Analysis of *Clostridium difficile* infections after cardiac surgery: Epidemiologic and economic implications from national data

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Objectives: *Clostridium difficile* infections (CDIs) have increased during the past 2 decades, especially among cardiac surgical patients, who share many of the comorbidity risk factors for CDI. Our objectives were to use a large national database to identify the regional-, hospital-, patient-, and procedure-level risk factors for CDI; and determine mortality, resource usage, and cost of CDIs in cardiac surgery.

Methods: Using the Nationwide Inpatient Sample database, we identified 349,122 patients who had undergone coronary artery bypass, valve, or thoracic-aortic surgery from 2004 to 2008. Of these, 2581 (0.75%) had been diagnosed with CDI. Multivariable regression analysis and the propensity method were used for risk adjustment.

Results: Compared with the West, CDIs were more likely to occur in the Northeast (odds ratio [OR], 1.28; 95% confidence interval [CI], 1.12-1.47) and Midwest (OR, 1.27, 95% CI, 1.11-1.46) and less likely in the South (OR, 0.80; 95% CI, 0.70-0.90). Medium-size hospitals (OR, 0.88; 95% CI, 0.78-0.99) had a lower risk of CDI than did large hospitals. Older age (>75 years; OR, 2.59; 95% CI, 1.93-3.49), longer preoperative length of stay (OR, 1.51; 95% CI, 1.43-1.60), Medicare (OR, 1.21; 95% CI, 1.05-1.39) and Medicaid (OR, 1.60; 95% CI, 1.31-1.96) coverage, and more comorbidities were associated with CDI. Among the matched pairs, patients with CDIs had greater mortality (302 [12%] vs 187 [7.2%], $P < .001$), a longer median length of stay (21 vs 11 days, $P < .001$), and greater median hospital charges (\$193,330 vs \$112,245, $P < .001$). The cumulative incremental cost of CDIs was an estimated \$212 million annually.

Conclusions: Our results have shown that CDI is associated with increased morbidity and resource usage. Additional work is needed to better understand the complex interplay among regional-, hospital-, and patient-level factors. (J Thorac Cardiovasc Surg 2014;148:2404-9)

Clostridium difficile infections (CDIs) are increasing at an alarming rate within many hospitalized patient populations, with a parallel increase in the severity of complications, likely because of more virulent strains of the disease.¹⁻⁴ Patients undergoing cardiac surgical procedures share many of the same demographic and comorbidity risk factors associated with an increased risk of CDI. Although population-based studies have clearly documented the poor outcomes of hospitalized patients with CDI in the absence of any surgical procedures, large-scale

epidemiologic data on the morbidity and mortality from secondary development of CDIs after cardiac surgery are lacking.

Previous studies have documented the significantly worse outcomes of patients with CDI in the inpatient surgical setting⁵ and in liver⁶ and solid-organ⁷ transplantation populations. A retrospective study of cardiac surgical patients reported that a longer duration of intensive care unit stay was associated with CDI but not greater mortality.⁸ Because that report was derived solely from the results of 2 large tertiary referral centers in the South, it might not be applicable to the nationwide cardiac surgical population and might not provide an accurate description of patient outcomes in other care settings.

Our objectives were to use a US-derived, nationwide, population-based database to identify the regional-, hospital-, patient-, and procedure-level risk factors for CDIs and determine the excess attributable mortality, resource usage, and cost of CDIs in cardiac surgical patients.

METHODS

Data

An institutional review board-exempt, 5-year period assessment of the Nationwide Inpatient Sample (NIS) Healthcare Cost and Utilization Project database was conducted for 2004 through 2008. The NIS is the largest

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Abbreviations and Acronyms

CDI	= <i>Clostridium difficile</i> infection
CI	= confidence interval
ICD-9-CM	= “International Classification of Diseases, Ninth Revision, Clinical Modification”
NIS	= Nationwide Inpatient Sample
OR	= odds ratio

all-payer inpatient discharge database. The patients include a 20% stratified sample of all discharges occurring in a given year from approximately 1000 hospitals in 32 to 37 states (depending on the year of the study). The database contains information on about 8 million discharges annually. Individual entries in the database contain information on demographics, comorbidity, hospital charges, length of stay, procedures, outcomes, and discharge. Discharge weights are provided, which allow extraction of nation-level estimates from the unweighted database information.

