Clostridium difficile infection after cardiac surgery: Prevalence, morbidity, mortality, and resource utilization

Suresh Keshavamurthy, MBBS, MS,[a] Colleen G. Koch, MD, MS, MBA,[b,c] Thomas G. Fraser, MD,[c,d] Steven M. Gordon, MD,[d] Penny L. Houghtaling, MS,[e] Edward G. Soltesz, MD, MPH,[a] Eugene H. Blackstone, MD,[a,e] and Gösta B. Pettersson, MD, PhD[a]

Objective: Despite increasing efforts to prevent infection, the prevalence of hospital-associated *Clostridium difficile* infections (CDI) is increasing. Heightened awareness prompted this study of the prevalence and morbidity associated with CDI after cardiac surgery.

Methods: A total of 22,952 patients underwent cardiac surgery at Cleveland Clinic from January 2005 to January 2011. CDI was diagnosed by enzyme immunoassay for toxins and, more recently, polymerase chain reaction (PCR) testing. Hospital outcomes and long-term survival were compared with those of the remaining population in propensity-matched groups.

Results: One hundred forty-five patients (0.63%) tested positive for CDI at a median of 9 days postoperatively, 135 by enzyme immunoassay and 11 by PCR. Its prevalence more than doubled over the study period. Seventy-seven patients (48%) were transfers from outside hospitals. Seventy-three patients (50%) were exposed preoperatively to antibiotics and 79 (56%) to proton-pump inhibitors. Patients with CDI had more baseline co-morbidities, more reoperations, and received more blood products than patients who did not have CDI. Presenting symptoms included diarrhea (107; 75%), distended abdomen (48; 34%), and abdominal pain (27; 19%). All were treated with metronidazole or vancomycin. Sixteen patients (11%) died in hospital, including 5 of 10 who developed toxic colitis; 3 of 4 undergoing total colectomy survived. Among matched patients, those with CDI had more septicemia ($P < .0001$), renal failure ($P = .0002$), reoperations ($P < .0001$), prolonged postoperative ventilation ($P < .0001$), longer hospital stay ($P < .0001$), and lower 3-year survival, 52% versus 64% ($P = .03$), than patients who did not have CDI.

Conclusions: Although rare, the prevalence of CDI is increasing, contributing importantly to morbidity and mortality after cardiac surgery. If toxic colitis develops, mortality is high, but colectomy may be lifesaving. (J Thorac Cardiovasc Surg 2014;148:3157-65)

⌒ Supplemental material is available online.

Clostridium difficile infection (CDI), caused by a gram-positive, spore-forming anaerobic bacillus, is the primary cause of health care–associated diarrhea,[1,2] and in a study sponsored by the National Institutes of Health, CDI was found to be the third most common infection occurring in the 65 days after cardiac surgery.[3] It is linked to increasing use of antibiotics, yet despite national and global initiatives over the last decade for appropriate antibiotic stewardship, the occurrence of CDI has increased 300% since 1993.[2] Reports of a more virulent strain of CDI,[4-7] associated patient morbidity and mortality, and increased resource utilization have further heightened awareness of this complication.[2,8,9]

Our objectives were to (1) determine the prevalence of hospital-acquired CDI after cardiac surgery in our institution, (2) identify patient characteristics and clinical manifestations associated with CDI and its treatment strategies, and (3) assess morbidity and mortality among patients with CDI.

PATIENTS AND METHODS
Patients

From January 2005 to January 2011, 22,952 adults underwent cardiac surgery at Cleveland Clinic. Baseline demographics, comorbidities, and perioperative variables were obtained from the Heart and Vascular Institute's Cardiovascular Information Registry (CVIR). Additional information on perioperative antibiotic use, presenting symptoms, and subsequent treatment of patients diagnosed with CDI was obtained from patient medical records and recorded in a REDCap database.[10] Cleveland Clinic's Institutional Review Board approved the use of these data for research; patient consent was waived.

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FIGURE 1. Occurrence of in-hospital *Clostridium difficile* infection (*CDI*) after cardiac surgery.

Diagnosis of CDI

CDI was diagnosed by a combination of symptoms and laboratory testing, supplemented in some cases by colonoscopy and laparotomy. These clinically diagnosed cases were entered prospectively into Cleveland Clinic's Infection Prevention surveillance registry. Before the 2nd quarter of 2009, an internal definition of hospital-acquired CDI was used that required a positive enzyme immunoassay (EIA) with onset of diarrhea more than 72 hours after admission or within 72 hours of discharge, or the development of pseudomembranous colitis or toxic megacolon more than 72 hours after admission. Currently, surveillance for hospital-acquired CDI is routinely performed prospectively using standard definitions.[11] Beginning in October 2010, the hospital's testing platform for CDI changed from an EIA to a polymerase chain reaction (PCR)–based one. In this study, the diagnosis was made by EIA in 135 patients and by PCR in 11. Our yearly incidence density of CDI in the entire hospital from 2006 through 2013 ranged from 6.1 to 11.9 per 10,000 patient-days (Table E1).

End Points

End points included general complications of cardiac surgery, defined as for the Society of Thoracic Surgeons National Database (see http://www. ctsnet.org/filerptDataSpecifications252_1_ForVendorsPGS.pdf), hospital death, and length of postoperative stay. In addition, specific gastrointestinal symptoms and signs of CDI, including operations performed for CDI complications and their outcome and time-related mortality, were recorded and tabulated for patients with CDI.

Follow-up for death was obtained through the CVIR, supplemented with information from the Social Security Death Master File, queried on October 27, 2011, before its demise in November 2011.[12,13] A lag time of 6 months resulted in a common closing date of April 27, 2011. Median follow-up for all patients was 2.5 years, with 25% of patients followed for more than 4.3 years and 10% more than 5.5 years; 182 patient-years of data were available for analysis in the CDI group. Median follow-up among CDI survivors was 1.4 years, with 25% followed for more than 2.5 years and 10% for more than 3.2 years.

Data Analysis

Data analysis consisted of describing the prevalence of CDI and identifying its incremental risk factors, then using this information as a basis for propensity-matched comparison of hospital outcomes and long-term survival. All analyses were performed using SAS statistical software (SAS version 9.2; SAS Institute, Inc, Cary, NC).

