The Burden of *Clostridium difficile* after Cervical Spine Surgery

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Abstract

Study Design Retrospective database analysis.

Objective The purpose of this study is to investigate incidence, comorbidities, and impact on health care resources of *Clostridium difficile* infection after cervical spine surgery.

Methods A total of 1,602,130 cervical spine surgeries from the Nationwide Inpatient Sample database from 2002 to 2011 were included. Patients were included for study based on *International Classification of Diseases Ninth Revision, Clinical Modification* procedural codes for cervical spine surgery for degenerative spine diagnoses. Baseline patient characteristics were determined. Multivariable analyses assessed factors associated with increased incidence of *C. difficile* and risk of mortality.

Results Incidence of *C. difficile* infection in postoperative cervical spine surgery hospitalizations is 0.08%, significantly increased since 2002 ($p < 0.0001$). The odds of postoperative *C. difficile* infection were significantly increased in patients with comorbidities such as congestive heart failure, renal failure, and perivascular disease. Circumferential cervical fusion (odds ratio [OR] = 2.93, $p < 0.0001$) increased the likelihood of developing *C. difficile* infection after degenerative cervical spine surgery. *C. difficile* infection after cervical spine surgery results in extended length of stay ($p < 0.0001$) and increased hospital costs ($p < 0.0001$). Mortality rate in patients who develop *C. difficile* after cervical spine surgery is nearly 8% versus 0.19% otherwise ($p < 0.0001$). Moreover, multivariate analysis revealed *C. difficile* to be a significant predictor of inpatient mortality (OR = 3.99, $p < 0.0001$).

Conclusions *C. difficile* increases the risk of in-hospital mortality and costs approximately $6,830,695 per year to manage in patients undergoing elective cervical spine surgery. Patients with comorbidities such as renal failure or congestive heart failure have increased probability of developing infection after surgery. Accepted antibiotic guidelines in this population must be followed to decrease the risk of developing postoperative *C. difficile* colitis.

Keywords
- cervical spine surgery
- clostridium difficile
- infection
- outcomes
- cost
- mortality
- database analysis

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Introduction

Hospital-acquired *Clostridium difficile* infection, resulting in pseudomembranous colitis, is the most important cause of health care–associated diarrhea.[1,2] Recent studies have shown that the incidence of *C. difficile* infection is rising, and it is becoming ever more challenging to treat because of emerging antibiotic-resistant strains.[3–5] The pathophysiology of *C. difficile* infection is associated with alterations in the gut microflora, which can be triggered by antibiotic administration.[6,7] Infection is characterized by constitutional symptoms, diarrhea and abdominal pain, and may lead to serious life-threatening complications such as toxic megacolon.[8] Importantly, *C. difficile* is a highly contagious pathogen that can spread through a hospital especially in the setting of improper hand-washing practices and contact-precaution protocols.[9] Consequently, proper perioperative administration of antibiotics, especially in high-risk patients, should be practiced to avoid this morbid and potentially fatal complication.

Postoperative *C. difficile* infection has been reported to increase length of stay (LOS), mortality, and costs.[5] Maltenfort et al demonstrated that *C. difficile* infection after total knee arthroplasty increased LOS stay by a week, hospital charges by nearly U.S. $40,000, and in-hospital mortality from 0.24 to 4.66%.[10] Similarly, Skovrlj et al previously described a 36.4-fold increase in mortality in patients with *C. difficile* after lumbar spine surgery.[11] Although an uncommon infection, it is clear that it has a significant impact.

Two key studies identified risk factors of *C. difficile* after orthopedic surgery. Campbell et al identified surgery $>$ 24 hours after admission, perioperative antibiotics, and proton pump inhibitors as risk factors for infection.[12] Jenkins et al, in a similar study assessing *C. difficile* risk factors after total joint arthroplasty, identified additional postoperative antibiotic use as a significant factor for acquiring infection.[13] However, these studies are limited by their relatively small sample size. Although there are studies examining *C. difficile* after lumbar spine surgery, there are currently no studies investigating the burden of *C. difficile* infection after cervical spine surgery. This study aims to identify incidence, prevalence, risk factors, and outcomes of *C. difficile* infection in a large sample of patients who underwent cervical spine surgery for degenerative causes.