Population

The population consisted of 349,122 patients who had undergone cardiac surgical procedures from 2004 to 2008 (this sample extrapolates to 1,709,770 cardiac surgical procedures in the entire US population). The most common procedures performed were coronary artery bypass grafting ($n = 246,174$ [71%]; codes 36.10-36.17, 36.19), isolated valve repair or replacement ($n = 53,933$ [15%]; codes 35.10-35.14, 35.20-35.28), isolated thoracic aneurysm repair ($n = 4145$ [1.2%]; code 38.45), or any combination of these procedures ($n = 44,870$ [13%]). Catheterizations and pacemaker implantations were excluded from the analysis. We examined the demographics and clinical characteristics, primary payer, preoperative comorbidities, surgical procedures, and treating hospital characteristics, such as hospital bed size, teaching status, and regional location, and correlated these with CDI status. The database entries containing “International Classification of Diseases, Ninth Revision, Clinical Modification” (ICD-9-CM) codes matching these procedures were extracted from the database for patients aged 18 to 100 years. The main exposure of interest was the presence of CDI during admission and was identified by the secondary diagnostic codes (ICD-9-CM code 008.45). The use of ICD-9-CM codes to identify patients with CDI has been validated in other studies, with good accuracy demonstrated.^{9,10}

Outcomes

Our outcomes of interest included hospital mortality, total hospital charges, total costs, length of stay, and discharge disposition. The need for a colectomy procedure was also determined in patients who developed CDI. Colectomy was defined as the presence of 1 of the following ICD-9-CM procedure codes: 45.72 to 45.76, 45.79, or 45.8.¹¹ The categories of disposition were routine discharge, transferred to another inpatient facility, transfer to another type of facility, and home healthcare. Total charges represented the amount hospitals billed for services and did not include professional fees. Total costs were derived from the total charges using a cost-to-charge ratio created by the Healthcare Cost and Utilization Project in accordance with accounting reports from the Centers for Medicare and Medicaid Services.¹² Hospital costs will tend to better estimate resource use, because hospital charges often reflect payer policies and other factors unrelated to resource use. The cost was calculated by multiplying the total charges by the hospital-specific cost-to-charge ratio. The costs were adjusted for inflation and converted to 2008 dollars using the appropriate Consumer Price Index.

Covariables

We considered the demographics, comorbidities, insurance status, hospital characteristics, and region in which the procedures had been performed. The patient-level variables included age, gender, race, and insurance status. Race/ethnicity was categorized as white, black, Hispanic, and other/missing. Certain states do not document race on discharge records; thus, race data were missing for approximately 25% of the study population. Insurance status was categorized as Medicare, Medicaid, private insurance, uninsured, and other according to the primary payer listed on the discharge record. The comorbidities for risk adjustment were derived from the secondary ICD-9-CM diagnosis codes using the Deyo modification of the Charlson comorbidity index.^{13,14} A hospital was considered a teaching hospital if it had an American Medical Association–approved residency program, was a member of the Council of Teaching Hospitals, or had a ratio of full-time equivalent interns and residents to beds of ≥ 0.25 . The hospital region was classified by the US Census Bureau as Northeast, Midwest, South, or West. The hospital bed size was classified as small, medium, or large, using an algorithm developed by the Healthcare Cost and Utilization Project. The surgical procedure was categorized as coronary artery bypass grafting, isolated valve repair or replacement, isolated aneurysm repair, or a combination of ≥ 2 of these.