Prevalence of CDI. Cumulative distribution and probability density functions were used to describe temporal data related to CDI. The instantaneous risk of CDI after cardiac surgery was estimated by a multiphase hazard model[14] in order to determine if risk increased with increasing length of stay.

Risk factors for CDI. Multivariable logistic regression analysis was used to identify patient characteristics associated with CDI. Variable selection from potential risk factors listed in Appendix E1 was by bootstrap aggregation,[15,16] using 500 bootstrap samples, automated stepwise regression, and a *P* value retention criterion of .05. Thereafter, results
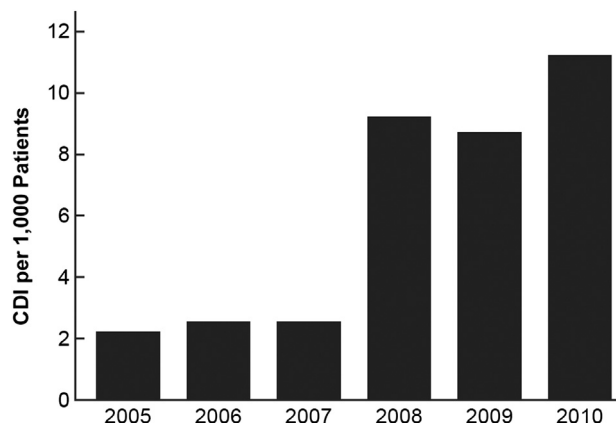
were aggregated, and risk factors identified in 50% of analyses were used to form a parsimonious explanatory model.

This parsimonious model was augmented with preoperative and intraoperative variables representing patient demography, symptoms, cardiac and noncardiac comorbidities, procedures, and support, to form a semisaturated model (see variables so identified in Appendix E1).

Propensity score development. A propensity score was calculated for each patient by solving the saturated model for the probability of being in the CDI group.[17-19] Then, using only the propensity score, patients who did not have CDI were matched 3 to 1 with patients with CDI using a greedy matching strategy.[20] All patients with CDI were matched. Figure E1 demonstrates that the resulting propensity-matched CDI and non-CDI groups were well matched.

Comparison of hospital outcomes. Group comparisons were made using the Wilcoxon rank sum test for continuous data and the χ^2 test for categorical data (or Fisher exact test when appropriate).

Time-related mortality. Because patients must survive to manifest CDI, death and CDI are of necessity competing risks. Thus, among matched patients, life tables were constructed with all at risk of death initially, with CDI patients censored at the time of diagnosis. Survival of patients with CDI was then estimated from the date of diagnosis. Nonparametric actuarial survival estimates were obtained using the Kaplan-Meier method. A parametric method was used to resolve the number of phases of instantaneous risk of death (hazard function) and to estimate shaping parameters.[14] (For additional details, see www.lerner.ccf.org/qhs/software/hazard.)

Presentation of Data

Continuous variables are summarized as the mean ± standard deviation and as equivalent 15th, 50th (median), and 85th percentiles when distributions were skewed. Categorical data are summarized by frequencies and percentages. Uncertainty is expressed by confidence limits equivalent to ± 1 standard error (68%).

RESULTS

Prevalence and Incidence of CDI

A total of 145 patients (0.63%) developed symptomatic CDI after cardiac surgery. Its prevalence increased from 2.2 per 1000 patients in 2005 to 11.2 per 1000 patients in 2010 (Figure 1). Median time from surgery to diagnosis was 9 days (15th and 85th percentiles, 4 and 22 days,
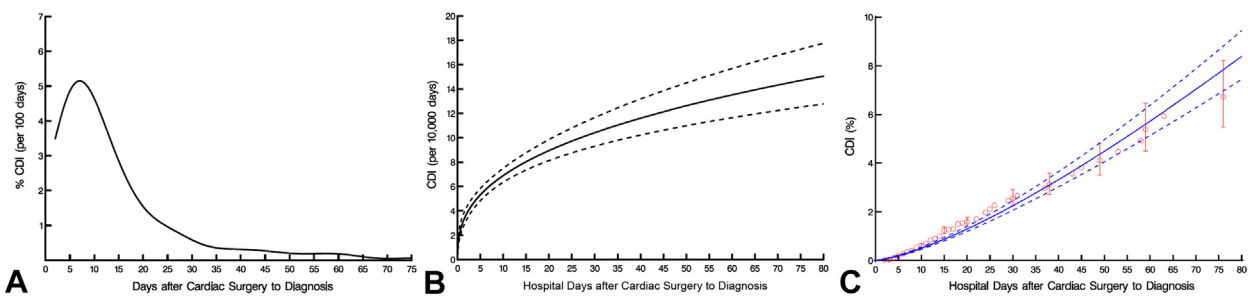
FIGURE 2. Characterization of onset of *Clostridium difficile* infection (*CDI*) after cardiac surgery. A, Distribution of the number of days between cardiac surgery and diagnosis. B, Instantaneous in-hospital risk of CDI after cardiac surgery. *Solid line* is parametric hazard enclosed within a dashed 68% confidence band equivalent to ±1 standard error (SE). C, Occurrence of CDI. Each *symbol* represents a diagnosis positioned on the vertical axis by the Kaplan-Meier estimator, and *vertical bars* are confidence limits equivalent to ±1 standard error. *Solid line* is parametric prevalence enclosed within a dashed 68% confidence band equivalent to ±1 SE.

respectively; range, 2-76 days) (Figure 2, A). However, when the competing risk of hospital discharge was accounted for, the incidence rose rapidly in the first few days after surgery, followed by a continued, but lower level, steady increase among patients with prolonged hospitalization (Figure 2, B). This resulted in an estimated in-hospital prevalence of 0.3% by 7 days, 2.6% by 30 days, and 5.5% by 60 days (Figure 2, C). Median time from peak white blood cell count to CDI diagnosis was 3 days (15th and 85th percentiles, 0 and 15 days, respectively; range, 0-70 days) (Figure E2).

Characterization of Patients With CDI

Seventy of the 145 patients with CDI (48%) were transfers from outside hospitals, with a Cleveland Clinic median preoperative stay of 7 days before surgery (Table 1). Forty-five patients were hospitalized only at Cleveland Clinic before surgery, with a median preoperative stay of 6 days, but 30 had been admitted on the day of surgery. Nine had undergone a colonoscopy for anemia or gastrointestinal symptoms before surgery.