Material and Methods

The Nationwide Inpatient Sample (NIS) database, under the auspices of the Healthcare Cost and Utilization Project (HCUP), was queried from 2002 to 2011.[14] The HCUP is a series of databases and related software tools developed through a federal–state–industry partnership, and it is the United States' most comprehensive source of hospital data. One of the more robust databases of the HCUP, the NIS contains a 20% stratified sample numbering an estimated 1,000 hospitals throughout the United States, including ~7 to 8 million hospital stays each year. Sample weights are created for each hospitalization based on the stratum the hospital belongs to (assigned by the American Hospital Association) by amassing the aggregate number of discharges in that stratum and dividing it by the total number of NIS discharges in that stratum.[15] Appropriately applying these sample weights gives ~40 million hospitalizations each year representing 96% of all U.S. hospital discharges. The NIS contains information on (but not limited to) hospital charges, procedures, diagnoses, and general patient characteristics. Institutional review board approval was not available for this study as the NIS contains no direct patient identifiers and is compliant with the Health Insurance Portability and Accountability Act of 1996 privacy rules.

Sample Selection

Hospitalizations with *C. difficile* diagnosis were identified by *International Classification of Diseases Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis code 008.45. Hospitalizations were selected for the study based on ICD-9-CM procedural codes for cervical spine procedures and diagnoses codes for degenerative conditions of cervical spine. The following procedural codes were included: anterior cervical fusion (81.02), posterior cervical fusion (81.03), refusion of cervical spine anterior technique (81.32), refusion of cervical spine posterior technique (81.33), posterior cervical decompression without fusion (03.09). Only hospitalizations of patients undergoing procedures for degenerative conditions including cervical spondylosis with and without myelopathy (721.1, 721.0), intervertebral disk (IVD) displacement with and without myelopathy (722.71, 722.0), IVD degeneration (722.4), postlaminectomy syndrome (722.81), calcification of IVD (722.91), other disorders of the cervical spine region including spinal stenosis (723.0–5), and ossification of the posterior longitudinal ligament (723.7) were selected.

Surgical Groups

Cervical spine procedures were further grouped to explore the risk of general procedure approach in the development of *C. difficile* infection. *Single-stage surgery* indicates anterior cervical fusion, posterior cervical fusion, or posterior decompression without fusion. *Circumferential fusion* includes those patients with concurrent anterior and posterior fusion during the hospitalization. *Primary fusion* included any cases of anterior or posterior fusion that were not coded as revision surgery. By contrast, *revision surgery* only included anterior or posterior fusion revisions.

Outcomes

Patients were characterized as those with and without *C. difficile* diagnosis. We analyzed the prevalence of *C. difficile* infection by patient age, insurance type, gender, race and Elixhauser Comorbidity Index. The Elixhauser Index, similar to the Charlson Comorbidity Index, is a comorbidity risk adjustment model that aids in stratifying patients who are at higher risk for mortality.[16] It includes updated diagnosis codes for comorbidities provided by the HCUP and adjusts for each single comorbidity's independent association with hospital death. It was chosen for its significant association with risk of mortality, especially beyond 30 days, as well as burden

of disease.[17–19] Moreover, charges were adjusted for inflation using the United States Bureau of Labor statistics yearly inflation calculator and are presented in 2011 U.S. dollars; charges were transformed into cost with the HCUP cost-to-charge ratio tool.[20,21] The cost-to-charge tool allows us to assess not just what hospitals billed for services, but how much hospital services actually cost or specific amounts hospitals received in payment.

Data Analysis

The statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, North Carolina, United States). Chi-square test was used for analysis of categorical variables, and Student *t* test was used for continuous variables. The statistical significance of the time trend in the rate of hospitalizations with *C. difficile* infection was determined using the Cochran-Armitage trend test. We took into account clinically relevant variables such as previously published literature on this topic and multicollinearity and multivariable logistic regression for *C. difficile* diagnosis, and we controlled for relevant procedure types (circumferential fusion versus single stage surgery), age > 65 years, sex, comorbidities (see **Appendix 1** for all included), hospital type (teaching versus nonteaching), location (urban versus rural), region (Northeast as reference), insurance type (uninsured versus insured), and common postoperative infections.[10,11] The logistic regression model investigating risk factors associated with inpatient mortality after degenerative cervical spine surgery was also done. The statistical analysis took into account the stratified sampling design of the NIS database. Surveyfreq, surveymeans, and surveylogistic procedures were used for analysis. Discharge weights, NIS_stratum, and cluster (hospital identification) variables were included to correctly estimate variance and to produce national estimates. Statistical significance was maintained at $p < 0.05$.

