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

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ABSTRACT

Objectives: The incidence and severity of *Clostridium difficile* infection (CDI) have increased rapidly over the past 2 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 5158 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 CDI and without CDI.

Results: *C. difficile* was the third most common infection observed (0.97%) and was more common in patients with preoperative comorbidities and complex operations. Antibiotic prophylaxis for >2 days, intensive care unit stay >2 days, and postoperative hyperglycemia were associated with increased risk of CDI. The median time to onset was 17 days; 48% of infections occurred after discharge. The additional length of stay due to infection was 12 days. The readmission and mortality rates were 3-fold and 5-fold higher, respectively, in patients with CDI compared with uninfected patients.

Conclusions: In this large multicenter prospective study of major infections following cardiac surgery, CDI was encountered in nearly 1% of patients, was frequently diagnosed postdischarge, and was associated with extended length of stay and substantially increased mortality. Patients with comorbidities, longer surgery time, extended antibiotic exposure, and/or hyperglycemic episodes were at increased risk for CDI. (J Thorac Cardiovasc Surg 2018;155:670-8)

Survival by time-varying *Clostridium difficile* infection status.

Central Message

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

Perspective

The incidence and severity of *Clostridium difficile* infection (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 one-half of patients (48%) first diagnosed after discharge. Limiting antibiotic prophylaxis to 2 days and controlling blood glucose levels may reduce the incidence of CDI.

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Abbreviations and Acronyms

CDC	= Centers for Disease Control and Prevention
CDI	= <i>Clostridium difficile</i> infection
CHF	= congestive heart failure
CI	= confidence interval
COPD	= chronic obstructive pulmonary disease
CTSN	= Cardiothoracic Surgery Trials Network
HR	= hazard ratio
ICU	= intensive care unit
IQR	= interquartile range
LOS	= length of stay
SSI	= surgical site infection
VAD	= ventricular assist device

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Clostridium difficile, a gram-positive, spore-forming anaerobic bacterium, 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, multicenter, and population-based studies.^{1-5,8,10-27} Although some of the increase in observed incidence may be due to the adoption of newer, more sensitive nucleic acid amplification tests, 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 exceed \$200 million for cardiac surgery patients alone²⁴ and nearly \$5 billion for CDIs in acute care facilities in the United States.^{25,29,30} The US Centers for Disease Control and Prevention (CDC) has identified CDI as an important cause of infectious disease–related death and has made its prevention a national priority.²⁵

Advanced age, blood product transfusions, heart failure, peripheral vascular disease, chronic obstructive pulmonary disease (COPD), liver disease, diabetes, history of stroke, renal failure, mechanical ventilation, urinary catheter use, decubitus ulcers, health care exposure (eg, hospitalization), and antibiotic exposure have been identified as risk factors

for CDI.^{8,9,24,31-34} Consequently, cardiac surgery would appear to be a particularly vulnerable population; yet the literature has focused primarily on surgical site infections (SSIs) 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 The CTSN study identified CDI as the third most common major infection, following pneumonia and bloodstream infection. 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 explore 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 5158 patients at 10 CTSN sites in the United States and Canada who participated in the prospective Management Practices and the Risk of Infection Following Cardiac Surgery study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01089712); NCT01089712) (Figure 1).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 received Institutional Review Board approval at each participating clinical center and at the data coordinating center.

Data

Demographic data, baseline laboratory values, comorbidities, surgical data, and management practices (eg, antimicrobial prophylaxis, glycemic control) were collected for the prospective cohort study. Comorbidities recorded included hypertension, hypercholesterolemia, diabetes, chronic lung disease, renal insufficiency (ie, 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 (ie, elective, urgent, or emergent), procedure, type of incision, operative time, use and duration of cardiopulmonary bypass and circulatory arrest, and blood transfusions.