Seventy-three patients had received preoperative antibiotic treatment for reasons varying from routine dental treatment, urinary tract infection, and respiratory infection to endocarditis. Seventy-nine were on proton-pump inhibitors, and 14 were on steroids.

After the heart operation, most patients had a complicated course. A quarter underwent reoperation for bleeding; 131 required inotropic support, and 61 needed a vasopressor. Many required extension of antibiotics beyond the 3 standard doses used for routine prophylaxis, and 96 were started on a new postoperative antibiotic drug for suspected or verified infections, including pneumonia, endocarditis, and wound infections (Table 2). Colonoscopy was required in 4 patients, 2 of whom demonstrated ischemia.

Presenting Symptoms

The presenting symptoms of CDI were diarrhea in 107 patients, distended abdomen in 48, and abdominal pain in 27 (see Table 1). Forty-eight patients underwent a computed tomography scan of the abdomen, and 8.5% had radiologic evidence of colitis, with 6 meeting criteria for pancolitis.

Risk Factors for CDI

Compared with patients who did not have CDI, those with CDI were older, more symptomatic, and had more comorbidities, such as heart failure, treated diabetes, chronic obstructive pulmonary disease, previous stroke, higher preoperative creatinine level, and lower preoperative hematocrit, and they were more likely to have been hospital transfers (Tables 2 and 3). Surgically, they had longer operative times, longer cardiopulmonary bypass times, and received more blood products.

Treatment

All 145 patients with CDI were treated with oral or intravenous metronidazole, oral vancomycin, or both (oral metronidazole, 117; intravenous metronidazole, 70; and oral vancomycin, 66; Table 1). Colonoscopy was performed in 9 patients, primarily for bleeding; 3 were reported to have normal results. A clinical picture of toxic colitis developed in 10; 2 were considered inoperable, 1 declined surgery (survived), and 7 underwent emergency laparotomy, with total colectomy in 4 (3 survived), limited resection with stoma in 1 (died), and exploration only in 2 (1 survived; the other died).

Outcomes

Patients with CDI had substantially more postoperative complications than matched patients without CDI, including strokes, reoperations for bleeding, valve dysfunction, graft occlusion, and renal failure (Table 3). They also had more hospital-acquired infections other than CDI, such as deep sternal wound infections and septicemia. However, among matched patients, hospital outcomes differed primarily with respect to the presence of septicemia, requirement for prolonged ventilation, renal failure, and

TABLE 1. Patient, procedure, and treatment characteristics of patients before and after developing _Clostridium difficile_ infections (N = 145)

Characteristic	No. of patients with data available	No. (%)
Preoperative		
History of CDI	145	5 (3.4)
Hospital transfer	145	67 (46)
In ICU before surgery	145	48 (33)
Preoperative antibiotic	145	72 (50)
Reason for antibiotic	72	
Urinary tract infection		16 (22)
Respiratory infection		16 (22)
Endocarditis		13 (18)
Dental treatment		8 (11)
Other infection		19 (26)
Proton-pump inhibitor	145	81 (56)
Steroids	145	15 (10)
Immunosuppression (other)	145	7 (4.8)
Bowel preparation within 30 d of surgery	145	15 (10)
Nasogastric tube	145	3 (2.0)
Previous abdominal surgery	145	57 (39)
History of IBD	145	8 (5.5)
Colonoscopy	145	9 (6.2)
Normal		3 (33)
Diverticulosis		4 (44)
Bleeding rectal ulcer		1 (11)
Suspected ischemia		1 (11)
Peri- and postoperative (before CDI diagnosis)		
Prophylactic antibiotic extended after 3 doses	145	32 (22)
New postoperative antibiotic	145	96 (66)
Reason for antibiotics	96	
High white blood cell count		71 (74)
Fever		36 (38)
Pneumonia		32 (33)
Reoperation for bleeding		23 (24)
Wound infection		14 (15)
Endocarditis		13 (13)
Other		40 (42)
Inotrope	145	132 (91)
Vasopressor	145	62 (43)
Tracheostomy	145	41 (28)
Bleeding/reexploration	145	35 (24)
Colonoscopy	145	4 (2.8)
Ischemia		2 (50)
Polyp		1 (25)
Normal		1 (25)
Symptoms and diagnosis of CDI		
Diarrhea	145	109 (75)
Abdominal distension	145	49 (34)
Fever	145	47 (32)
Abdominal pain	145	27 (19)
CT scan	145	48 (33)
Colitis		14 (29)
Pancolitis		6 (13)

(Continued)

TABLE 1. Continued

Characteristic	No. of patients with data available	No. (%)
Free air		0 (0)
Distended bowel		13 (27)
Normal		15 (31)
Management of CDI		
Antibiotics*	145	145 (100)
Oral flagyl		117 (81)
Intravenous flagyl		70 (48)
Oral vancomycin		66 (46)
Colonoscopy	145	9 (6.2)
Colitis		2 (22)
Rectal ulcer		1 (11)
Diverticula and AVMs		1 (11)
AVMs		2 (22)
Normal or nonspecific		3 (44)
Surgery/laparotomy	145	7 (4.8)
Limited bowel resection with stoma		1 (14)
Colectomy		4 (57)
Exploration		2 (29)
Microscopy (operative specimen)	145	5 (3.4)
Pseudomembranous colitis		3 (60)
Ischemic colitis		1 (20)
Cytomegalovirus		1 (20)

CDI, _Clostridium difficile_ infection; _ICU_, intensive care unit; _IBD_, inflammatory bowel disease; _CT_, computed tomography; _AVMs_, arteriovenous malformations. *Not mutually exclusive.

reoperation for bleeding. Resource utilization was high, as reflected in longer duration of postoperative ventilatory support, and longer stays in the intensive care unit and in hospital (Table 4). In-hospital mortality was higher among patients with CDI (11%), particularly if toxic colitis developed (50%, see earlier), but was similar among matched patients.

Survival after diagnosis of CDI at 30 days, 6 months, and 1, 2, and 3 years was 88%, 70%, 63%, 59%, and 52%, respectively (Figure E3). Survival among matched patients without CDI at the same intervals was 90%, 82%, 77%, 70%, and 64% ($P = .03$ by time-varying covariable analysis; Figure 3), with a prolonged higher risk of death for at least 6 months.