Results

A total of 1,602,130 cervical spine surgeries were performed for degenerative conditions from 2002 to 2011. From this total, 1,270 hospitalizations were identified to have a concurrent *C. difficile* diagnosis. The incidence of *C. difficile* has been significantly increasing in the period queried (►**Fig. 1**). A total of 3,044 (0.19%) patients without *C. difficile* infection died in the hospital after cervical spine surgery. Although only 101 patients with *C. difficile* infection died, this number accounted for 7.9% of all patients who acquired *C. difficile* infection after cervical spine surgery ($p < 0.0001$).

Patients with *C. difficile* infection were more likely to be male ($p < 0.0015$) and more likely to be over the age of 65, with a mean age of 66.8 years versus 53.4 years in those without *C. difficile* ($p < 0.0001$; ►**Table 1**). Patients with *C. difficile* infection were also more likely to have undergone posterior cervical fusion and circumferential fusion when compared with those without postoperative *C. difficile* infection (►**Table 1**).

In multivariable logistic regression modeling for postoperative *C. difficile* infection, age > 65 was identified to be a

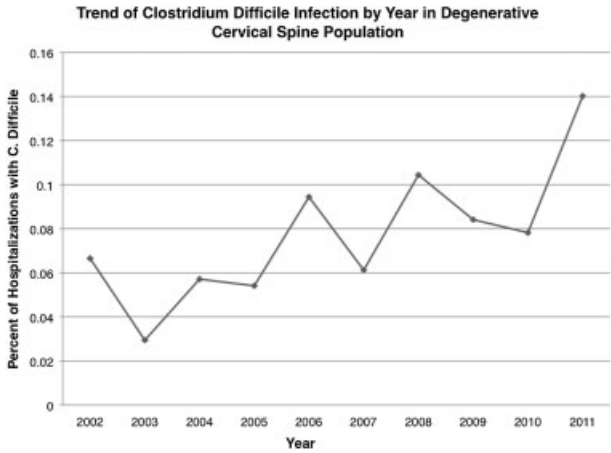

Fig. 1 Trend of *Clostridium difficile* infection by year in degenerative cervical spine population from 2002 to 2011.

significant risk factor for acquiring infection (odds ratio [OR] = 2.63, 95% confidence interval [CI] = 1.86 to 3.73, $p < 0.0001$). Congestive heart failure, peripheral vascular disease, paralysis, chronic lung disease, renal failure, coagulation, and fluid/electrolyte disorders were all significant predictors of postoperative *C. difficile* infection (►**Table 2**). A diagnosis of pneumonia, postoperative infection not otherwise specified, and urinary tract infections were also significantly associated postoperative *C. difficile* colitis. Circumferential fusion when referenced to single-stage surgery also increased the odds of postoperative infection (OR = 2.93, 95% CI = 1.75 to 4.90, $p < 0.0001$).

Multivariate regression analysis in patients undergoing degenerative cervical spine surgery identified *C. difficile* infection as a significant risk factor for inpatient mortality (OR = 3.99, 95% CI = 2.15 to 7.38, $p < 0.0001$; ►**Table 3**). In addition to increasing the odds of infection, circumferential fusion was also significantly associated with increased overall inpatient mortality in this population (OR = 2.74, 95% CI = 1.92 to 3.91, $p < 0.0001$).

Discussion

This study demonstrates that *C. difficile* infection after cervical spine surgery for degenerative pathology is a rare, yet morbid and fatal postoperative complication. The rate of *C. difficile* infection significantly increased after cervical spine surgery from 2002 to 2011, and overall prevalence was 0.08%. There are multiple reasons for this observation, from better reporting to improved diagnostic techniques. There is growing evidence that postoperative *C. difficile* incidence may be increasing due to evolving antibiotic-resistant strains, such as the hypervirulent strain NAP1/BI/027.[6,22] Our study indicates that *C. difficile* is a significant independent risk factor associated with inpatient mortality in patients after cervical spine surgery.

