratify our analysis by specific operation performed, and so it is unclear if specific surgical procedures are associated with increased or decreased risk for developing post-surgical CDAD.

In summary, CDAD infrequently complicates abdominal surgery. We have been able to describe several potentially avoidable pre-operative exposures (e.g. antibiotic and PPI use) that increase the risk of post-surgical CDAD. It appears that post-surgical CDAD is a disease that is different from CDAD on the medical service, with different exposure profiles and better outcomes.

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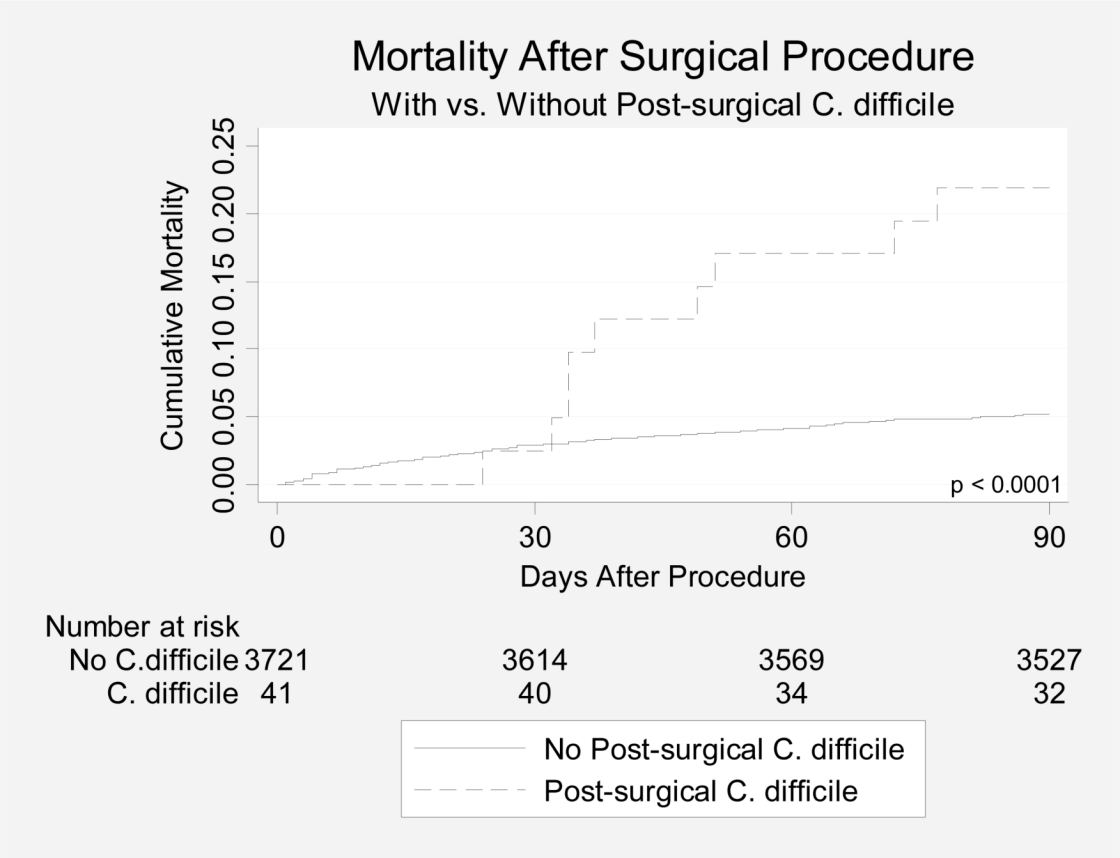

Figure 1.

