HHS Public Access

Author manuscript

J Thorac Cardiovasc Surg. Author manuscript; available in PMC 2019 February 01.

Published in final edited form as:

J Thorac Cardiovasc Surg. 2018 February ; 155(2): 670–678.e1. doi:10.1016/j.jtcvs.2017.09.089.

A multi-institutional cohort study confirming the risks of *Clostridium difficile* infection associated with prolonged antibiotic prophylaxis

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Clinical Trial Registry Number: NCT01089712

Conflicts of Interest: All authors have no conflicts of interest to disclose.

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Abstract

Objectives—The incidence and severity of *Clostridium difficile* infections has increased rapidly over the past two decades particularly in elderly patients with multiple comorbidities. This study sought to characterize the incidence and risks of these infections in cardiac surgery patients.

Methods—A total of 5,158 patients at 10 Cardiothoracic Surgical Trials Network sites in the US and Canada participated in a prospective study of major infections after cardiac surgery. Patients were followed for infection, readmission, reoperation, or death up to 65 days after surgery. We compared clinical and demographic characteristics, surgical data, management practices, and outcomes for patients with and without *C. difficile* infections.

Results—*C. difficile* was the third most common infection observed (0.97%) and was more common in patients with preoperative co-morbidities and complex operations. Antibiotic prophylaxis > 2 days, intensive care unit stay > 2 days, and postoperative hyperglycemia were associated with increased risk of *C. difficile* infection. Median time to onset was 17 days; 48% of infections occurred post-discharge. Additional length of stay due to infection was 12 days. The readmission and mortality rates, respectively, were three and five times higher in patients with *C. difficile* infection compared to uninfected patients.

Conclusions—In this large multi-center prospective study of major infections following cardiac surgery, *C. difficile* infection was encountered in nearly 1% of patients, was frequently diagnosed post-discharge, extended length of stay, and substantially increased mortality. Patients with comorbidities, longer surgery time, extended antibiotic exposure and/or hyperglycemic episodes have an increased risk of *C. difficile* infection.

Clostridium difficile is a gram-positive, spore-forming anaerobic bacterium that is the most common source of hospital-acquired gastrointestinal infection.[1–7] *C. difficile* infection (CDI) can cause a wide spectrum of illness ranging from mild diarrhea to pseudo-obstruction, pseudomembranous colitis, prolonged ileus, toxic megacolon, large bowel perforation, hemodynamic collapse, multisystem organ failure, shock, and death.[3,6,8–10]

Both the incidence and severity of CDI have been increasing worldwide since the mid- to late-1990s as evidenced by a variety of single-site, multi-center, and population-based studies.[1–5,8,10–27] Though some increase in observed incidence may be due to the adoption of newer, more sensitive nucleic acid amplification tests (NAATs), the rates of colectomy and mortality continue to climb.[5–7,10–14,16,18,20,23] Estimates of hospital cost increases directly due to CDI are as high as $77,000[1,4,19,20,28] with cumulative annual costs estimated to be greater than $200 million for cardiac surgery patients alone[24] and nearly $5 billion for CDIs in acute care facilities in the United States.[25,29,30] The United States Centers for Disease Control and Prevention has identified CDI as an important cause of infectious disease death and made its prevention a national priority.[25]

Advanced age, blood product transfusions, heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, liver disease, diabetes, history of stroke, renal failure, mechanical ventilation, urinary catheters, decubitus ulcers, health care exposure (e.g. hospitalization), and antibiotic exposure have been identified as risk factors for CDI.[8,9,24,31–34] Cardiac surgery patients, therefore, would appear to be a particularly vulnerable population, yet the literature has focused primarily on surgical site infections and bloodstream infections in this population.[35,36]

The Cardiothoracic Surgical Trials Network (CTSN), funded by the National Institutes of Health and the Canadian Institutes of Health Research, recently conducted a large multicenter prospective cohort study with the primary objective of identifying management practices associated with infections occurring within 65 days after cardiac surgery.[37] Indeed, this study showed that CDI was the third most common major infection following pneumonia and bloodstream infection. In order to provide a more thorough understanding of CDI and how it affects patients undergoing cardiac surgery, we analyzed this cohort to determine the incidence of CDI and its association with adverse outcomes as well as demographic variables and management practices associated with increased risk of developing CDI.

METHODS

Population

The study cohort included all 5,158 patients (Figure 1, CONSORT Diagram) at 10 Cardiothoracic Surgical Trials Network (CTSN) sites in the United States and Canada who participated in the prospective Management Practices and the Risk of Infection Following Cardiac Surgery study (NCT01089712).[37] All patients at the participating sites who had a clinical indication for cardiac surgery, did not have an active systemic infection, were at least 18 years of age, and provided written informed consent were enrolled between February and September 2010. The study was approved by Institutional Review Boards at each participating clinical center and at the data coordinating center (DCC).

Data

Demographic data, baseline laboratory values, comorbidities, surgical data, and management practices (e.g. antimicrobial prophylaxis, glycemic control) were collected for the prospective cohort study. Comorbidities collected included hypertension, hypercholesterolemia, diabetes, chronic lung disease, renal insufficiency (history of renal insufficiency/failure and/or serum creatinine > 2.0 preoperatively), congestive heart failure (CHF), history of infective endocarditis, cerebrovascular accident, peripheral vascular disease, congenital heart disease, and valvular heart disease. Surgical characteristics captured included procedure status (elective, urgent, emergent), procedure, type of incision, operative time, use and duration of bypass and circulatory arrest, and blood transfusions.