Participants were followed for up to 65 days to determine the incidences of major and minor infections, all-cause mortality, reoperation, and hospital readmission. The 10 major infections included were deep incisional SSI occurring at the primary chest incision, deep incisional SSI occurring at a secondary incision site (eg, saphenous harvest and groin cannulation sites), mediastinitis, infectious myocarditis or pericarditis, endocarditis, cardiac device infection, pneumonia, empyema, *C 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 SSIs, symptomatic urinary tract infections, and asymptomatic bacteriuria. Infections were classified based on definitions from the CDC and the National Healthcare Safety Network surveillance,³⁸ and all major infections were adjudicated by an Event Adjudication Committee that included 3 infectious disease experts. Infections other than *C difficile* in this cohort have been previously described in detail.^{37,39,40}

FIGURE 1. CONSORT diagram.

All data were entered into an electronic data capture system and submitted to the data coordinating center, 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 demographic data, operative characteristics, and postoperative management by a CDI or no CDI during follow-up. We adjusted for patient-level risk factors and management factors but not for site, to avoid obscuring risks related to management practices that may vary by site. Patients missing the 60-day follow-up visit were censored at the time of last contact.

Variables with a P value $\leq .20$ were considered when building the multivariable proportional hazards model of time to onset of CDI using a backward 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, given that some previous studies have found a differential risk of hyperglycemia.^{43–46} Residuals were plotted to confirm that continuous numerical variables included in the final model could be treated as linear. Akaike information criterion 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 whole³⁷ 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; serum 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 multistate time-inhomogeneous Markov model⁴⁷ 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 2 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 $\leq .05$. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and R 3.1.1 (R Institute for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

The study cohort included a total of 5158 patients who enrolled in the study and underwent cardiac surgery between February and September 2010. Patient characteristics of the overall cohort have been reported previously³⁷ and are summarized in Table 1. In brief, the mean age was 64.4 ± 13.2 years, median body mass index was 28.2 kg/m^2 (interquartile range [IQR] 25.1–32.3), and the proportion of women was 33.1%. Common comorbidities included diabetes mellitus (22.7% of patients), heart failure (29.2%), and COPD (14.5%). The most common procedures were isolated valve surgery (36.4%) and isolated coronary artery bypass grafting (32.5%); 90.5% of patients underwent sternotomy, and 18.6% of patients had undergone previous cardiac surgery.

CDI was the third most common infection observed (0.97%) after pneumonia (2.38%) and bloodstream infections (1.09%). Compared with patients without CDI, those with CDI were more likely to have a higher serum creatinine level, a lower ejection fraction, previous cardiac surgery, and renal failure (with or without dialysis). Median surgery and bypass times were longer in the patients with CDI, and patients with CDI were more likely to have undergone combined procedures, ventricular assist device (VAD) placement or replacement, or heart transplantation than patients without CDI. Patients with CDI were also more likely to have received more than 48 hours of postoperative antibiotic prophylaxis, were less likely to have received second-generation cephalosporins as postoperative antibiotic prophylaxis, and were more likely to have longer times in the intensive care unit (ICU) and on ventilation (Table 2). Postoperative hyperglycemic episodes and infections other than CDI were also more common in the patients with CDI.

Frequency, Severity, and Timing of CDI

A total of 52 CDIs were identified 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 before hospital discharge in 52% of patients ($n = 26$) (Table 3), and on the day of discharge in 2 patients. Ten patients had a major infection before the onset of CDI (20.0%), 6 patients had a minor infection before CDI (12.0%), and 2 patients had both a major and a minor infection before CDI.