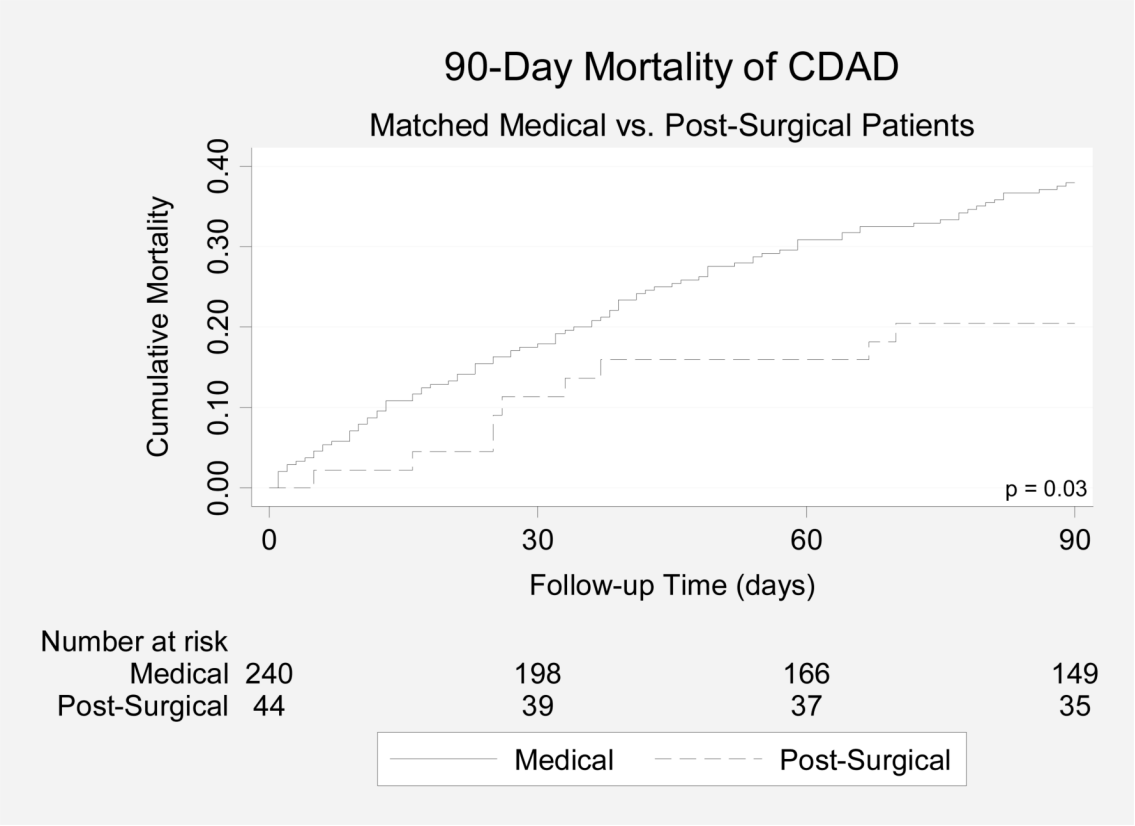

Figure 2A.