DISCUSSION
Prevalence and Incidence of CDI

We report an increasing prevalence of CDI that parallels national and global trends.[2] In part, this may reflect more sensitive testing, but the increase in prevalence was evident a year before PCR techniques supplanted EIA, and the increase was greater for patients undergoing cardiac surgery than for the hospital as a whole (Table E1).

Although time to diagnosis peaked at 6 to 7 days after surgery then decreased sharply, this does not take into

TABLE 2. Patient and procedure characteristics: before matching and matched groups

Variable	No CDI: before matching (n = 22,807)			CDI (n = 145)			No CDI: matched (n = 435)	
	No. of patients with data available	No. (%) or mean ± SD	P*	No. of patients with data available	No. (%) or mean ± SD	P†	No. of patients with data available	No. (%) or mean ± SD
Demographics								
Age (y)	22,807	63 ± 14	.001	145	67 ± 14	.7	435	67 ± 14
Female	22,807	7818 (34)	.15	145	58 (40)	>.9	435	174 (40)
Race	22,634			145			434	
White		20,145 (89)	.18		124 (86)	.6		379 (87)
Black		1425 (6.3)	.10		14 (9.7)	.6		36 (8.3)
Other		1064 (4.7)	>.9		7 (4.8)	.8		19 (4.4)
Body surface area (m²)	22,241	2.02 ± 0.28	.4	144	2.01 ± 0.29	.3	425	1.98 ± 0.28
Hospital transfer	22,671	4788 (21)	<.0001	145	70 (48)	.8	435	206 (47)
Symptoms								
NYHA functional class	22,588		<.0001	145		.8	434	
I		6141 (27)			21 (14)			55 (13)
II		9555 (42)			47 (32)			156 (36)
III		5573 (25)			54 (37)			147 (34)
IV		1319 (5.8)			23 (16)			78 (18)
Emergency surgery	21,882		.8	145	5 (3.4)	.4	421	22 (5.2)
Cardiac comorbidity								
LVEF (%)	14,323	51 ± 13	.002	57	43 ± 17	.5	192	45 ± 16
Myocardial infarction	22,807	5829 (26)	.01	145	50 (34)	.4	435	134 (31)
Heart failure	22,787	6081 (27)	<.0001	145	67 (46)	.8	435	195 (45)
Endocarditis	22,788	1250 (5.5)	.3	145	11 (7.6)	.7	435	37 (8.5)
Previous cardiac surgery	22,802	6365 (28)	.3	145	46 (32)	.7	435	145 (33)
Noncardiac comorbidity								
Hypertension	22,788	15,974 (70)	.7	145	104 (72)	.8	435	307 (71)
Stroke	22,807	2161 (9.5)	.004	145	24 (17)	.8	435	69 (16)
Pharmacologically treated diabetes	22,566	4530 (20)	.008	141	41 (29)	.5	434	114 (26)
PAD	22,807	2220 (9.7)	.10	145	20 (14)	.9	435	62 (14)
COPD	22,787	3445 (15)	<.0001	145	48 (33)	.9	435	147 (34)
Smoking	22,701	12,181 (54)	.11	144	87 (60)	.6	434	272 (63)
Creatinine (mg/dL)	22,786	1.2 ± 0.90	<.0001	145	1.6 ± 1.3	.5	434	1.5 ± 1.3
Renal dialysis	22,787	387 (1.7)	<.0001	145	9 (6.2)	.15	435	15 (3.4)
Hematocrit (%)	22,801	38 ± 6.3	<.0001	145	35 ± 6.0	>.9	434	35 ± 6.4
Procedure								
Isolated CABG	22,807	3940 (17)	.7	145	23 (16)	.8	435	72 (17)
Isolated valve	22,807	6918 (30)	.07	145	34 (23)	.4	435	88 (20)
Combined CABG/valve	22,807	3283 (14)	.002	145	34 (23)	.6	435	92 (21)
Aortic root, ascending aorta	22,807	3990 (17)	.6	145	23 (16)	.2	435	89 (20)
Other cardiac	22,807	4676 (21)	.8	145	31 (21)	.9	435	94 (22)
Surgical invasiveness	22,042			145			419	
Full incision		17,818 (81)	<.0001		136 (94)	.6		398 (95)
Minimal		3130 (14)	.006		9 (6.2)	.14		14 (3.3)
Percutaneous/ports		1094 (4.8)	.007		0 (0)	.19		7 (1.7)
CPB time (min)	22,807	95 ± 55	<.0001	145	128 ± 58	.16	435	120 ± 65
Myocardial ischemic time (min)	22,807	69 ± 42	.0004	145	83 ± 53	.19	435	77 ± 50
Intra-/postoperative IABP	22,807	566 (2.5)	<.0001	145	17 (12)	.3	435	39 (9.0)
Blood product use	22,807	11,456 (50)		145	134 (92)		435	386 (89)
RBC transfusion		10,491 (46)	<.0001		128 (88)	.18		364 (84)
FFP		4869 (21)	<.0001		84 (58)	.03		206 (47)

CDI, Clostridium difficile infection; *SD*, standard deviation; *NYHA*, New York Heart Association; *LVEF*, left ventricular ejection fraction; *PAD*, peripheral arterial disease; *COPD*, chronic obstructive pulmonary disease; *CABG*, coronary artery bypass grafting; *CPB*, cardiopulmonary bypass; *IABP*, intra-aortic balloon pump; *RBC*, red blood cell; *FFP*, fresh frozen plasma. *Unmatched versus CDI. †Matched versus CDI.