The increased risk of *C. difficile* infection after degenerative cervical spine surgery in patients with certain comorbidities such as advanced chronic kidney disease (CKD) that cause impaired immunity is well recognized in the literature.[23,24]

Table 1 Demographic information of patients with and without *Clostridium difficile* infection after degenerative cervical spine surgery

Population	*C. difficile* (1,270)	No *C. difficile* (1,600,860)	*p* Value
Sex (%)			0.002
Male	59.2	49.6	
Female	40.8	50.4	
Mean age	66.8	53.4	<0.0001
Age groups, y (%)			<0.0001
0–44	6.1	24.7	
45–65	34.3	55.7	
> 65	59.6	19.6	
Race (%)			<0.0001
White	60.9	62.4	
Black	11.2	7.2	
Hispanic	7.4	3.8	
Asian or Pacific	3.1	0.9	
Native American	0.4	0.3	
Other	2.3	1.7	
Missing race	14.7	23.6	
Insurance (%)			<0.0001
Medicare	63.8	24.5	
Medicaid	11.5	8.6	
Private	19.9	55.5	
Uninsured	1.6	1.7	
Other	2.7	9.4	
Elixhauser Comorbidity Index	7.6	0.5	<0.0001
Hospital size (%)			0.001
Small	5.5	11.6	
Medium	17.7	21.9	
Large	76.8	66.5	
Hospital location (%)			0.073
Rural	1.9	4.8	
Urban	98.1	95.2	
Hospital teaching status (%)			0.001
Nonteaching	34.7	46.6	
Teaching	65.3	53.4	
Procedures (*n*, Rate %)			
Anterior cervical fusion	467 (36.8)	1,225,346 (76.54)	<0.0001
Posterior cervical fusion	258 (20.3)	88,766 (5.5)	<0.0001
Fusion revision anterior approach	20 (1.6)	27,172 (1.7)	0.919
Fusion revision posterior approach	19 (1.5)	13,362 (0.8)	0.235
Circumferential fusion	150 (11.8)	28,534 (1.8)	<0.0001
Posterior cervical decompression without fusion	356 (28.0)	217,680 (13.6)	<0.0001
All cervical surgeries	1,270 (0.08)	1,600,860	–
Mortality total cases, *n* (% population)	101 (7.9%)	3,044 (0.19%)	<0.0001

(*Continued*)

Table 1 (*Continued*)

Population	*C. difficile* (1,270)	No *C. difficile* (1,600,860)	*p* Value
Common postoperative complications			
Pneumonia	137 (10.8%)	2,342 (0.15%)	<0.0001
Urinary tract infection	355 (27.96%)	22,197 (1.38%)	<0.0001
Postoperative infection, not otherwise specified	58(4.6%)	2,252 (0.14%)	<0.0001

Patients with CKD have dysfunctional gastric acid secretion and are susceptible to infections that may require antibiotics, thus making this patient population particularly vulnerable.[24,25] There is a similar, although distinct, risk seen in those patients who have been on prolonged treatment with proton pump inhibitors prior to surgery.[12,26] Patients in this population with postoperative infection like pneumonia have understandably higher odds for postoperative *C. difficile* colitis, presumably due to the use of antibiotics to treat such infections. However, not all cases of *C. difficile* in this population had these common infections and thus there may have been some cases in which the administration of antibiotics was suboptimal.

The increased rate of *C. difficile* in patients with Medicare versus private insurance may be due to an age effect that cannot be completely explained by the NIS. However, because most patients eligible for Medicare are, at minimum, 65 years of age or with a severe medical comorbidity, it is possible that the Medicare beneficiaries are slightly sicker and at an increased risk of infection.[27] Indirectly supporting this age effect is the fact that in multivariate analysis for *C. difficile* infection, age > 65 was a significant independent variable for the risk of infection.

Although the NIS has limitations with respect to detailed surgical techniques, such as explicit procedure (e.g., anterior corpectomy and fusion), our study shows the effect different general procedures had on *C. difficile* incidence and overall inpatient mortality. Posterior approaches had a higher incidence of *C. difficile* when compared with anterior approaches, likely because the anterior approach is relatively muscle-sparing and the posterior approach is muscle-splitting and may be associated with longer LOS, which may lead some surgeons to expose these patients to prolonged antibiotic administration. In multivariate analyses for postoperative *C. difficile* diagnosis and inpatient mortality, circumferential fusion was associated with increased likelihood of postoperative *C. difficile* colitis and increased risk for in-hospital death. Increased incidence of *C. difficile* infection and general inpatient mortality in these cases may be due to the invasive nature of the combined approach, leading to longer operating times, increased perioperative antibiotic administration, and a more difficult postoperative course.