Risk Factors Associated With CDI

Renal failure was the sole preoperative patient characteristic associated with a higher risk of CDI in multivariable

TABLE 1. Patient and operative characteristics

Characteristic	<i>C difficile</i> (n = 50)	No <i>C difficile</i> (n = 5108)	Overall (n = 5158)	Hazard ratio	<i>P</i> value*
Demographics					
Age, y, mean (SD)	64.5 (13.4)	64.4 (13.2)	64.4 (13.2)	1.001	.9533
Male sex, n (%)	36 (72.0)	3414 (66.8)	3450 (66.9)	1.264	.4577
Race, n (%)					.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, median (IQR)	28.8 (25.0-34.2)	28.2 (25.1-32.2)	28.2 (25.1-32.3)	1.003	.8847
Baseline laboratory values, median (IQR)					
WBC, $\times 10^3/\text{mL}$	7.0 (5.6-8.6)	7.0 (5.7-8.4)	7.0 (5.7-8.4)	0.991	.8799
Creatinine, mg/dL	1.2 (1.0-1.6)	1.0 (0.8-1.2)	1.0 (0.8-1.2)	1.186	.0027
Hemoglobin, g/dL	13.1 (11.0-14.4)	13.4 (12.0-14.5)	13.4 (12.0-14.5)	0.890	.1161
Cardiac morbidity					
Heart failure, n (%)	23 (46.0)	1482 (29.0)	1505 (29.2)	2.093	.0092
Ejection fraction, %, median (IQR)	50.0 (35.0-55.0)	55.0 (48.0-60.0)	55.0 (48.0-60.0)	0.962	<.0001
Previous cardiac surgery, n (%)	16 (32.0)	942 (18.4)	958 (18.6)	2.071	.0163
Baseline circulatory support, n (%)	3 (6.0)	132 (2.6)	135 (2.6)	2.383	.1447
History of infective endocarditis, n (%)	0 (0.0)	61 (1.2)	61 (1.2)		.9817
Noncardiac morbidity					
Diabetes, n (%)†	12 (24.0)	1157 (22.7)	1169 (22.7)	1.084	.8081
COPD, n (%)					.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, n (%)					.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-dependent	9 (18.0)	497 (9.7)	506 (9.8)	7.428	
History of cerebrovascular accident	7 (14.0)	513 (10.0)	520 (10.1)	1.458	.3551
Operative					
Surgery time, h, median (IQR)	5.1 (4.2-6.6)	4.2 (3.3-5.2)	4.2 (3.3-5.2)	1.458	<.0001
Bypass time, h, median (IQR)‡	2.1 (1.6-3.1)	1.8 (1.3-2.3)	1.8 (1.3-2.3)	1.523	.0011
Sternotomy, n (%)	48 (96.0)	4621 (90.5)	4669 (90.5)	2.512	.2018
Surgery type, n (%)					.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, n (%)					<.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 hospital, n (%)	4 (8.0)	717 (14.0)	721 (14.0)	0.535	.2302
Preoperative antibiotic prophylaxis, n (%)					.0344
First-generation cephalosporin	23 (46.0)	1836 (36.0)	1859 (36.1)	0.922	
Second-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 before surgery, median (IQR)	0.0 (0.0-4.0)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	1.008	.7761

SD, Standard deviation; BMI, body mass index; IQR, interquartile range; WBC, white blood cell; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting; VAD, ventricular assist device. *Based on a Cox proportional hazards model in which the outcome is time to *C difficile* infection and the predictor is patient or operative characteristic. †Insulin or oral medications. ‡91.1% of patients had on-pump surgical procedures.