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TABLE 3. Incremental risk factors for *Clostridium difficile* infection

Risk factor	Estimate ± SE	Odds ratio (68% CLs)	P	Reliability (%)*
Demographics				
Older age†	0.21 ± 0.092	See Figure E4, *A*	.02	50
Hospital transfer	0.44 ± 0.179	1.5 (1.3, 1.8)	.006	71
Comorbidities				
Lower HDL	−0.021 ± 0.0065	See Figure E4, *B*	.001	67
Increased creatinine‡	0.36 ± 0.158	See Figure E4, *C*	.02	51
COPD	0.71 ± 0.182	2.0 (1.7, 2.4)	<.0001	90
Hypertension (less risk)	−0.45 ± 0.196	0.64 (0.52, 0.77)	.02	58
Procedural				
Insertion of temporary mechanical assist device	0.94 ± 0.23	2.9 (2.4, 3.7)	<.0001	93
Blood use intra- or postoperatively	1.3 ± 0.37	3.9 (2.7, 5.6)	.0003	80
Intra- and postoperative cardiac RBC transfusion units§	0.44 ± 0.110	See Figure E4, *D*	<.0001	59
More recent date of operation	0.32 ± 0.057	See Figure E4, *E*	<.0001	99
Intercept	−7.83 ± 0.56		<.0001	–

C-statistic = 0.85. *SE*, Standard error; *CL*, confidence limits; *HDL*, high-density lipoprotein cholesterol; *COPD*, chronic obstructive pulmonary disease; *RBC*, red blood cell. *Percent of times factor appeared in 500 bootstrap models. †Exp(age/50), exponential transformation. ‡Log(creatinine), logarithmic transformation. §Log(RBC units), logarithmic transformation.

account the rapidly diminishing number of patients not yet discharged after 7 days. The hazard function accounts for this and demonstrates that risk of CDI continues to increase the longer a patient is hospitalized. As a result, cumulative incidence of CDI increases exponentially to more than 5% at 60 days. Although an inference might be that continued hospital exposure is the cause of this increasing incidence, we caution the reader that we do not know whether patients who did not have CDI may have been diagnosed with CDI after hospital discharge. The National Heart, Lung, and Blood Institute (NHLBI)-funded Cardiothoracic Surgery Clinical Trials Network infection study, which extended to 60 days beyond hospital discharge, showed that nearly half the infections occurred after discharge. Thus, the

general pattern of incidence of infection, including CDI, is unclear because these late infections have not previously been studied.

The epidemiology of CDI has changed over time, with reports of a previously uncommon and more virulent strain, BI/NAP1/027, increasingly associated with disease outbreaks.[4-7] This strain is characterized by a 16- to 23-fold increase in production of toxins A and B.[7] Hypervirulence is manifested clinically by a high fever, unstable hemodynamics, and the development of toxic megacolon.[8] Some have hypothesized that widespread use of fluoroquinolone antibiotics may have selectively allowed for proliferation of this strain.[11] We do not know how many of our patients with CDI had this strain.

TABLE 4. Outcomes before matching with and without CDI, and matched group

Variable	No CDI: before matching (n = 22,807)		CDI (n = 145)		No CDI: matched (n = 435)
	No. (%) or mean ± SD	P*	No. (%) or mean ± SD	P†	No. (%) or mean ± SD
Complications					
Septicemia	562 (2.5)	<.0001	19 (13)	<.0001	15 (3.4)
Deep sternal wound infection	148 (0.70)	.07	3 (2.1)	.4	4 (0.92)
Hospital death	820 (3.6)	<.0001	16 (11)	.8	44 (10)
Permanent stroke	427 (1.9)	.001	8 (5.5)	.3	15 (3.4)
Perioperative MI	66 (0.30)	.5	0 (0)	>.9	2 (0.46)
Atrial fibrillation	5509 (24)	.0001	55 (38)	.07	130 (30)
Ventilation >24 h	4299 (19)	<.0001	96 (66)	<.0001	194 (45)
Renal failure requiring dialysis	615 (2.7)	<.0001	24 (17)	.002	33 (7.6)
Reoperation for bleeding	1100 (4.8)	<.0001	20 (14)	.03	34 (7.8)
Lengths of stay‡					
ICU (h)§	40 (22, 126)	<.0001	264 (69, 801)	<.0001	90 (24, 281)
Postoperative (d)§	7.1 (4.9, 15)	<.0001	21 (10, 49.5)	<.0001	11 (6.1, 26)
Hospital (d)§	9.0 (5.3, 21)	<.0001	27 (13, 59)	<.0001	16 (8.0, 36)

CDI, *Clostridium difficile* infection; *SD*, standard deviation; *MI*, myocardial infarction; *ICU*, intensive care unit. *Unmatched versus CDI. †Matched versus CDI. ‡Median (15th, 85th percentiles). §No CDI: before matching group. Data available for 22,660 patients.
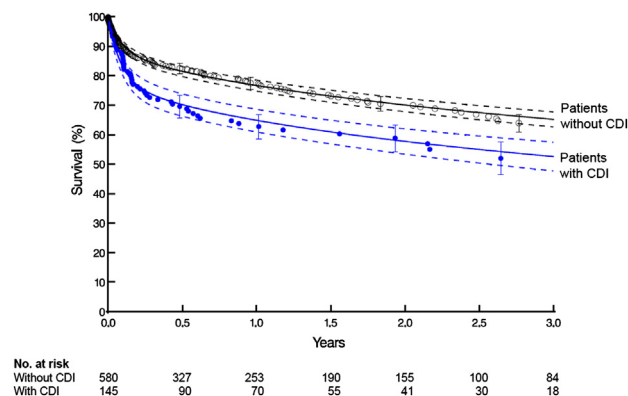
FIGURE 3. Survival of propensity-matched patients stratified by whether or not the patient had a *Clostridium difficile* infection (*CDI*). Time zero for the upper curve is the date of surgery, with patients censored at occurrence of CDI (competing-risks analysis). Time zero for the lower curve is the time of CDI diagnosis. Each *symbol* represents a death, *vertical bars* are 68% confidence limits equivalent to ± 1 standard error, and *solid lines* are parametric estimates enclosed within a 68% confidence band.