Table 2 Independent risk factors increasing the odds of *Clostridium difficile* after cervical spine surgery

Risk factor	Odds ratio	Low 95% CI	High 95% CI	*p* Value
Age > 65 y	2.63	1.86	3.73	<0.0001
Hispanic	1.52	0.93	2.49	<0.0001
Asian	2.00	0.91	4.39	<0.0001
Other race	1.41	0.60	3.29	<0.0001
Congestive heart failure	2.79	1.82	4.28	<0.0001
Perivascular disease	2.32	1.27	4.21	0.006
Paralysis	2.27	1.48	3.50	0.0002
Chronic lung disease	1.58	1.12	2.23	0.0097
Renal failure	2.04	1.26	3.30	0.0039
Coagulation	2.31	1.25	4.27	0.0075
Fluid/electrolyte disorders	6.54	4.49	9.52	<0.0001
Circumferential surgery	2.93	1.75	4.90	<0.0001
Pneumonia	5.80	3.33	10.10	<0.0001
Postoperative infection	6.95	3.08	15.67	<0.0001
Urinary tract infection	5.12	3.28	8.00	<0.0001

Abbreviation: CI, confidence interval.

Table 3 Independent risk factors increasing the odds of inpatient mortality after cervical spine surgery

Risk factor	Odds ratio	Low 95% CI	High 95% CI	*p* Value
Clostridium difficile	3.99	2.15	7.38	<0.0001
Age > 65 y	3.82	3.05	4.8	<0.0001
Teaching hospital	1.29	1.05	1.59	0.016
Congestive heart failure	3.81	2.8	5.18	<0.0001
Paralysis	5.12	4.02	6.52	<0.0001
Neurologic complications	1.8	1.29	2.52	0.001
Pulmonary circulatory disorders	6.47	4.06	10.32	<0.0001
Renal failure	2.33	1.64	3.29	<0.0001
Acquired immune deficiency	3.33	1.1	10.07	0.033
Coagulation	3.93	2.8	5.51	<0.0001
Fluid/electrolyte disorder	5.27	4.15	6.68	<0.0001
Circumferential surgery	2.74	1.92	3.91	<0.0001

Abbreviation: CI, confidence interval.

Despite no antibiotic data available in the NIS, there are some important considerations that should be addressed. Because the development of *C. difficile* infection is not necessarily dependent on the type of procedure but rather antibiotic administration, it is critical that spine surgeons follow the hospital-instituted antibiotic guidelines to avoid potential complications. The use of any antibiotics, but more commonly clindamycin, cephalosporins (second-generation or higher), fluoroquinolones, and multiple regimens, is believed to modify the normal gut microflora, predisposing to *C. difficile*

Table 4 Costs and length of stay in patients with or without *Clostridium difficile* after degenerative cervical spine surgery

	Hospital costs (U.S. $)			Length of stay (d)		
	No *C. difficile*	*C. difficile*	*p* Value	No *C. difficile*	*C. difficile*	*p* Value
Fusion revision[a]						
Mean	19,542	100,676	<0.0001	3.25	22.81	<0.0001
Median	14,777	88,006	<0.0001	1.55	17.82	<0.0001
Q1	10,403	48,199		0.69	5.72	
Q3	22,709	110,284		2.95	32.53	
Circumferential fusion[b]						
Mean	40,865	71,002	<0.0001	7.06	24.98	<0.0001
Median	34,510	66,805	<0.0001	4.16	19.09	<0.0001
Q1	24,085	31,765		2.49	7.62	
Q3	49,849	78,973		7.38	28.64	
Single-stage surgery[c]						
Mean	13,892	64,431	<0.0001	2.37	25.2	<0.0001
Median	11,342	48,045	<0.0001	0.88	19.39	<0.0001
Q1	8,309	30,077		0.43	11.29	
Q3	16,036	79,298		1.9	30.82	
All cervical surgeries						
Mean	14,520	66,237	<0.0001	2.48	25.1	<0.0001
Median	11,530	53,785	<0.0001	0.91	19.15	<0.0001
Q1	8,399	30,321		0.44	10.9	
Q3	16,550	81,868		1.97	31.07	

[a]Anterior fusion revision or posterior fusion revision.
[b]Concurrent anterior and posterior fusion.
[c]Anterior fusion, posterior fusion, or posterior decompression without fusion.

colitis.[4,22,28] Currently, The Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery, developed in a collaborative effort by the American Society of Health Care Pharmacist, recommends a single dose of cefazolin or any other first-generation cephalosporin 1 hour prior to surgical incision, as antibiotic prophylaxis for orthopedic spine surgeries with or without instrumention.[29] These same guidelines indicate that clindamycin or vancomycin may be used in those patients who have a β-lactam allergy.