Statistical Analysis

The mean, median, and standard deviation were calculated for all continuous outcomes, and frequency counts and percentages were used for categorical outcomes. Appropriate statistical tests were used for the categorical (chi-square test) and continuous (Student *t* test) outcomes to compare the unadjusted differences by CDI status. All data included in the present study were unweighted data from the NIS database.

Matching and Outcomes

Propensity scores, or the conditional probability of having CDI, were estimated for each subject using a multivariable logistic regression model in which the presence of CDI was the dependent variable and patient demographics, payer status, comorbidities, hospital characteristics, and procedure type were the independent variables.¹⁵ The purpose of the propensity score was to balance the covariables for patients with and without CDI to assess the outcomes without influence from known factors.¹⁶ To match those with and without CDI, we used a 1:1 greedy matching algorithm with a caliper of 0.2 times the standard deviation of the linear propensity score.¹⁷ The balance of covariables before and after matching was assessed by calculating the standardized differences between those with and without CDI.¹⁸ We also performed chi-square tests for all covariables before matching and used McNemar’s test in the matched sample. Propensity matching resulted in 2850 well-matched CDI and non-CDI patient pairs with respect to demographics, comorbidities, surgical procedures, and institutional characteristics (ie, region, teaching status; Table 1 and Figure 1).

All analyses were performed using the Statistical Analysis Systems for Unix, version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS**CDI Prevalence**

Of the 349,122 discharge records included in our study, 2581 patients (0.75%) had acquired CDI during their hospital stay. The rate of CDI increased from 5.7 to 8.2 cases/1000 patients from 2004 to 2008, peaking during 2007 at 8.4 cases/1000 patients. Patients with and without CDI differed in a number of baseline factors (Figure 1).

TABLE 1. Distribution of baseline characteristics for propensity-matched patients with and without *Clostridium difficile* infection

Characteristic	CDI (n = 2580)	No CDI (n = 2580)	P value
Age group (y)			.7
0-44	70 (2.7)	65 (2.5)	
45-54	203 (7.9)	183 (7.1)	
55-64	425 (16)	405 (16)	
65-74	814 (32)	840 (33)	
≥75	1068 (41)	1087 (42)	
Gender			.8
Male	1549 (60)	1556 (60)	
Female	1031 (40)	1024 (40)	
Race or ethnicity			.8
White	1594 (62)	1624 (63)	
Black	154 (6.0)	141 (5.5)	
Hispanic	130 (5.0)	133 (5.2)	
Other or missing	702 (27)	682 (26)	
Primary payer			.5
Medicare	1788 (70)	1829 (71)	
Medicaid	148 (5.7)	121 (4.7)	
Private	522 (20)	510 (20)	
Uninsured	54 (2.1)	51 (2.0)	
Other	68 (2.6)	69 (2.7)	
Comorbidities			
Myocardial infarction	912 (35)	896 (35)	.6
Heart failure	1129 (44)	1158 (45)	.4
Peripheral arterial disease	261 (11)	259 (10)	.9
Cerebrovascular disease	262 (10)	230 (8.9)	.13
COPD	698 (27)	718 (28)	.5
Rheumatoid disease	32 (1.2)	29 (1.1)	.7
Peptic ulcer disease	45 (1.7)	38 (1.5)	.4
Mild liver disease	11 (0)	7 (0)	.3
Diabetes	448 (17)	442 (17)	.8
Diabetes and complications	105 (4.1)	103 (4.0)	.9
Hemiplegia or paraplegia	36 (1.4)	32 (1.2)	.6
Renal disease	338 (13)	340 (13)	>.9
Cancer	63 (2.4)	62 (2.4)	>.9
Moderate to severe liver disease	12 (0)	6 (0)	.16
AIDS	9 (0)	6 (0)	.4
Surgical procedure			
Isolated CABG	1461 (57)	1488 (58)	.4
Isolated valve repair	518 (20)	492 (19)	.4
Isolated aneurysm repair	76 (2.9)	69 (2.7)	.6
Combination surgery	525 (20)	531 (21)	.8
Hospital characteristics			
Region			.8
Northeast	719 (28)	719 (28)	
Midwest	626 (24)	611 (24)	
South	798 (31)	829 (32)	
West	437 (17)	421 (16)	
Teaching status			>.9
Teaching	1738 (67)	1737 (67)	
Nonteaching	842 (33)	843 (33)	
Hospital bed size			.3
Small	171 (7)	149 (5.8)	
Medium	412 (16)	392 (15)	
Large	1997 (77)	2039 (79)	