Characteristics of Patients With CDI and Risk Factors for CDI

Our patients with CDI had several previously well-described risk factors, including previous exposure to antibiotics,[8,21,22] preoperative hospitalization, and longer duration of hospitalization.[23,24] Half had been treated with broad-spectrum antibiotics before the CDI diagnosis.[21,22,25,26] More than half were on a proton-pump inhibitor, which is linked to increased occurrence of CDI.[27-29] Increased gastric pH allows survival of CDI spores.[28,29]

Other known risk factors illustrated by our study included older age[1,2,8,21,22,26] and previous colonoscopy or gastrointestinal surgery[1,21,28]; some patients were immunocompromised.[1,9,28] Patients with CDI also had a high comorbidity burden, which is associated with greater susceptibility to CDI.[30,31]

Only 5 of our patients had a history of CDI, and none had been diagnosed as carriers.[32] This may suggest that symptomless colonization with *C difficile* is protective and associated with a reduced risk for *C difficile*–associated diarrhea. Others have noted that an alteration in normal fecal flora, followed by colonization with *C difficile* and subsequent release of toxins, are necessary steps in the development of *C difficile* diarrhea.[33]

Although a limitation of our study is that previous antibiotic use, previous gastrointestinal surgery, immunocompromise, and proton-pump inhibitor use were known only for CDI patients, surrogates for this, such as hospital transfer status, chronic pulmonary disease, and some comorbidities known for all patients, were associated with the occurrence of CDI. However, during multivariable analysis, it was evident that surgical factors such as blood product use and the need to insert a temporary circulatory assist device

were powerful risk factors. Both cardiopulmonary bypass and blood product use are associated with alterations in immunology and elaboration of cytokines.[34] Both have the potential to raise levels of free iron, which is associated with infection.[35] We have investigated these associations in detail at this institution, particularly red blood cell transfusion,[36] and our findings have been corroborated by the NHLBI-funded Cardiothoracic Surgery Clinical Trials Network postcardiac surgery infection study.[3] The mechanism remains elusive, but it further emphasizes the value of blood conservation and protocols to reduce intraoperative bleeding and the use of blood products. The study also highlights the vulnerability of patients who require temporary circulatory support after cardiac surgery, with the potential for gut ischemia from low cardiac output.

Presentation and Diagnosis

More than 70% of our patients presented with diarrhea, as well as abdominal pain, distension, and leukocytosis. Cytotoxins produced by *C difficile* lead to symptoms, typically within 48 to 72 hours of infection.[21]

Laboratory diagnosis of CDI involved testing for stool toxins and, less commonly, stool cultures. Our change in the testing platform from EIA to PCR was based on the Hookman and Barkin[21] report of laboratory testing for CDI: EIA, 73% sensitivity, 98% specificity; real-time PCR, 93% sensitivity, 97% specificity; cell culture assay, 77% sensitivity, 97% specificity; and anaerobic culture for toxigenic *C difficile* strains, 100% sensitivity, 96% specificity. Although stool cultures are sensitive tests, they are associated with long turnaround times compared with the relatively rapid turnaround times for PCR testing.[37] If colonoscopy is performed, it may demonstrate colonic inflammation and, if CDI is advanced, may show the presence of pseudomembranes, diagnostic for CDI.[38] The fact that only one third of the patients had a computed tomography scan and only 9 had a colonoscopy, and one third of these examinations were read as normal, strongly suggests that the abdominal presentation of CDI was relatively benign in most patients.

Treatment

All our patients were treated with antibiotic therapy (vancomycin, metronidazole, or both). Patients with clinical symptoms of toxic colitis were offered surgery if operable. Three of 4 patients undergoing colectomy survived.

We have not tried treatment with monoclonal antibodies against *C difficile* toxins, which has been reported to be successful.[39] Nor have we used nitazoxanide and rifaximin, fidaxomicin, probiotics, or anionic polymers, as suggested by others.[8,38] Antibiotic treatment does not reestablish normal flora in the bowel; hence, some advocate fecal bacteriotherapy for patients with chronic relapsing CDI who fail conventional treatment.[9,40-42]

Outcomes

CDI was associated with increased hospital morbidity, mortality, and resource utilization, and prolonged high risk of death for at least 6 months after surgery. Complications related to CDI led in part to this increased use of resources via the need for additional surgical procedures, pharmacotherapy, and increased length of stay. However, in most of our cases, the CDI manifestations were benign and the CDI was just another marker of the severity of comorbidities and patient and operative complexity.[43] In other general hospital settings, higher mortality, longer lengths of stay, and higher costs have been documented.[44]

Clinical Implications

The increasing prevalence of CDI after heart surgery is concerning and costly, and more effective efforts to limit its spread are needed. Our study has shown that the complex and complicated patients are most vulnerable.

The mode of CDI transmission is via the fecal-oral route of *C difficile* spores; hence, vigilance regarding environmental reservoirs, including asymptomatic *C difficile* carriers, is warranted. *C difficile* spores are resilient and can survive on surfaces for months despite standard sterilization treatments.[21,38] We believe that a high level of suspicion plus early diagnosis and treatment can reduce the deleterious consequences.

Strengths and Limitations

This study was conducted in a quaternary care setting with high-acuity patients undergoing cardiac surgery, 20% of whom were transferred from other hospitals. Thus, our findings may not be generalizable to other settings. One strength of our study is the detailed information available case by case for patients with CDI, which cannot be achieved with purely administrative data. However, as noted earlier, many traditional risk factors for CDI were not available for the patients without CDI. Toward the end of the study period, diagnostic testing evolved, and it is not clear how this affected the detection of CDI. We also recognize that CDI cannot be randomized, and the use of propensity score methods for so-called natural experiments such as this may be considered controversial by some. We believe, however, that risk adjustment is superior to multivariable analysis of outcomes.[18]

CONCLUSIONS

CDI is an important contributor to morbidity and mortality after cardiac surgery, and the risk of CDI increases during prolonged hospitalization. Although risk factors such as prolonged hospitalization, antibiotics, proton-pump inhibitors, comorbidities, and high-risk operations were common among patients with CDI, the strongest risk factors in this setting were perioperative ones, including blood product use and the need for temporary circulatory support. If toxic colitis develops, mortality is high, but colectomy may be lifesaving.

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APPENDIX E1. VARIABLES CONSIDERED IN THE ANALYSES

Demographic

Age (years),* gender,* race (white/black/other),* weight (kg), height (cm), weight/height ratio, body surface area (m^2), body mass index (kg/m^2).*

Symptoms and Status

New York Heart Association functional class (I-IV),* emergency operation,* hospital transfer.*

Cardiac Comorbidity

Previous myocardial infarction,* atrial fibrillation,* complete heart block or pacer, ventricular arrhythmia, heart failure,* endocarditis,* coronary artery disease (number of systems ≥50%),* previous cardiac operation,* surgery number.