TABLE 2. Postoperative characteristics

Characteristic	<i>C difficile</i> (n = 50)	No <i>C difficile</i> (n = 5108)	Overall (n = 5158)	Hazard ratio	P value*
Days of postoperative antibiotic prophylaxis, n (%)					<.0001
2 (24-48 h)	13 (26.0)	2107 (41.2)	2120 (41.1)		
1 (0-24 h)	11 (22.0)	2585 (50.6)	2596 (50.3)	0.692	
3 (>48 h)	26 (52.0)	416 (8.1)	442 (8.6)	10.033	
Postoperative antibiotic prophylaxis, n (%)					.0358
First-generation cephalosporin	19 (38.0)	1721 (33.7)	1740 (33.7)	0.721	
Second-generation cephalosporin	14 (28.0)	2270 (44.4)	2284 (44.3)	0.404	
Other	17 (34.0)	1117 (21.9)	1134 (22.0)		
ICU LOS, d, median (IQR)	5.0 (2.0-8.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	1.069	<.0001
Ventilation duration, d, median (IQR)	1.0 (0.6-2.1)	0.6 (0.4-1.0)	0.6 (0.4-1.0)	1.087	.0001
Packed RBCs, units, median (IQR)†	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 <i>C difficile</i>), d, median (IQR)	10.0 (7.0-17.0)	7.0 (6.0-10.0)	7.0 (6.0-10.0)	1.069	<.0001
Non- <i>C difficile</i> infection, n (%)‡	14 (28.0)	551 (10.8)	565 (11.0)	3.180	.0002
Hyperglycemia, n (%)	37 (74.0)	2191 (43.0)	2228 (43.3)	3.766	<.0001

ICU, Intensive care unit; LOS, length of stay; IQR, interquartile range; RBC, red blood cell. *Based on a Cox proportional hazards model in which the outcome is time to *C difficile* infection and the predictor is postoperative characteristic. †48.1% of patients received packed RBC transfusions. ‡Onset of non-*C difficile* infection before the onset of *C difficile* infection. ||Hyperglycemia was defined as 1 or more blood sugar measurements above 180 mg/dL during the first 48 h postoperatively.

analysis ($P = .004$); hazard ratio for dialysis-dependent renal failure compared with no renal failure was 5.08 (95% CI, 1.94-13.28). Approximately one-half of patients were admitted on the day of surgery (median days admitted before surgery, 0.0; IQR, 0.0-2.0); preoperative LOS was not associated with an increased risk of CDI in the multivariable model. Operative and postoperative variables associated with greater CDI risk include hyperglycemia (HR = 2.894, $P = .0011$; 95% CI, 1.53-5.47; $P = .001$) and days of postoperative antibiotic prophylaxis (HR = 5.356, $P < .0001$ for 3 days vs 2 days; 95% CI, 2.61-10.99; $P < .001$). An ICU LOS >2 days was also associated with increased risk of CDI (HR, 2.451, $P = .0079$; 95% CI, 1.27-4.75; $P = .008$) (Figure 3). There was no evidence of a differential effect of hyperglycemia by diabetes status ($P = .327$).

FIGURE 2. Cumulative incidence of *C difficile* infections.

LOS 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 with 17.4 ± 12.0 days for patients diagnosed with CDI after discharge and 11.0 ± 9.1 days for the patients without CDI. A multistate Markov model was used to estimate the incremental LOS of the index hospitalization following surgery; the mean excess LOS of the index hospitalization due to CDI was 12.3 ± 3.2 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 within the first 30 days after surgery (0.43 readmissions per patient month of follow-up), whereas 602 patients without CDI were readmitted 642 times within the first 30 days after surgery (0.13 readmissions per patient month of follow-up). Over the entire 65-day follow up period, readmission rates were

TABLE 3. Infection timing for patients with *C difficile* infection (n = 50)

Timing	Value
<i>C difficile</i> onset	
Before index hospital discharge, n (%)	26 (52.0)
Time of onset, d, median (IQR)	17.0 (8.0-30.0)
Other infections, n (%)	
Major infection before <i>C difficile</i>	10 (20.0)
Minor infection before <i>C difficile</i>	6 (12.0)
Any infection (major or minor) before <i>C difficile</i>	14 (28.0)

IQR, Interquartile range.

FIGURE 3. Risk factors for *C. difficile* infections. Determined by using a multivariate proportional hazards regression model with death as a competing risk. ICU, Intensive care unit; CDI, *Clostridium difficile* infection.

0.23 per patient month of follow-up for patients with CDI, compared with 0.09 for those without CDI.