Data presented as n (%). CDI, *Clostridium difficile* infection; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting; AIDS, acquired immunodeficiency syndrome.

CDI Predictors

We found a number of predictors of CDI in the cardiac surgical setting. Regional differences were present, with a greater incidence of CDI in the Northeast (odds ratio [OR], 1.28; 95% confidence interval [CI], 1.12-1.47) and Midwest (OR, 1.27; 95% CI, 1.11-1.46) than in the South and a greater risk in teaching hospitals (OR, 1.14; 95% CI, 1.04-1.26). Patients with Medicare and Medicaid insurance had greater odds of developing CDI (OR, 1.21; 95% CI, 1.05-1.39; and OR, 1.60; 95% CI, 1.31-1.96; respectively) than patients with private insurance. Of the surgical procedures, patients who had undergone isolated coronary artery bypass grafting were less likely to develop CDI (OR, 0.69; 95% CI, 0.61-0.78) than those undergoing other procedures. Most cardiac surgical procedures were performed in large (urban hospitals with ≥325-450 beds; two thirds of patients were treated in teaching hospitals; [Table 2](#)).

Patient demographics such as older age, female gender, longer preoperative hospital length of stay, and greater comorbidity burden (eg, heart failure, chronic obstructive pulmonary disease, acute myocardial infarction, and liver disease) were associated with an increased prevalence of CDI. Other factors that increased the risk included emergency surgery and hospital transfers ([Table 2](#)).

Matching and Outcomes

Patients with and without CDI had a high comorbidity burden, which is common in those undergoing cardiac surgical procedures. Unadjusted outcomes are presented in [Table 3](#). The propensity-adjusted outcomes for these patients are listed in [Table 4](#). The median length of stay for those who developed CDI was nearly double that of those who did not (21 vs 11 days, $P < .001$), hospital mortality was significantly greater (n = 302 [12%] vs n = 187 [7.2%], $P < .001$), and the total median charges (\$193,330 vs \$112,245, $P < .001$) and hospital costs (\$65,809 vs \$39,094, $P < .001$) were greater. Among the patients with CDI, 69 (2.7%) required subsequent colectomy during the same hospital stay. Also, significant differences were found in the discharge disposition, with the patients with CDI more commonly transferred to other inpatient care facilities (n = 1246 [48%] vs 775 [15%], $P < .001$, respectively).

For all cardiac surgical patients in the United States, the incremental average cost annually for CDI was estimated at ≥\$212 million according to the weighted estimate of patients with CDI (n = 12,772 [0.75%]) for the 5-year period ([Table 5](#)).

DISCUSSION

We report the regional-, local-, and patient-specific variation in the risk of developing CDI after cardiac surgical

FIGURE 1. Covariance balance plot for patients with and without *Clostridium difficile* infections before and after propensity matching. LOS, Length of stay; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; AIDS, acquired immunodeficiency syndrome.

procedures. For those who acquired CDI, mortality was increased, the associated costs of care were greater, and the need for more intensive services in the follow-up period was greater. Our findings of regional and local variation in the occurrence of CDI, with a heightened risk for procedures performed in the Northeast and Midwest and in large, urban, and/or teaching hospitals, suggest the need for more intense examination of regional practices and an opportunity for process improvement.