Noncardiac Comorbidity

Peripheral arterial disease,* carotid disease,* hypertension,* pharmacologically treated diabetes,* insulin-treated diabetes,* non–insulin-dependent diabetes, chronic obstructive pulmonary disease,* history of smoking,* preoperative renal dialysis,* previous stroke,* creatinine (mg/dL),* blood urea nitrogen (mg/dL), bilirubin (mg/dL),* creatinine clearance, glomerular filtration rate, hematocrit (%),* total cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL),* low-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL).

Experience

Date of operation (years since January 1, 2005),* surgeon.*

Procedural

Coronary artery bypass grafting,* number of internal thoracic arteries used,* aortic valve procedure,* mitral valve procedure,* tricuspid valve procedure,* aortic procedure, septal myectomy,* mechanical assist device,* transplant,* surgical invasiveness (full,* minimal, percutaneous/ports).

Support

On-pump,* cardiopulmonary bypass time (minutes),* aortic clamp used,* aortic clamp time (minutes), circulatory arrest,* circulatory arrest time (minutes), total operating room time (minutes).*

Blood Use

Intraoperative: red blood cell units, platelets, fresh frozen plasma, cryoprecipitate, any intraoperative blood use. Postoperative: red blood cell units,* platelets, fresh frozen plasma, cryoprecipitate, any postoperative blood use. Total: red blood cell units,* platelets, fresh frozen plasma, cryoprecipitate, any intraoperative or postoperative blood use.*
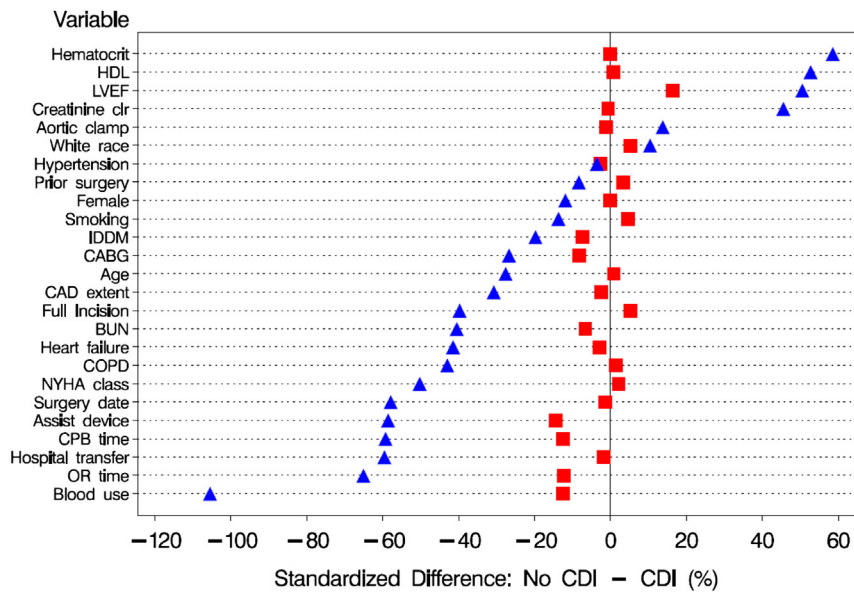
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* Variables used in the propensity model.

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FIGURE E1. Covariable balance description before (*triangles*) and after (*squares*) matching between the no CDI and CDI groups.* *HDL*, High-density lipoprotein; *LVEF*, left ventricular ejection fraction; *clr*, clearance; *IDDM*, insulin-dependent diabetes; *CABG*, coronary artery bypass grafting; *CAD*, coronary artery disease; *BUN*, blood urea nitrogen; *COPD*, chronic obstructive pulmonary disease; *NYHA*, New York Heart Association; *CPB*, cardiopulmonary bypass; *OR*, operating room; *CDI*, *Clostridium difficile* infection. *Austin PC, Mamdani MM. A comparison of propensity score methods: a case study estimating the effectiveness of post-AMI statin use. *Stat Med.* 2006;25:2084-106.
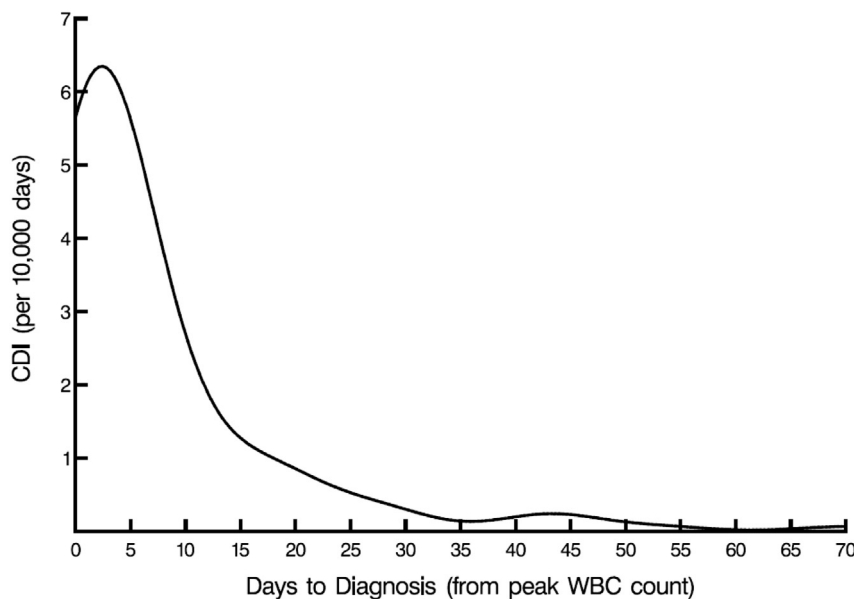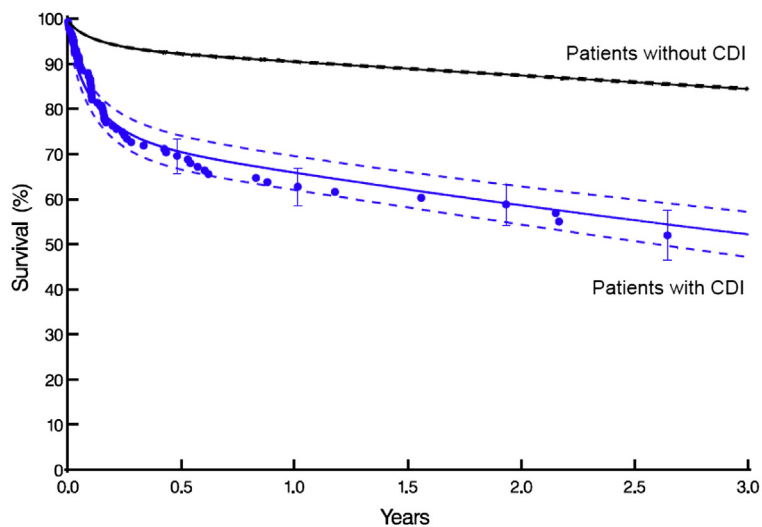

FIGURE E2. Characterization of the onset of *Clostridium difficile* infection (*CDI*) after cardiac surgery. Days between peak white blood cell (*WBC*) count and diagnosis of CDI.