Participants were followed for up to 65 days to determine incidence of major and minor infections, all-cause mortality, reoperation, and hospital readmission. The 10 major infections included were deep incisional surgical site infection occurring at the primary chest

incision; deep incisional surgical site infection (SSI) occurring at a secondary incision site (e.g., saphenous harvest and groin cannulation sites); mediastinitis; infectious myocarditis or pericarditis; endocarditis; cardiac device infection; pneumonia; empyema; *Clostridium difficile* colitis; and bloodstream infection. CDI was diagnosed according to standard clinical practice at each site. Minor infections were defined as primary and secondary superficial incisional surgical site infections; symptomatic urinary tract infections; and asymptomatic bacteriuria. Infections were classified based on definitions from the Centers for Disease Control and Prevention (CDC) and the National Healthcare Safety Network surveillance[38], and all major infections were adjudicated by an Event Adjudication Committee (EAC) that included three infectious disease experts. Infections other than *C. difficile* in this cohort have been previously described in detail.[37,39,40]

All data were entered into an electronic data capture system and submitted to the DCC which was responsible for electronic and local monitoring of the data for quality assurance.

Statistical Analysis

Univariable proportional hazards regression models were used to assess differences in patient demographics, operative characteristics, and post-operative management by whether or not a patient ever had a CDI. We adjusted for patient-level risk factors and management factors but not site in order to avoid obscuring risks related to management practices that may vary by site. Patients missing 60 day visits were censored at time of last contact.

Variables with a p-value ≤ 0.20 were then considered when building the multivariable proportional hazards model of time to onset of CDI using a backwards stepwise process. This model included death as a competing risk using the method of Fine and Gray[41]. Assumptions of the Fine-Gray model were checked by testing for an interaction between time and each of the covariates and by plotting the Schoenfeld-type residuals over time.[42]

An interaction between diabetes and hyperglycemia was explored as some studies have found a differential risk of hyperglycemia.[43–46] Residuals were plotted to confirm continuous numerical variables included in the final model could be treated as linear. AIC values were considered in final model selection.

The cumulative incidence function of CDI was plotted, again treating death as a competing risk.[41] A multivariable extended Cox model was also used to assess the relationship between time to death and a time-varying indicator for CDI, adjusting for factors found to be predictive of mortality in the cohort as a whole[37] and for other non-*C. difficile* infection as a time-varying covariate. Survival estimates for the hypothetical average patient in the cohort (age 64 years, creatinine 1.165 mg/dL, no diabetes or heart failure, no other infection) were generated from the proportional hazards regression model and plotted by time-varying CDI status.

A multi-state time-inhomogeneous Markov model[47] was used to determine the excess length of stay (LOS) of the index hospitalization due to CDI. The model assumed a single initial state (index surgical procedure), one intermediate state (CDI), and two absorbing states

(hospital discharge and death). A bootstrap standard error and 95% confidence interval (CI) for the excess LOS was computed based on 1000 bootstrap samples.

All variables included in the final models had a p-value ≤ 0.05, and all analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC) and R 3.1.1.

RESULTS

Patient Characteristics

The study cohort included a total of 5,158 patients who enrolled in the study and underwent cardiac surgery between February and September 2010. Patient characteristics of the overall cohort have been previously reported[37] and are shown in Table 1. Briefly, the mean age was 64.4 ± 13.2 years, median body mass index (BMI) was 28.2 kg/m^2 (interquartile range [IQR] 25.0 – 34.2), and the proportion of women was 33%. Common comorbidities included diabetes mellitus (23% of patients), heart failure (29%), and chronic obstructive pulmonary disease (COPD, 14%). The most common procedures were isolated valve surgery (36%) and isolated coronary artery bypass grafting (33%); 91% of patients underwent sternotomy; and 19% of patients had previously undergone cardiac surgery.

CDI was the third most common infection observed (0.97%) after pneumonia (2.38%) and blood stream infections (1.09%). Compared to patients without CDI, patients with CDI were more likely to have higher creatinine, lower ejection fractions, prior cardiac surgery, and renal failure (with or without dialysis). Median surgery and bypass times were longer for patients with CDI, and patients with CDI were more likely to have undergone combined procedures, ventricular assist device (VAD) placement or replacement, or heart transplant than patients without CDI. Patients with CDI were also more likely to have received more than 48 hours of post-operative antibiotic prophylaxis; were less likely to have received 2nd generation cephalosporins as the post-operative antibiotic prophylaxis; and were more likely to have longer times in the ICU and on ventilation (Table 2). Post-operative hyperglycemic episodes and infections other than CDI were also more common in patients with CDI.

Frequency, Severity, and Timing of CDI

There were 52 identified CDIs in 50 patients during the 65 day follow up period (0.97%). Two of the patients with CDI (4%) required total colectomy. Median time to CDI onset was 17 days after surgery (IQR, 6–28 days; Figure 2). Onset of CDI occurred prior to hospital discharge in 52% of patients (n = 26) (Table 3); onset of CDI occurred on the day of discharge in two patients. Ten patients had a major infection prior to CDI (20%), and six patients had a minor infection prior to CDI (12%); two patients had both a major and a minor infection prior to onset of CDI.