A recent large hospital-based study in Barcelona, Spain, found risk factors for CDI consistent with our results. That epidemiologic study, which examined 365 episodes of CDI, found significant risk associated with advanced patient age and a high comorbidity score.¹⁹ Previous studies have found links between CDI and mortality and morbidity in scenarios other than cardiac surgery. In a study using NIS data to examine patients who had undergone liver transplantation from 2004 to 2008, Ali and colleagues⁶ identified CDI as an independent risk factor for mortality. Again, comorbidities and advanced patient age were risk factors for CDI.

Another NIS database study by Pant and colleagues⁷ in a solid-organ transplant population reported increased mortality, length of stay, and hospital charges for patients who developed CDI.

In contrast to our investigation, a 2007 study by Crabtree and colleagues⁸ found similar risk factors for CDI in cardiac surgical patients but no increase in 30-day mortality. Similarly, a study involving 151 lung transplant recipients did not identify a significant increase in mortality or any significant risk factors for the 7 patients who had developed CDI during their initial hospitalization.²⁰

In addition to patient health burden, the economic burden of CDI on cardiac surgical patients is great, with an estimated cumulative incremental cost of \$212 million annually. An important aspect of our findings was the large incremental cost of CDI to patients undergoing cardiac surgery. Zerey and colleagues⁵ analyzed all inpatient records in the NIS from 1999 to 2003 and made a related observation, finding a mean \$77,483 increase in total hospital charges for patients with CDI.

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TABLE 2. Predictors of acquiring postoperative *Clostridium difficile* infection

Variable	Adjusted OR (95% CI)
Age group (y)	
0-44	Referent
45-54	1.19 (0.88-1.62)
55-64	1.41 (1.06-1.88)
65-74	2.03 (1.51-2.72)
≥75	2.59 (1.93-3.49)
Female gender	1.18 (1.08-1.29)
Nontransfers	0.85 (0.76-0.94)
Elective	0.78 (0.71-0.87)
Preoperative length of stay	1.51 (1.43-1.60)
Race or ethnicity	
White	Referent
Black	1.16 (0.96-1.39)
Hispanic	1.11 (0.92-1.34)
Other or missing	0.98 (0.88-1.09)
Primary payer	
Private	Referent
Medicare	1.21 (1.05-1.39)
Medicaid	1.60 (1.31-1.96)
Uninsured	1.00 (0.73-1.38)
Other	1.33 (1.01-1.77)
Comorbidities	
Myocardial infarction	1.13 (1.02-1.24)
Heart failure	1.76 (1.60-1.92)
Peripheral arterial disease	0.86 (0.73-1.01)
Cerebrovascular disease	1.15 (0.99-1.32)
Dementia	0.58 (0.14-2.34)
COPD	1.23 (1.12-1.36)
Rheumatoid disease	0.68 (0.45-1.02)
Peptic ulcer disease	1.47 (1.06-2.05)
Mild liver disease	0.79 (0.39-1.60)
Diabetes	0.64 (0.57-0.71)
Diabetes and complications	0.82 (0.66-1.02)
Hemiplegia or paraplegia	2.11 (1.40-3.19)
Renal disease	1.49 (1.30-1.71)
Cancer	1.29 (0.98-1.70)
Moderate to severe liver disease	3.47 (1.83-6.59)
AIDS	3.93 (1.90-8.11)
Surgical procedure	
Isolated CABG	0.69 (0.61-0.78)
Isolated valve repair	1.00 (0.87-1.15)
Isolated aneurysm repair	2.93 (2.17-3.95)
Hospital characteristics	
Region	
Northeast	1.28 (1.12-1.47)
Midwest	1.27 (1.11-1.46)
South	0.80 (0.70-0.90)
West	Referent
Teaching hospital	1.14 (1.04-1.26)
Hospital bed size	
Small	1.12 (0.95-1.32)
Medium	0.88 (0.78, 0.99)
Large	Referent

Total patients, 349,122; total cases of CDI, 2581. OR, Odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; AIDS, acquired immunodeficiency syndrome; CABG, coronary artery bypass grafting.

