Clostridium difficile Infection After Subarachnoid Hemorrhage: A Nationwide Analysis

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BACKGROUND: *Clostridium difficile* infection (CDI) is an important cause of hospital-acquired morbidity and mortality.

OBJECTIVE: To evaluate the incidence of, predictors for, and effects on outcome by CDI after aneurysmal subarachnoid hemorrhage.

METHODS: Data were extracted from the Nationwide Inpatient Sample (2002-2011). Patients with subarachnoid hemorrhage who underwent microsurgical or endovascular aneurysm repair were included. Multivariate logistic regression was used to determine the independent predictors of developing CDI. Additional models were constructed to assess the impact of CDI on mortality, length of stay, and discharge disposition.

RESULTS: Of the 18 007 patients who were included, 1.9% (n = 346) developed CDI. Patients who developed CDI were significantly older and had more comorbidities ($P \leq .001$). Independent predictors of developing CDI were Medicaid payer status; ventriculostomy; mechanical ventilation; a greater number of noninfectious complications; and the development of a urinary tract infection; pneumonia; meningitis/ventriculitis; and sepsis (all $P \leq .02$). Only 1.5% of patients with CDI required gastrointestinal surgery. Although CDI was not associated with differential mortality, it was associated with increased adjusted odds of a hospital stay of at least 24 days (odds ratio, 3.16; 95% confidence interval, 2.32-4.29; $P < .001$) and of a nonroutine hospital discharge (odds ratio, 1.64; 95% confidence interval, 1.13-2.39; $P = .01$).

CONCLUSION: In this nationwide analysis, both infectious and noninfectious complications, as well as ventriculostomy, mechanical ventilation, and insurance status were independent predictors of CDI. Although CDI was not associated with mortality, it was associated with a longer hospital stay and nonroutine hospital discharge.

KEY WORDS: Cerebral aneurysm, *Clostridium difficile*, Hospital acquired infection, Length of stay, Nationwide Inpatient Sample, Subarachnoid hemorrhage

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Since its discovery in 1978, the incidence of *Clostridium difficile* infection (CDI) has increased rapidly internationally.[1] The development of CDI involves exposure to the pathogen and alterations in the normal intestinal flora and immune system in the setting of a stress state. Pathogenic strains of CDI release a toxin that disrupts microtubules and tight junctions, disrupting the integrity of intestinal epithelium and leading to the release of inflammatory mediators.[2] The typical presentation of CDI involves a combination of diarrhea, leukocytosis, and/or fever, but some cases of CDI may progress to pseudomembranous colitis, toxic megacolon, and subsequent bowel perforation, which are associated with high mortality. The cost of treating CDI in the United States alone is estimated to be at least $1.5 billion.[2] The primary risk factor for CDI is antibiotic use.[3] However, additional known risk factors include acid-suppressive medications (proton pump inhibitors and histamine 2 receptor antagonists),

ABBREVIATIONS: CDI, Clostridium difficile infection; **CI,** confidence interval; **ICD-9,** *International Classification of Diseases, 9th Revision*; **ICD-9-CM,** *International Classification of Diseases, 9th Revision, Clinical Modification*; **IQR,** interquartile range; **NICU,** neurological intensive care unit; **NIS,** Nationwide Inpatient Sample; **SAH,** subarachnoid hemorrhage

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advanced age, longer hospital stay, colonization pressure, infectious contacts, and the utilization of medical devices including mechanical ventilation.[2-15] Corticosteroids and laxative usage have also been suggested to be risk factors for CDI.[16] Diabetes mellitus, hematologic malignancies, and renal disease are comorbidities that are known to be associated with CDI.[10,16,17]

CDI is a potential complication for surgical and intensive care unit patients, and has been shown in these populations to be associated with inferior outcomes, including increased mortality and longer length of hospital stay.[6,18-25] Although the documented increased incidence of CDI is alarming, this rise in *C. difficile* is not inexorable. Antibiotic stewardship programs have been associated with decreased CDI.[26] Additionally, previous studies in Canada have shown that comprehensive prevention programs have decreased this incidence of CDI by 27%.[27]

Despite the prevalence of CDI, few studies have evaluated the impact of CDI on patients undergoing neurosurgical intervention or receiving care in a neurological intensive care unit,[28] and no nationwide study to date has evaluated the impact of CDI on the outcomes of patients with aneurysmal subarachnoid hemorrhage (SAH). The goal of this study is to utilize a nationally representative patient population to examine the association between CDI and cerebral aneurysm repair after SAH to evaluate the following questions: (1) What is the national prevalence of CDI after aneurysmal SAH (as estimated by the Nationwide Inpatient Sample)? (2) What are the patient- and hospital-level predictors of developing CDI after SAH? (3) What is the impact of the development of CDI on the periprocedural outcomes after SAH?