Risk Factors Associated with CDI

Renal failure was the only preoperative patient characteristic associated with a higher risk of CDI in multivariable analysis (hazard ratio [HR] 5.08 for dialysis-dependent renal failure compared to no renal failure; 95% CI, 1.94 – 13.28; p = 0.004). Approximately half of patients were admitted on the day of surgery (median days admitted prior to surgery 0.0,

IQR 0.0 – 2.0); preoperative LOS was not associated with increased risk of CDI in the multivariable model. Operative and postoperative variables associated with greater CDI risk include hyperglycemia (HR 2.89; 95% CI, 1.53 – 5.47; p = 0.001) and days of post-operative antibiotic prophylaxis (HR 5.36 for 3 days versus 2 days; 95% CI, 2.61 – 10.99, p < 0.001). Being in the intensive care unit (ICU) longer than 2 days was also associated with increased risk of CDI (HR 2.45; 95% CI, 1.27 – 4.75, p =0.008, Figure 3). There was no evidence of a differential effect of hyperglycemia by diabetes status (p = 0.327).

Length of Stay and Readmissions

For the 26 patients whose onset of CDI occurred during the index hospitalization, the observed mean LOS from hospital admission was 35.3 ± 21.6 days compared to 17.4 ± 12.0 days and 11.0 ± 9.1 days for patients diagnosed with CDI after discharge and for patients without CDI, respectively. A multi-state Markov model was used to estimate the incremental LOS of the index hospitalization following surgery; excess LOS of the index hospitalization due to CDI was 12.29 ± 3.22 days (bootstrap 95% CI, 7.39 – 17.76).

Thirteen patients who acquired CDI during the follow up period were readmitted a total of 15 times in the first 30 days after surgery (0.4343 readmissions per patient month of follow up), whereas 602 patients without CDI were readmitted 642 times in the first 30 days after surgery (0.1310 readmissions per patient month of follow up). Over the entire 65 day follow up period, readmission rates were 0.2255 versus 0.0903 per patient month of follow up for patients with and without CDI, respectively.

CDI and Mortality

Death occurred more frequently during the 65 day follow up period in patients with CDI than in patients without CDI (10.0% vs. 1.8%, p < 0.001). In a proportional hazards regression model treating CDI as a time-dependent variable, CDI had a substantial impact on survival (hazard ratio [HR]: 5.45; 95% CI: 2.14–13.87). The model included non-*C. difficile* infection as a time-varying covariate (HR: 4.06; 95% CI: 2.49 – 6.62). The model also adjusted for sex (HR: 0.54 (male); 95% CI: 0.36–0.80), age (HR: 1.04; 95% CI: 1.02–1.05), baseline creatinine (HR: 1.20; 95% CI: 1.09–1.31), CHF (HR: 2.01; 95% CI: 1.34–3.02), diabetes (HR: 1.57; 95% CI: 1.03–2.38) which were previously shown to be predictors of mortality independently of CDI (Table 4).[37] The effect of CDI on survival for an average patient in the cohort (male, age 64, creatinine 1.165 mg/dL, no diabetes or heart failure) is shown in the Central Picture.

DISCUSSION

Most previous studies of major infections in cardiac surgery patients have focused on a subset of infections, predominantly surgical site infections and bloodstream infections[35,36], yet a recent large prospective cohort study showed that *Clostridium difficile* infections (CDI) were the third most common major infection after pneumonia and bloodstream infections.[37] Additionally, most of these studies have focused on the first 30 days after surgery and/or the index hospitalization period as this is the timeframe for which national databases such as the

Premier Perspective Comparative database, the Nationwide Inpatient Sample database, and the Society of Thoracic Surgeons database collect events.[24,35,48]

Recent results of an active surveillance study funded by the Centers for Disease Control and Prevention's Emerging Infections Program showed that while the majority of CDI cases in the United States were related to healthcare exposure (i.e. an inpatient or outpatient visit within 12 weeks prior to the collection of a *C. difficile*-positive stool sample), only 24% of cases observed had an in-hospital onset.[25] The data from the CTSN infection study, therefore, provide a unique opportunity to examine the incidence of CDI in the cardiac surgery population and risk factors associated with its occurrence as well as the relationship between CDI and adverse outcomes.

As would be expected based on the CDC's surveillance, nearly half of all CDIs (48%) occurred after index hospital discharge, and 25% of all CDIs occurred after day 30 in our study. This may explain why frequency of CDI in this study (50 patients, or 0.97%) was higher than the 0.21–0.75% reported elsewhere from national databases of cardiac surgery patients.[24,48,49] CDI was more common than expected during study planning and was, in fact, collected as an "other" serious infection. Diagnosis was therefore not protocolized but determined according to standard clinical care at each site.

Comorbidities have been frequently associated with risk of CDI.[1,2,8,9,11,17,24,31,33,34,50] Not surprisingly, we found that patients who developed CDI were more likely to suffer from renal failure pre-operatively and were more likely to have longer ICU stays. Duration of ICU stay and procedure were related --VAD and transplant patients spent longer in the ICU than patients undergoing other procedures. Acute hyperglycemia was associated with an increased risk of CDI. It is unclear, however, if hyperglycemia is indicative of a sicker, more vulnerable patient or if hyperglycemia in and of itself increases the risk of infection, particularly since diabetes was not associated with risk of CDI and we did not observe a differential risk of hyperglycemia by diabetes.

Unlike other studies[9,12,13,17], however, we did not find significantly higher incidence with older age, diabetes, increased BMI, or COPD; with urgent or emergent procedure status; in women; or in Caucasian patients. In contrast, African Americans were the racial group that contracted CDI most frequently. Given that only 50 patients in this cohort contracted CDI and the cohort was predominantly male, the analysis may have simply been underpowered to detect a difference. It is also possible that varying diagnostic criteria by site may have obscured any risks associated with demographics. There was not a statistically significant difference in CDI incidence in patients who did not undergo a sternotomy compared to those who did though it's worth noting that the incidence in both groups is low, so a difference would have to be fairly large to be detectable.