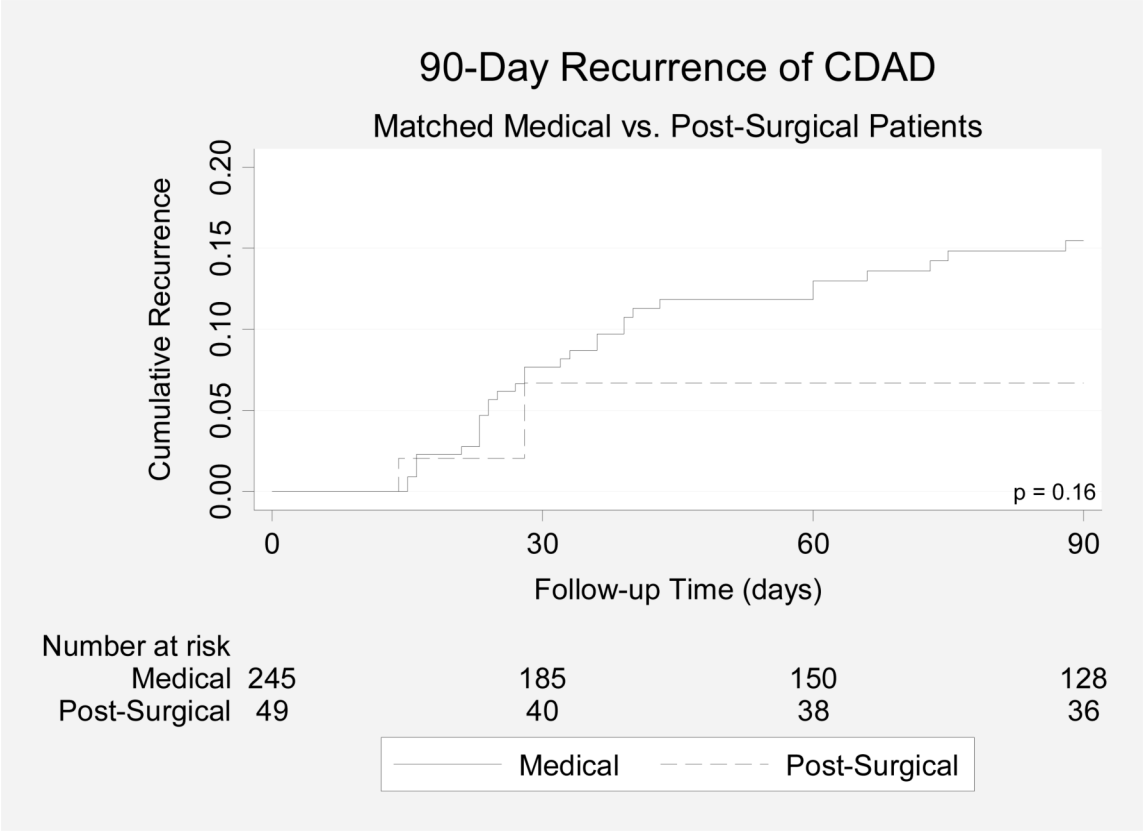

Figure 2B.

Table 1

Description of Patient Population

	All Procedures (n = 3904)	Post-surgical CDAD (n = 46)
Age	52.9 ± 18.8	65.5 ± 15.7
Male No. (%)	1304 (33.4)	12 (26.1)
Race/ethnicity No. (%)		
White	739 (18.9)	13 (28.3)
Black	1166 (29.9)	14 (30.4)
Hispanic	1609 (41.2)	17 (37.0)
Other/Unknown	388 (9.9)	2 (4.3)
Antibiotics given*	1042 (26.8)	22 (47.8)
Cephalosporin†	96 (2.5)	4 (8.7)
Fluoroquinolone	254 (6.5)	12 (26.1)
Clindamycin	37 (0.9)	2 (4.3)
Imipenim	42 (1.1)	0 (0.0)
Proton-Pump Inhibitor given‡	391 (10.0)	13 (28.3)
Prior Hospitalization§	805 (20.6)	19 (41.3)
Admission Albumin	3.69 ± 0.77	3.05 ± 0.90
White Blood Cell Count	11.5 ± 4.9	11.4 ± 5.7
Charlson Score	2.31 ± 2.57	3.74 ± 3.31
Hospital		
Moses Division Hospital	2287 (58.6)	31 (67.4)
Weiler Division Hospital	1617 (41.4)	15 (32.6)

Continuous variables reported as mean ± standard deviation

Dichotomous variables reported as number (percent)

* any antibacterial given within 30 days before surgical procedure

† 3rd or 4th generation cephalosporins: cefipime, ceftriaxone, cefpodoxime, cefota

‡ any PPI given within 10 days before surgical procedure

§ any hospitalization within 180 days before surgical procedure

Table 2

Pre-Operative Factors Associated with Post-operative Toxin Positivity on Bivariate Analysis

	Bivariate Analysis Odds Ratio (95% CI) p-value	Adjusted Analysis* Odds Ratio (95% CI) p-value
Age†	1.46 (1.24 - 1.73) <0.001	
Pre-operative Abx‡	2.54 (1.42 - 4.55) 0.002	1.94 (1.07 - 3.52) 0.03
High-risk Abx§	4.80 (2.57 - 8.98) <0.001	3.42 (1.80 - 6.50) <0.001
Pre-operative PPI‖	3.62 (1.89 - 6.95) <0.001	2.32 (1.18 - 4.58) 0.01
Prior Hospitalization	2.75 (1.52 - 4.97) 0.001	2.27 (1.30 - 3.96) 0.004
Low Albumin¶	2.51 (1.70 - 3.71) <0.001	2.05 (1.29 - 3.25) 0.002