CDI and Mortality

Mortality during the 65-day follow-up period was higher in the patients with CDI compared with those without CDI (10.0% vs 1.8%; $P < .001$). In a proportional hazards regression model treating CDI as a time-dependent variable, CDI had a substantial impact on survival (HR, 5.449; 95% CI, 2.14-13.87). The model included non-*C. difficile* infection as a time-varying covariate (HR, 4.063; 95% CI, 2.49-6.62). The model also adjusted for male sex (HR, 0.535; 95% CI, 0.36-0.80), age (HR, 1.036; 95% CI, 1.02-1.05), baseline serum creatinine (HR, 1.20; 95% CI, 1.09-1.31), CHF (HR, 2.011; 95% CI, 1.34-3.02), and diabetes (HR, 1.569; 95% CI, 1.03-2.38), all of which were previously identified as predictors of mortality independent of CDI (Table 4).³⁷ The effect of CDI on survival for an average patient in the cohort (male, age 64, serum 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 SSIs and bloodstream infections,^{35,36} yet a recent large prospective cohort study identified CDI as the third most common major infection after pneumonia and bloodstream infections.³⁷ Most previous studies have focused on the first 30 days after surgery and/or the index hospitalization period because this is the time frame in which events are collected for national databases, such as the Premier Perspective Comparative database, the Nationwide Inpatient Sample database, and the Society of Thoracic Surgeons database.^{24,35,48}

TABLE 4. Impact of *C. difficile* infection on mortality

Variable	Hazard ratio	95% confidence interval	P value
<i>C. difficile</i> infection status*	5.449	(2.14-13.87)	.0004
Male sex	0.535	(0.36-0.8)	.0023
Age	1.036	(1.02-1.05)	<.0001
Creatinine, per mg/dL	1.199	(1.09-1.31)	.0001
Diabetes (yes/no)	1.569	(1.03-2.38)	.0350
Non- <i>C. difficile</i> infection status†	4.063	(2.49-6.62)	<.0001
Heart failure (yes/no)	2.011	(1.34-3.02)	.0007

**C. difficile* infection status is a time-varying covariate. †Non-*C. difficile* infection status is a time-varying covariate and refers to infection before the onset of *C. difficile* infection.

Recent results of an active surveillance study funded by the CDC's Emerging Infections Program showed that whereas the majority of CDI cases reported in the United States were related to health care exposure (ie, an inpatient or outpatient visit within 12 weeks before collection of a *C. difficile*-positive stool sample), only 24% of cases had an in-hospital onset.²⁵ Thus, the data from the CTSN infection study provide a unique opportunity to examine the incidence of CDI in the cardiac surgery population and to explore risk factors associated with its occurrence, as well as the relationship between CDI and adverse outcomes.

As would be expected based on the CDC surveillance results, in the present study, nearly one-half of all CDIs (48%) occurred after index hospital discharge, and 25% of all CDIs occurred after 30 days. This may explain why the frequency of CDI in this study (50 patients; 0.97%) was higher than the 0.21% to 0.75% reported from other 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. Thus, the diagnosis was not protocolized, but rather was determined according to standard clinical practice at each site.

Comorbidities have been frequently associated with the 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 preoperatively and more likely to have longer ICU LOS. Duration of ICU LOS and procedure were related; VAD and transplant recipients spent longer in the ICU than patients undergoing other procedures. Acute hyperglycemia was associated with an increased risk of CDI; however, whether hyperglycemia is indicative of a sicker, more vulnerable patient or if hyperglycemia in and of itself increases the risk of infection is unclear, particularly because diabetes was not associated with the risk of CDI and we did not observe a differential risk of hyperglycemia by diabetes.

We did not find a significantly higher incidence of CDI associated with older age, diabetes, increased body mass index, or COPD; with urgent or emergent procedure status; in women; or in Caucasian patients as has been observed in other studies.^{9,12,13,17} 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, our analysis may simply have 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, although it is worth noting that the incidence in both groups was 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} Because the present 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, given that 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 the index hospitalization or during a readmission hospitalization. Readmissions for CDI occurred in close proximity to hospital discharge, consistent with the CDC's surveillance study findings.