Moreover, other studies have identified additional risk factors for CDI, including malignancy, chemotherapy, intra-abdominal therapy, malnutrition and previous CDI.[33,34] As this study was designed to focus on management practices and the risk of infection, many of the variables identified in other studies as risk factors of CDI were not collected in this study.

Although patients with CDI were readmitted more often during the 65 day follow-up period, this appears to be indicative of the fact that hospital exposure and comorbidities increase the risk of CDI as readmissions tended to be for reasons other than CDI; only 7 of the 31 readmissions in this group were due to CDI. In most cases, onset of CDI occurred during index hospitalization or during a readmission hospitalization. Readmissions for CDI occurred in close proximity to a hospital discharge, consistent with the CDC's surveillance study.

As was observed in other reports[1–4,6,8,9,12,17,21,32,50–52], mortality increased substantially with CDI. This observation held after adjusting for age, sex, diabetes, CHF, baseline creatinine, and time-varying non-*C. difficile* infection (HR = 5.45, 95% CI: 2.14–13.87, $p < 0.001$). Mortality observed in patients with CDI in this cohort of cardiac surgery patients (10.0%) was comparable to the death rates from healthcare-associated CDI in surgical and non-surgical patients in the US and Canada over the same time period (6–35%).[53,54] Despite the fact that patients with CDI tended to generally be at higher risk of adverse outcomes, we did not observe any increase in any major adverse cardiac or cerebrovascular events other than death (MI, CVA, or TIA) at any point during the 65 day follow up. A single CVA occurring after onset of CDI was the only non-fatal reported adverse event among the 50 patients ever diagnosed with CDI.

Risk of CDI increases substantially with prolonged antibiotic exposure as suppression of the bowel flora allows *C. difficile* bacteria to grow[55] ; this effect is thought to be particularly pronounced with second generation cephalosporins.[56] Antibiotic prophylaxis lasting 48 hours or less was protective of CDI but antibiotic prophylaxis lasting 3 days or longer was associated with higher risk of CDI regardless of type of antibiotic prophylaxis. We had anticipated that a prior post-operative infection would increase the risk of CDI as the initial post-operative infection would presumably result in antibiotic treatment yet only 28% of first CDI cases occurred after another infection (major or minor), and other (non-*C. difficile*) infection was not significantly associated with increased risk of CDI.

Though type of antibiotic was significant in univariable analyses with 2nd generation cephalosporins associated with a decreased hazard of CDI, the finding did not hold in a multivariable model, possibly because the type of antibiotic was correlated with the duration the antibiotic was given. This may also be due to the limited size of the study (50 patients with CDI) as a recent analysis of 154,200 cardiac surgery patients in the Premier database showed antibiotic prophylaxis with cephalosporin was associated with decreased CDI risk (though it did not distinguish between 1st and 2nd generation cephalosporins).[49] That study also confirmed increased risk of CDI with antibiotic prophylaxis that extended past 48 hours.

Limitations

Despite a cohort of over 5,000 patients, the number of patients with CDI was low, limiting power. CDI was potentially underreported in this study because it was not included in the predefined list of major infections in the protocol; instead, it was captured as a serious "other" infection. Diagnostic criteria were not protocolized, and we do not know how each diagnosis was made (i.e. NAAT vs. other methods). However, the study was designed to

capture all post-operative infections, all events were reviewed and adjudicated by an Event Adjudication Committee of infectious disease experts, and follow up through end of study was 98% complete. Given the thoroughness of data capture and the fact that the reported incidence in this study was higher than in other studies,[1,2,4,13] we believe the chance of bias due to underreporting is low.

Medications other than prophylactic antibiotics were not captured in the database which precluded analysis of antibiotics administered for other infections that occurred prior to CDI. It also precluded analysis of medications such as proton pump inhibitors that have been previously shown to be risk factors for CDI.[48,57] However, other infections, serious or not (before the onset of CDI for patients with CDI), were not associated with an increased risk of CDI.

Discharge disposition was also not captured in the database, precluding analysis to determine if patients discharged to a rehabilitation or nursing facility were at increased risk of post-discharge CDI compared to patients who were discharged home.

Lastly, the excess LOS due to CDI should be interpreted with caution as it does not take into account other potentially informative covariates (e.g. index surgical procedure). As the study was designed to focus on management practices and infection, other complications and adverse events were not collected, and these may have affected LOS overall or in the ICU.

CONCLUSION

CDI was a common infection following cardiac surgery and was associated with significant increases on LOS and mortality. Despite intense efforts to reduce the incidence of healthcare-associated infections, there are still opportunities to improve adherence to quality improvement measures, particularly glycemic control and optimal duration of antibiotic prophylaxis (≤ 48 hours), to reduce the rates of CDI. High-risk patients, such as those with renal failure or undergoing complex procedures such as VAD placement or transplant who will spend an extended length of time in the ICU, are particularly vulnerable to CDI and may warrant additional precautions to reduce the morbidity and mortality associated with CDI. Providers should continue to be vigilant about CDI after discharge as onset is frequently more than two weeks after surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding: A cooperative agreement (U01 HL088942) funded by the National Heart, Lung, and Blood Institute and the National Institute of Neurological Disorders and Stroke of the NIH and the Canadian Institutes of Health Research.