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FIGURE E3. Unadjusted survival stratified by whether or not the patient had a *Clostridium difficile* infection (*CDI*). Time zero for the upper curve is the date of surgery, with patients censored at occurrence of CDI. Time zero for the lower curve is the time of the CDI diagnosis. Each *symbol* on the lower curve represents a death positioned on the vertical axis by the Kaplan-Meier estimator, and *vertical bars* are confidence limits equivalent to ± 1 standard error. The *solid line* for both curves is parametric survival enclosed within a dashed 68% confidence band. The number of patients at risk is given below the horizontal axis.
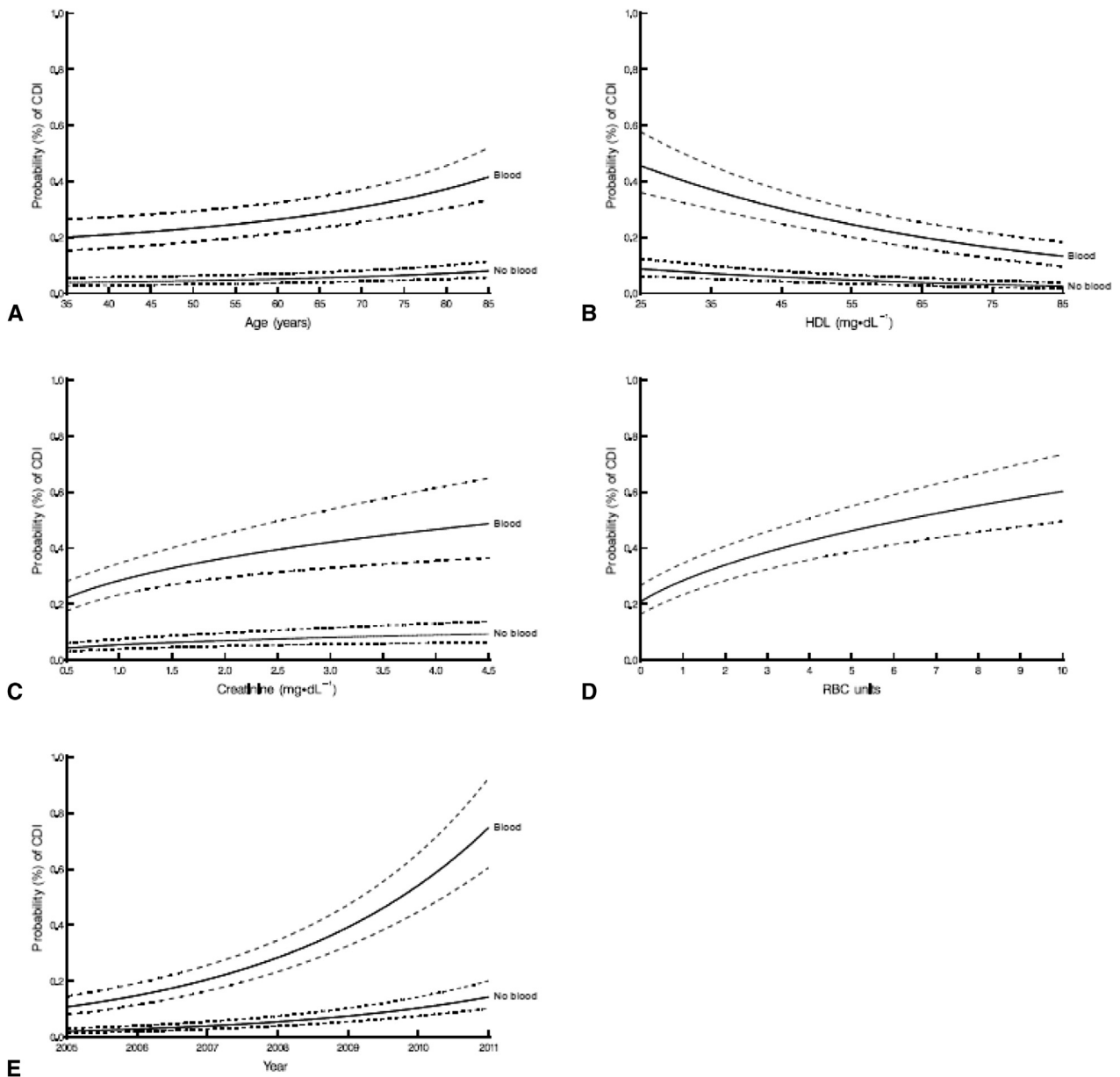
FIGURE E4. Effect of continuous risk factors on the probability of developing *Clostridium difficile* (*CDI*) infection using nomograms of the logistic regression equation. *Solid lines* are parametric estimates enclosed within a 68% confidence band. Simulations are based on the logistic model (Table 3) for a 65-year-old patient with hypertension, no chronic obstructive pulmonary disease, high-density lipoprotein (*HDL*) level 48 mg/dL, creatinine level 1.0 mg/dL, no hospital transfer, and no ventricular assist device, stratified by use of blood products. A, Age at operation. B, Preoperative HDL level. C, Preoperative creatinine level. D, Red blood cell (*RBC*) units transfused. E, Date of operation.

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TABLE E1. Hospital-wide occurrence of *Clostridium difficile* infection per 10,000 patient-days

Year	Number	Patient-days	Rate per 10,000 patient-days
2006	203	332,119	6.11
2007	191	333,758	5.72
2008	209	339,221	6.16
2009	204	356,612	5.72
2010	264	348,522	7.57
2011	409	343,073	11.92
2012	368	361,681	10.17
2013	317	358,587	8.84