These evidence-based guidelines and others, such as the Surgical Care Improvement Project, are not universally followed, and clinical experience shows that spine surgeons may utilize modified antibiotic practices that can lead to rare but potentially deadly infections such as *C. difficile* colitis.

The economic impact of *C. difficile* must also not be overlooked. Cervical spine patients with *C. difficile* infection cost approximately $6,830,695 per year to manage as calculated by median costs and total number of patients with infection averaged over our study period (►**Table 4**), which is a significant impact on health resources despite being a rare occurrence.

Limitations

Several important conclusions cannot be made due to limitations when using the NIS. One such limitation is the absence of data on antibiotic administration. Because weakening the resistance and altering the normal intestinal microbiota by antibiotics remains the single most important risk factor for colonization and susceptibility to infection, important observations about dosage, duration, and high-risk antibiotics would have been of vital importance.[30] The identified risk factors such as increased incidence of postoperative infections, certain comorbidities such as CKD, or complex two-step procedures such as circumferential surgery may be surrogates for the use of multiple or more broad-spectrum antibiotics rather than being the primary risk factors.

Despite relatively reliable medical tests to diagnose *C. difficile* infection, the method of diagnosis is not available when using the NIS.[4] Errors in *C. difficile* diagnosis may stem from prophylactically identifying patients experiencing an active infection at the first sign of postoperative diarrhea. Although these patients may indeed have *C. difficile* infection, the diagnosis cannot be confirmed until proper laboratory tests are performed, which may lead to an overestimation of *C. difficile* incidence. However, these same conclusions may lead to an underestimation because some patients with postoperative diarrhea may be falsely classified as not having an active infection.

Conclusion

With the use of the NIS, we were able to accurately investigate the national trend of *C. difficile* infection after elective cervical spine surgery for degenerative causes. Postoperative *C. difficile* infection in this population results in extended hospital stay, greater costs, and increased inpatient mortality. Although being a rare infection after cervical spine surgery, it is significantly increasing in incidence likely due to novel antibiotic-resistant strains and improper antibiotic use. Due to the fatal impact this infection carries, proper pre- and postoperative antibiotic stewardship should be practiced in this population especially in patients > 65 years of age and with high-risk comorbidities such as diabetes with chronic complications and CKD.

Disclosures
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Appendix 1 Factors included in multivariable analyses

Dependent variable	Risk factors included
Clostridium difficile	Age > 65 years, *insurance (*insured versus uninsured*), race (*White as reference*), hospital region (*Northeast as reference*), hospital teaching status (*nonteaching reference*), hospital location (*urban versus rural*), hospital bed size (*large as reference*), comorbidities (perivascular disease, chronic hypertension, paralysis, neurological complications, pulmonary circulatory disorders, chronic lung disease, diabetes without complications, diabetes with chronic complications, renal failure, acquired immune deficiency syndrome, rheumatoid arthritis/collagen vascular disease, coagulation, obesity, fluid/electrolyte disorders, drug abuse, depression, circumferential surgery (*single stage surgery as reference*), pneumonia, urinary tract infection, postoperative infection not otherwise specified).
Inpatient mortality	Diagnosis of *Clostridium difficile*, age > 65 years, insurance *(insured versus uninsured)*, race *(White as reference)*, hospital region (*Northeast as reference)*, hospital teaching status *(nonteaching reference)*, hospital location *(urban versus rural)*, hospital bed size *(large as reference)*, comorbidities (perivascular disease, chronic hypertension, paralysis, neurological complications, pulmonary circulatory disorders, chronic lung disease, diabetes without complications, diabetes with chronic complications, renal failure, acquired immune deficiency syndrome, rheumatoid arthritis/collagen vascular disease, coagulation, obesity, fluid/electrolyte disorders, drug abuse, depression, circumferential surgery (*reference single stage surgery as reference*).

*Insured patients (Private, Medicare, or Medicaid).