Abbreviations

BMI	Body mass index

CABG	Coronary artery bypass grafting
CDC	Centers for Disease Control and Prevention
CDI	*C. difficile* infection
CHF	Congestive heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CTSN	Cardiothoracic Surgery Trials Network
DCC	Data coordinating center
EAC	Event adjudication committee
HR	Hazard ratio
ICU	Intensive care unit
IQR	Interquartile range
LOS	Length of stay
MI	Myocardial infarction
NAAT	Nucleic acid amplification test
SD	Standard deviation
TIA	Transient ischemic attack
VAD	Ventricular assist device
WBC	White blood cells

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Central Message

Prolonged antibiotic prophylaxis (> 48 hours) was associated with risk of CDI, the third most common major infection after cardiac surgery. CDI was associated with a substantial increase in mortality.

Perspective Statement

The incidence and severity of CDI has increased recently. Our study found that CDI was associated with longer length of stay, frequent readmissions, and decreased survival. Median time to onset of CDI was > 2 weeks postoperatively with nearly half of patients (48%) first diagnosed after discharge. Limiting antibiotic prophylaxis to 2 days and controlling blood glucose may reduce the incidence of CDI.

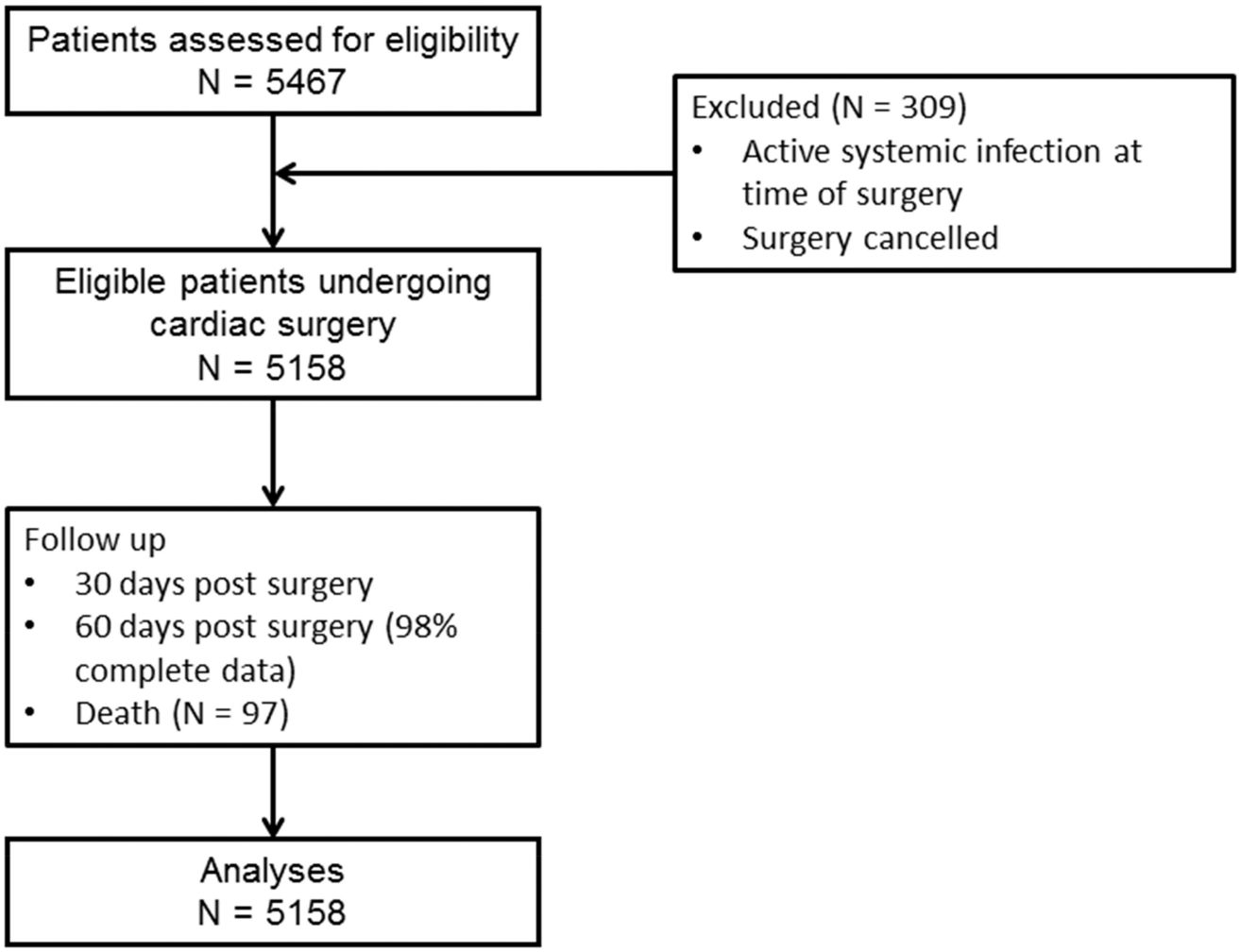


Figure 1.
CONSORT Diagram

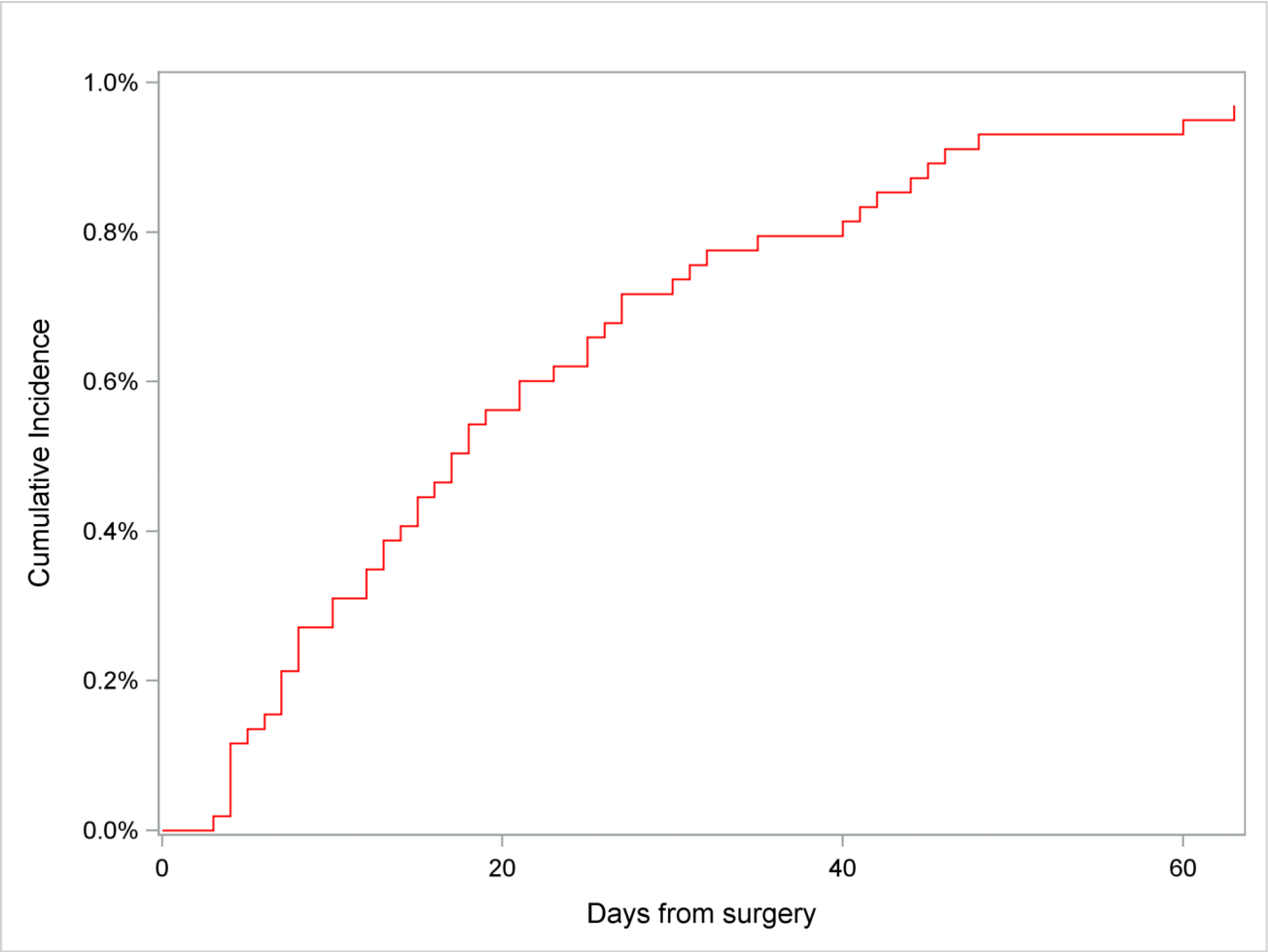


Figure 2.
Cumulative Incidence of *C. difficile* Infections

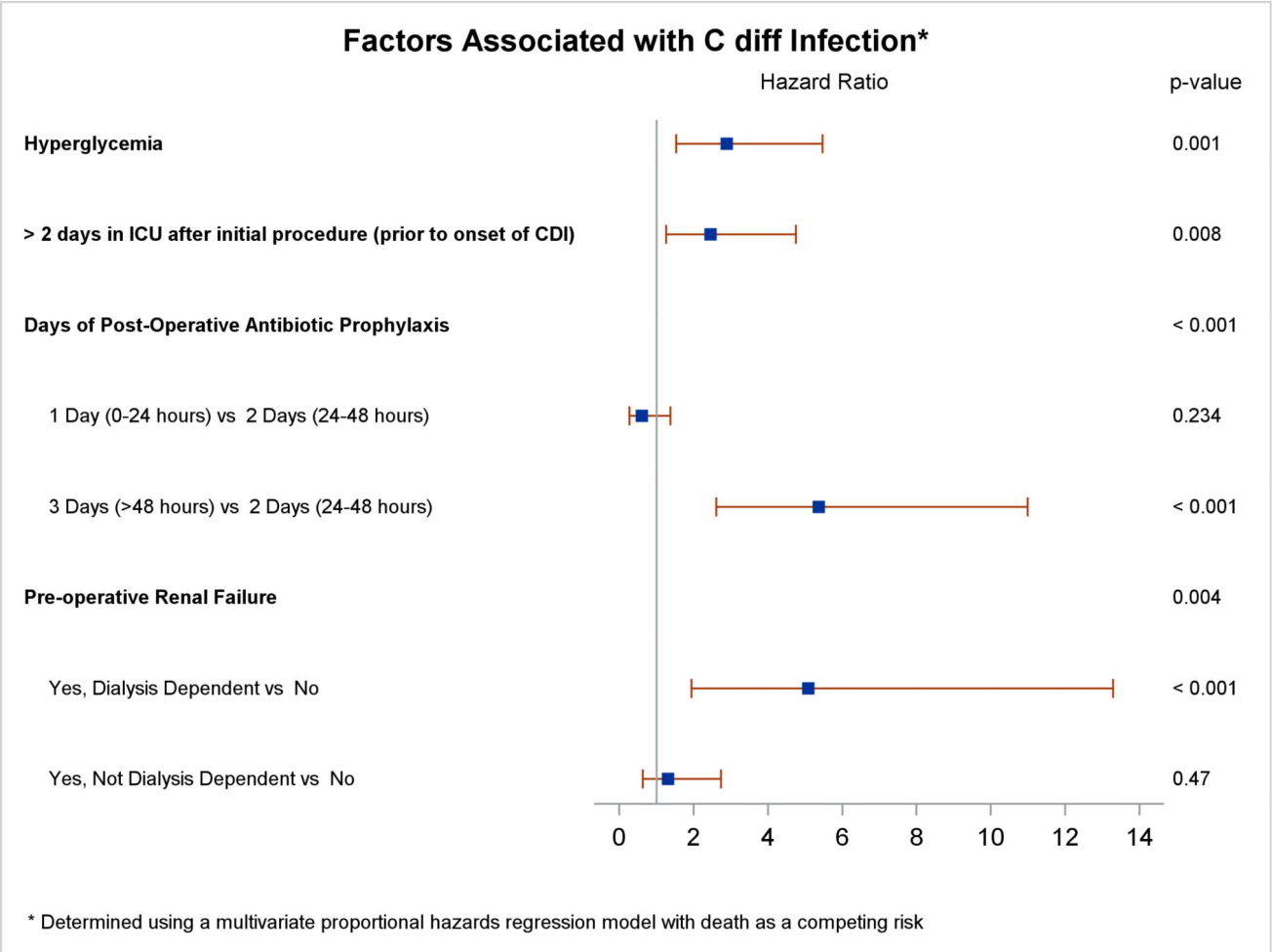
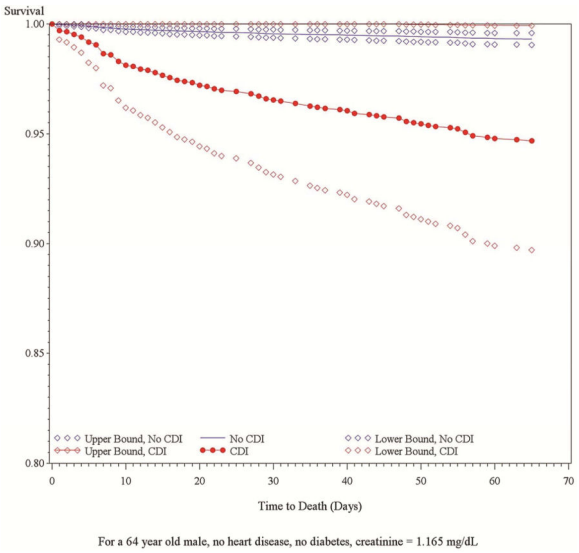


Figure 3.
Risk Factors for *C. difficile* Infections



Central Picture.
Survival by Time-Varying *C. difficile* Infection Status

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Table 1

Patient and operative characteristics[a]

	C. diff (N = 50)	No C. diff (N = 5108)	Overall (N = 5158)	Hazard Ratio	P-value[b]
Demographics					
Age, mean (SD)	64.5 (13.4)	64.4 (13.2)	64.4 (13.2)	1.001	0.9533
Male	36 (72.0)	3414 (66.8)	3450 (66.9)	1.264	0.4577
Race					0.0581
White	37 (74.0)	4285 (83.9)	4322 (83.8)	0.420	
Black	11 (22.0)	529 (10.4)	540 (10.5)		
Other	2 (4.0)	294 (5.8)	296 (5.7)	0.332	
BMI	28.8 (25.0, 34.2)	28.2 (25.1, 32.2)	28.2 (25.1, 32.3)	1.003	0.8847