As was observed in other reports,^{1-4,6,8,9,12,17,21,32,50-52} CDI was associated with significantly increased mortality. This finding held after adjusting for age, sex, diabetes, CHF, baseline creatinine, and time-varying non-*C difficile* infection (HR, 5.449; 95% CI, 2.14-13.87; $P < .0004$). Mortality observed in patients with CDI in this cohort of cardiac surgery patients (10.0%) was comparable to the death rates from health care-associated CDI in surgical and nonsurgical patients in the United States 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 for adverse outcomes, we did not observe an increase in any major adverse cardiac or cerebrovascular events other than death (ie, myocardial infarction, cerebrovascular accident, or transient ischemic attack) at any point during the 65-day follow-up. A single case of cerebrovascular accident occurring after onset of CDI was the sole nonfatal reported adverse event among the 50 patients ever diagnosed with CDI.

The risk of CDI increases substantially with prolonged antibiotic exposure, because suppression of the bowel flora allows *C difficile* to flourish.⁵⁵ This effect is thought to be particularly pronounced with second-generation cephalosporins.⁵⁶ Antibiotic prophylaxis lasting ≤ 48 hours was protective against CDI, but antibiotic prophylaxis lasting ≥ 3 days was associated with higher risk of CDI regardless of type of antibiotic prophylaxis provided. We had anticipated that a previous postoperative infection would increase the risk of CDI, because the initial postoperative 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 an increased risk of CDI.

Although the type of antibiotic was significant in univariable analyses, with second-generation cephalosporins associated with a decreased risk of CDI, the finding did not hold in a multivariable model, possibly because the type of antibiotic was correlated with the duration of antibiotic treatment. This also may be related to the limited size of the study (50 patients with CDI). A recent analysis of 154,200 cardiac surgery patients in the Premier database showed an association between antibiotic prophylaxis with cephalosporin and decreased risk of CDI (although it did not distinguish between first- and second-generation cephalosporins).⁴⁹ That study also confirmed an increased risk of CDI with antibiotic prophylaxis that extended past 48 hours.

Limitations

In this cohort of more than 5000 patients, the number of patients with CDI was low, limiting this study's statistical power. CDI was potentially underreported, 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 (ie, nucleic acid amplification test vs other methods). However, the study was designed to capture all postoperative infections, all events were reviewed and adjudicated by an Event Adjudication Committee of infectious disease experts, and follow-up through the end of the study was 98% complete. Given the thoroughness of data capture and the fact that the reported incidence in this study was higher than that in other studies,^{1,2,4,13} we believe the likelihood of bias due to underreporting is low.

Medications other than prophylactic antibiotics were not captured in the database, which precluded an analysis of antibiotics administered for other infections occurring before CDI. It also precluded an analysis of medications, such as proton pump inhibitors, that have been previously identified as risk factors for CDI.^{48,57} However, other infections, serious or not serious (before the onset of CDI

in patients with CDI), were not associated with an increased risk of CDI.

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

Finally, the data on excess LOS due to CDI should be interpreted with caution, because these data do not take into account other potentially informative covariates (eg, index surgical procedure). Because this study was designed to focus on management practices and infection, other complications and adverse events were not collected, and these variables may have affected LOS overall or in the ICU.

CONCLUSIONS

CDI is a common infection following cardiac surgery and is associated with significant increases in LOS and mortality. Despite intense efforts to reduce the incidence of health care–associated infections, opportunities to improve adherence to quality improvement measures remain, 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 those 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, because onset frequently occurs more than 2 weeks after surgery.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: *Clostridium difficile* infection, cardiac surgery, antibiotic prophylaxis

APPENDIX E1. CTSN INVESTIGATORS

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