*Adjusted for age and Charlson co-morbidity score

†Odds ratio for each 10-year increment in age

‡Any antibiotic given within 30 days prior to the procedure

§Cephalosporin (3rd & 4th generation), flouroquinolones, clindamycin, imipenim

‖Proton pump inhibitor given within 10 days prior to the procedure

¶Odds ratio for each loss of 1 g/dl

Table 3

Comparison of CDAD in Medical vs. Post-Surgical Patients

	Medical CDAD (n = 432)	Post-Surgical CDAD (n = 49)	p value
Age	67.9 ± 17.1	64.4 ± 15.8	0.09
Male	162 (37.5)	12 (24.5)	0.07
Race/Ethnicity			0.89
White	121 (28.0)	14 (28.6)	0.93
Black	142 (32.9)	15 (30.6)	0.75
Hispanic	142 (32.9)	18 (36.7)	0.59
Other/Unknown	27 (6.2)	2 (4.1)	0.55
Any antibiotic given*	368 (85.2)	48 (98.0)	0.01
Cephalosporin†	131 (30.3)	9 (18.4)	0.08
Quinolone	196 (45.4)	21 (42.9)	0.74
Clindamycin	10 (2.3)	3 (6.1)	0.12
Imipenim	29 (6.7)	5 (10.2)	0.37
Proton-Pump Inhibitor given‡	252 (58.3)	19 (38.8)	0.009
Prior Hospitalization§	290 (67.1)	21 (42.9)	0.001
Admission Albumin	2.72 ± 0.71	2.66 ± 0.70	0.69
White Blood Cell Count//	15.7 ± 14.2	14.5 ± 5.4	0.49
Charlson Score	3.13 ± 2.48	3.63 ± 3.25	0.54
Community Aquired¶	162 (37.5)	3 (6.1)	< 0.001
Hospital			0.47
Moses Division Hospital	268 (62.0)	33 (67.3)	
Weiler Division Hospital	164 (38.0)	16 (32.7)	

Continuous variables reported as mean ± standard deviation and compared using a t-test or Wilcoxon rank-sum test as appropriate

Dichotomous variables reported as number (percent) and compared using a chi-squared test

* any antibacterial given within 30 days before diagnosis of CDAD

† 3rd or 4th generation cephalosporins: cefipime, ceftriaxone, cefpodoxime, cefotaxime

‡ any PPI given within 10 days before diagnosis of CDAD

§ any previous hospitalization within 180 days before diagnosis of CDAD

// measured at the time of CDAD diagnosis

¶ infection discovered within 48hrs of admission

Appendix 1

Comparison of two hospital sites

	Weiler (n = 1612)	Moses (n = 2278)	p value
Post-surgical CDAD	15 (0.9)	31 (1.4)	0.22
Age	54.5 ± 18.7	51.7 ± 18.8	<0.001
Male	504 (31.2)	800 (35.0)	0.01
Race			<0.001
White	423 (26.2)	316 (13.8)	<0.001
Black	473 (29.3)	693 (30.3)	0.5
Latino	597 (37.0)	1012 (44.3)	<0.001
Oth/Unknown	122 (7.6)	266 (11.6)	<0.001
Any antibiotic given*	438 (27.1)	604 (26.5)	0.67
Cephalosporin†	39 (2.4)	57 (2.5)	0.86
Quinolone	114 (7.1)	140 (6.1)	0.26
Clindamycin	14 (0.9)	23 (1.0)	0.65
Imipenim	19 (1.2)	23 (1.0)	0.62
PPI‡	166 (10.3)	225 (9.8)	0.65
Prior Hosp§	328 (20.3)	477 (20.9)	0.67
Admission Albumin	3.58 ± 0.82	3.74 ± 0.73	<0.001
Charlson Score	2.50 ± 2.74	2.18 ± 2.43	0.002

Continuous variables reported as mean ± standard deviation

Dichotomous variables reported as number (percent)

*any antibacterial given within 30 days before surgical procedure

†3rd or 4th generation cephalosporins: cefipime, ceftriaxone, cefpodoxime, cefotaxin

‡any PPI given within 10 days before surgical procedure

§any hospitalization within 180 days before surgical procedure

Appendix 2

Comparison of Matched Cohorts

	Medical CDAD (n = 245)	Post-Surgical CDAD (n = 49)	p value
Age	65.0 ± 17.3	64.4 ± 15.8	0.80
Male	78 (31.8)	12 (24.5)	0.31
Charlson Score	3.46 ± 2.55	3.63 ± 3.25	0.86
Community Acquired	15 (6.1)	3 (6.1)	1.00

Continuous variables reported as mean ± standard deviation and compared using a t-test or Wilcoxon rank-sum test as appropriate

Dichotomous variables reported as number (percent) and compared using a chi-squared test