Baseline Laboratories					
WBC, $\times 10^3$/ml	7.0 (5.6, 8.6)	7.0 (5.7, 8.4)	7.0 (5.7, 8.4)	0.991	0.8799
Creatinine, mg/dL	1.2 (1.0, 1.6)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.186	0.0027
Hemoglobin, g/dL	13.1 (11.0, 14.4)	13.4 (12.0, 14.5)	13.4 (12.0, 14.5)	0.890	0.1161
Cardiac morbidity					
Heart failure	23 (46.0)	1482 (29.0)	1505 (29.2)	2.093	0.0092
Ejection fraction	50.0 (35.0, 55.0)	55.0 (48.0, 60.0)	55.0 (48.0, 60.0)	0.962	<.0001
Previous cardiac surgery	16 (32.0)	942 (18.4)	958 (18.6)	2.071	0.0163
Baseline circulatory support	3 (6.0)	132 (2.6)	135 (2.6)	2.383	0.1447
History of infective endocarditis		61 (1.2)	61 (1.2)	0.000	0.9817
Noncardiac morbidity					
Diabetes[c]	12 (24.0)	1157 (22.7)	1169 (22.7)	1.084	0.8081
COPD					0.1895
None	38 (76.0)	4374 (85.6)	4412 (85.5)		
Mild or moderate	10 (20.0)	634 (12.4)	644 (12.5)	1.814	
Severe	2 (4.0)	100 (2.0)	102 (2.0)	2.303	
Renal Failure					0.0008
No	36 (72.0)	4526 (88.6)	4562 (88.4)		
Yes, Dialysis Dependent	5 (10.0)	85 (1.7)	90 (1.7)	2.309	
Yes, Not Dialysis	9 (18.0)	497 (9.7)	506 (9.8)	7.428	