METHODS

Data Source

Data were extracted from the Nationwide Inpatient Sample (NIS, Healthcare Cost and Utilization Project, Agency Healthcare Research and Quality) from 2002 to 2011. The NIS is a 20% stratified sample of nonfederal hospitals and the largest all-payer national database in the United States,[29] and it has been utilized extensively to evaluate the outcomes of patients with aneurysmal SAH.[30-45]

Inclusion and Exclusion Criteria

Patients were included if they had an *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) diagnosis codes of SAH (430) or intracranial hemorrhage (431, 432.9); underwent aneurysm repair by microsurgical clipping (39.51) or endovascular embolization (39.72, 39.75, 39.76, 39.79); were aged 18 years or greater; and had a nonelective hospital admission. Admissions with a diagnosis code for a cerebrovascular malformation (747.81), syphilitic aneurysm (094.87), and cerebral arteritis (437.4), as well as with a procedure code for arteriovenous malformation repair (39.53) or stereotactic radiosurgery (923.x) were excluded.

Length of hospital stay was extracted. Because of the need to monitor for vasospasm, almost all patients with aneurysmal SAH have hospitalizations of at least 4 days unless they die shortly after aneurysm repair; however, those who die shortly after aneurysm repair are less likely to have had time to develop CDI. Thus, to specifically evaluate the impact of CDI on outcomes, only patients with a hospitalization of at least 4 days were included.

Patient Stratification

Patients were stratified based on CDI (008.45). The use of this ICD-9-CM code to identify CDI has previously been validated, with a pooled estimated positive predictive value of 87% and negative predictive value of 99.7%.[46]

Predictor Variables

Patient age, sex, and year of hospital admission were extracted. Age was evaluated categorically (18-44, 45-54, 55-64, and ≥65 years); these divisions were selected because they were the closest 5-year intervals to the median, lower, and upper quartiles of the study population. Admission year was divided into groups of 3 years (2002-2005, 2006-2008, 2009-2011) each of which included approximately one-third of the study population. Comorbidities were evaluated using the Elixhauser et al[47] comorbidity index, which is coded directly in NIS. Neurological deficits, paralysis, and electrolyte complications were excluded given the potential misclassification with SAH and its associated complications. Comorbidities present in 20 or fewer patients (lymphoma and hemorrhagic peptic ulcer) were also excluded. Patient insurance status was extracted, categorized as either private, Medicare, Medicaid, self-pay, or other. Hospital size, teaching status, and geographic region as encoded in the NIS were also evaluated.

All clinical data available in the NIS are encoded through *International Classification of Diseases, 9th Revision* (ICD-9) codes; therefore, pertinent clinical data without corresponding ICD-9 codes (such as Hunt-Hess grade) could not be extracted. However, additional diagnosis or procedure codes that are available for severity adjustment were utilized. Ventriculostomy (022, 0221) was evaluated because of its association with higher Hunt-Hess grades and symptomatic hydrocephalus; intraparenchymal or intraventricular hemorrhage (431) was analyzed because of its association with higher Fisher grade; and nonoperative mechanical ventilation (967.x) as well as diagnosis codes of coma (780.01, 780.03) and stupor (780.02, 780.09) were utilized as a markers of poor mental status. The treatment modality used for aneurysm repair was also used as a covariate to partially account for variations in institutional practice and aneurysm location. Decompressive craniectomy (01.25), cerebral herniation (348.4), and cerebral edema (348.5) were extracted to partially account for documented elevated intracranial pressure. Neurological deficits were evaluated based on diagnosis codes for aphasia (438.1.x, 784.3) or hemiparesis/plegia (342.x, 438.2.x-5x); because these ICD-9-CM codes do not specify if the diagnosis was present on admission, these deficits include those resulting from the initial hemorrhage, periprocedural complications, and delayed ischemic neurological deficit.

Complications and their treatment may predispose to the development of CDI: thus, both infectious and noninfectious complications were extracted. Infectious complications evaluated included urinary tract infections (595.0, 599.90, 996.64); pneumonia (481-486, 5070, 997.31); sepsis (38.x, 995.9.x); meningitis/ventriculitis (320.x, 322.0, 322.9); and other infections (including bacteremia 790.7, central venous catheter-associated infections 999.31, intracranial abscess 324.1, surgical site infections 998.59, systemic candidiasis 128, and other infections 041.x). Noninfectious complications evaluated included neurological (seizures 345.xx, stroke 433.x and 434.x, vasospasm 435.x, and

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neurological complications after procedure 997.01, 997.09); cardiac including myocardial infarction (410.xx, 248.xx, 427.5, 785.xx); pulmonary including respiratory failure (514.x, 518.xx, 512.x); renal (584.x); venous thromboembolic (453.x, 415.x); hematologic complications (285.x and 998.1.x); and sodium disturbances (253.5, 253.6, 276.0, 276.1). The total number of systems impacted by noninfectious complications was summed and evaluated categorically.