TABLE 3. Unadjusted outcomes for patients with and without *Clostridium difficile* infection

Variable	CDI (n = 2581)	No CDI (n = 346,541)	P value
Median length of stay (d)	21	8	
Median total charges (US\$)	\$193,255	\$88,736	
Median total cost (US\$)	\$65,799	\$31,125	
Hospital mortality	302 (12)	11,220 (3.2)	<.0001
Discharge disposition			<.0001
Home healthcare	577 (22)	110,660 (32)	
Inpatient facility	1246 (48)	62,794 (18)	
Other transfer	306 (12)	11,532 (3.3)	
Routine/home transfer	447 (17)	161,264 (47)	

Data presented as n (%), unless otherwise noted. CDI, *Clostridium difficile* infection.

Study Limitations

We recognize that our study had several limitations. The present study made use of a large administrative database with the potential for under- or overdiagnosis and coding errors. The incidence of CDI might have been underestimated, because data in the NIS database is limited to a patient's hospital stay. CDI could certainly have been diagnosed after a patient's discharge. The results of toxin assays and other tests used to diagnose CDI are unavailable in the NIS, and the coding does not differentiate hospital-acquired CDI from preoperative CDI. Nonetheless, several studies have confirmed that ICD-9-CM codes can be an acceptable surrogate to track CDI, with a pooled estimated positive predictive value of 87% and negative predictive value of 99.7%.²¹ Although Dubberke and colleagues¹⁰ have found that the use of the CDI ICD-9-CM code without the "present on admission" flag cannot distinguish between hospital-acquired from community-acquired disease states, we believe that the rate of community-acquired CDI in the cardiac surgery population will be very low because the presence of CDI would likely postpone cardiac surgery in most instances. The duration of antibiotic use is an important risk factor for the development of CDI, but the NIS does not provide data on antibiotic type or duration of use. Although we were able to perform a robust risk

TABLE 4. Risk-adjusted outcomes among propensity-matched pairs

Variable	CDI (n = 2580)	No CDI (n = 2580)	P value
Median length of stay (d)	21	11	<.001
Median total charges (US\$)	\$193,330	\$112,245	<.001
Median total cost (US\$)	\$65,809	\$39,094	<.001
Mortality	302 (12)	187 (7.2)	<.001
Disposition			<.001
Home healthcare	577 (22)	836 (32)	
Inpatient facility	1246 (48)	775 (15)	
Other transfer	309 (12)	189 (7.3)	
Routine or home transfer	446 (17)	778 (30)	

Data presented as n (%), unless otherwise noted. CDI, *Clostridium difficile* infection.

TABLE 5. Total and average cost annually for cardiac surgical patients with *Clostridium difficile* infection

Year	Total cost (US\$)	Median cost (US\$)	15th-85th percentile
2004	\$145,069,123	\$57,861	\$30,587-120,679
2005	\$203,069,363	\$63,660	\$34,244-137,653
2006	\$217,922,600	\$61,398	\$32,244-129,781
2007	\$234,752,447	\$70,147	\$37,626-151,942
2008	\$262,275,350	\$76,875	\$39,915-164,819
2004-2008	\$1,063,088,883	—	—
Average annual cost	\$212,617,777	—	—

adjustment using the Deyo modification of the Charlson comorbidity index, certain key covariates such as the degree of frailty and severity of comorbidities are not available in the NIS. Despite these limitations, our study leveraged the large number of patients in the NIS database to evaluate the association of CDI with the outcomes in cardiac surgery patients, controlling for potential confounding variables, including demographics, comorbidities, institution, and payer.

CONCLUSIONS

Our findings suggest that location is an important factor in the development of CDI. Variations in the prevalence of CDI both regionally and locally suggest an opportunity for process improvement in high-risk locations. The occurrence of CDI infections is also related to patient characteristics and is associated with greater mortality and increased resource usage in the cardiac surgical setting. Additional work is needed to better understand the transmission of CDI, the role of potentially modifiable risk factors, and the key features specific to regional hospitals that appear to increase the risk.

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