	C. diff (N = 50)	No C. diff (N = 5108)	Overall (N = 5158)	Hazard Ratio	P-value[b]
Dependent					
History of cerebrovascular accident	7 (14.0)	513 (10.0)	520 (10.1)	1.458	0.3551
Operative					
Surgery time, hours	5.1 (4.2, 6.6)	4.2 (3.3, 5.2)	4.2 (3.3, 5.2)	1.458	<.0001
Bypass time, hours[d]	2.1 (1.6, 3.1)	1.8 (1.3, 2.3)	1.8 (1.3, 2.3)	1.523	0.0011
Sternotomy	48 (96.0)	4621 (90.5)	4669 (90.5)	2.512	0.2018
Surgery Type					0.4590
Elective	33 (66.0)	3773 (73.9)	3806 (73.8)		
Urgent	15 (30.0)	1199 (23.5)	1214 (23.5)	1.430	
Emergent	2 (4.0)	136 (2.7)	138 (2.7)	1.681	
Procedure					<.0001
Isolated CABG	9 (18.0)	1668 (32.7)	1677 (32.5)	0.407	
Isolated valve	12 (24.0)	1866 (36.5)	1878 (36.4)	0.487	
CABG + valve	9 (18.0)	683 (13.4)	692 (13.4)		
Transplant or VAD	10 (20.0)	112 (2.2)	122 (2.4)	6.499	
Thoracic aortic	6 (12.0)	422 (8.3)	428 (8.3)	1.080	
Other	4 (8.0)	357 (7.0)	361 (7.0)	0.847	
Other					
Transferred from outside ospital	4 (8.0)	717 (14.0)	721 (14.0)	0.535	0.2302
Pre-operative antibiotic prophylaxis					0.0344
1st generation cephalosporin	23 (46.0)	1836 (36.0)	1859 (36.1)	0.922	
2nd generation cephalosporin	13 (26.0)	2232 (43.7)	2245 (43.6)	0.431	
Other	14 (28.0)	1036 (20.3)	1050 (20.4)		
Days admitted prior to surgery	0.0 (0.0, 4.0)	0.0 (0.0, 2.0)	0.0 (0.0, 2.0)	1.008	0.7761

[a] Continuous variables are expressed as mean (SD) or median (IQR) and categorical variables as count (%).

[b] Based on Cox proportional hazards model where outcome is time to C. diff infection and predictor is patient or operative characteristic.

[c] Insulin or oral medications.

[d] 91.1% of patients had on-pump surgical procedures.

Key: CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; SD, standard deviation; VAD, ventricular assist device; WBC, white blood cells

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Table 2

Postoperative characteristics[a]

	C. diff (N = 50)	No C. diff (N = 5108)	Overall (N = 5158)	Hazard Ratio	P-value[b]
Days of post-operative antibiotic prophylaxis					<.0001
2 Days (24–48 hours)	13 (26.0)	2107 (41.2)	2120 (41.1)		
1 Day (0–24 hours)	11 (22.0)	2585 (50.6)	2596 (50.3)	0.692	
3 Days (>48 hours)	26 (52.0)	416 (8.1)	442 (8.6)	10.033	
Post-operative antibiotic prophylaxis					0.0358
1st generation cephalosporin	19 (38.0)	1721 (33.7)	1740 (33.7)	0.721	
2nd generation cephalosporin	14 (28.0)	2270 (44.4)	2284 (44.3)	0.404	
Other	17 (34.0)	1117 (21.9)	1134 (22.0)		
ICU days	5.0 (2.0, 8.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	1.069	<.0001
Ventilation duration, days	1.0 (0.6, 2.1)	0.6 (0.4, 1.0)	0.6 (0.4, 1.0)	1.087	0.0001
Packed red blood cells, unit[c]	2.0 (0.0, 8.0)	0.0 (0.0, 3.0)	0.0 (0.0, 3.0)	1.225	<.0001
LOS from surgery (truncated at onset of C. diff), days	10.0 (7.0, 17.0)	7.0 (6.0, 10.0)	7.0 (6.0, 10.0)	1.069	<.0001
Non- *C. difficile* infection[d]	14 (28.0)	551 (10.8)	565 (11.0)	3.180	0.0002
Hyperglycemia	37 (74.0)	2191 (43.0)	2228 (43.3)	3.766	<.0001

[a] Continuous variables are expressed as median (IQR). Categorical variable is described as count (%).

[b] Based on Cox proportional hazards model where outcome is time to C. diff infection and predictor is postoperative characteristic.

[c] 48.1% of patients received packed red blood cell transfusions.

[d] Onset of non- *C. difficile* infection prior to onset of CDI for *C. difficile* patients.

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Table 3

Infection timing for patients with C. diff[a]

	C. diff (N = 50)
C. diff Onset	
Before index hospital discharge	26 (52.0)
Time to C. diff onset, days	17.0 (8.0, 30.0)
Other Infections	
Major infection before C. diff	10 (20.0)
Minor infection before C. diff	6 (12.0)
Any infection (major or minor) before C. diff	14 (28.0)

[a]Continuous variable is expressed as median (IQR); categorical variables are expressed as frequency (percent).

Table 4

Impact of CDI on Mortality

	Hazard Ratio	95% Confidence Interval	p-value
CDI status[a]	5.449	(2.14, 13.87)	0.0004
Male	0.535	(0.36, 0.8)	0.0023
Age	1.036	(1.02, 1.05)	<.0001
Creatinine, per mg/dL ?	1.199	(1.09, 1.31)	0.0001
Diabetes (yes/no)	1.569	(1.03, 2.38)	0.0350
Non-*C. difficile* infection status[b]	4.063	(2.49, 6.62)	<.0001
Heart Failure (yes/no)	2.011	(1.34, 3.02)	0.0007

[a] CDI status is a time-varying covariate.

[b] Non- *C. difficile* infection status is a time-varying covariate and refers to infection prior to the onset of CDI.