Outcomes

Outcomes evaluated included in-hospital mortality and length of hospital stay, both of which are directly encoded in the NIS; length of stay was evaluated both as a continuous variable and as a categorical variable, evaluating the proportion of patients with a hospital stay longer than the upper quartile of the interquartile range for the total study population. A nonroutine discharge was defined as any discharge other than to home, and was only evaluated for patients discharged from the hospital alive. Additional gastrointestinal procedures were evaluated, including colonoscopy (45.2.x) and surgical interventions: partial (45.7.x) or total (45.8.x) colectomy, colostomy or ileostomy (46.1.x, 46.2.x), and exploratory laparotomy (54.11, 54.19).

Sensitivity Analysis

Because the primary analysis was restricted to patients with a hospital stay of at least 4 days, a sensitivity analysis was performed to assess for congruity with the primary analysis without patient exclusion based on length of stay.

Statistical Analysis

All statistical analyses were performed using STATA Version 13 (College Station, Texas) after accounting for the survey design of the NIS. Baseline patient and hospital characteristics, treatment variables, and complications were compared using the χ^2 test. Predictors of developing CDI were determined by performing univariate logistic regression on each demographic variable (including individual medical comorbidities) using survey statistics; to increase the sensitivity of this initial screening stage, those with a P value of $<.10$ in univariate analyses were included in the multiple variable logistic regression model using forward prediction. C-statistics assessed the discriminatory capacity of each logistic regression model. Thereafter, hierarchical multivariate logistic regression models were constructed with all defined predictor variables to evaluate outcomes; analysis of in-hospital mortality also included length of hospital stay as an additional covariate owing to the association with hospital stay and CDI. Multivariate linear regression models evaluated length of stay as a continuous variable, which was logarithmically transformed due to nonnormal distribution. A P value of less than .05 was considered statistically significant.

RESULTS

Demographics of Study Population

Of the 18 007 admissions included in the study population, 1.9% (n = 346) had an associated diagnosis code for CDI. The demographics of patients, the hospitals at which they were treated, treatment variables, and other complications are compared by CDI in Table 1. The median age was 53 (interquartile range [IQR], 45-63) years for the total population, and was 57 (IQR, 48-66) years for those who developed CDI. The incidence of CDI was 1.6% for those admitted between 2002 and 2005, 2.0% for those admitted between 2006 and 2008, and 2.2% for those admitted between 2009 and 2011. The median number of comorbidities was 1 (IQR, 1-2) overall and 2 (IQR, 1-3) for those with CDI. Many predictors evaluated varied by CDI (Figure), including patient age, year of admission, and number of comorbidities.

Regression Modeling

Univariate logistic regression modeling compared each predictor variable with the development of CDI (Table 2). Variables that were significant in univariate models were then included in the final multiple variable logistic regression model (Table 3). The C-statistic of this model was 0.77.

Outcomes

The outcomes evaluated are compared based on the development of CDI in Table 4 and CDI was not found to be associated with differential in-hospital mortality (odds ratio [OR], 0.93; 95% confidence interval [CI], 0.53-1.63; P = .80). Among patients who developed CDI, only 1.2% underwent colectomy, 0.9% colostomy or ileostomy, and 0.6% exploratory laparotomy; the total rate of gastrointestinal surgery was 1.5%. The median length of hospital stay was 16 (IQR, 11-24) days in the entire population and 29 (IQR, 21-44) days for patients who developed CDI. When evaluated as a continuous variable, length of hospital stay was significantly longer for patients who developed CDI (by 33.47%, 95% CI, 28.15-38.79; $P < .001$, $R^2 = 0.34$). Moreover, CDI was associated with increased odds of a hospital stay of at least 24 days (OR, 3.16; 95% CI, 2.32-4.29; $P < .001$) and of a nonroutine hospital discharge (OR, 1.64; 95% CI, 1.13-2.39; $P < .01$).

Sensitivity Analysis

In the sensitivity analysis that did not use exclusion based on length of hospital stay, 18 695 patients were included in whom 1.9% (n = 346) had a diagnosis of CDI. Multivariate logistic regression identified the same significant predictors of developing CDI as the primary analysis, with the exception that the tumor comorbidity was only of borderline significance (P = .06, other data not shown). In this analysis, CDI was not associated with differential in-hospital mortality (OR, 0.83; 95% CI, 0.49-1.42; P = .50, C: 0.93), but was associated with increased odds of a hospital stay of at least 24 days (OR, 3.18; 95% CI, 2.34-4.33; $P < .001$, C: 0.86) and of a nonroutine hospital discharge (OR, 1.63; 95% CI, 1.20-2.37; P = .01, C: 0.84).

DISCUSSION

Although CDI is one of the most important hospital-acquired infections today, there are limited data on CDI in neurological intensive care units (NICUs) or after neurosurgical intervention. Earlier publications evaluating the prevalence of hospital-acquired infections in NICUs found very low rates of CDI,[48] and therefore

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TABLE 1. Demographics of Patients Undergoing Aneurysm Repair After Subarachnoid Hemorrhage, Stratified by *C. difficile* Infection[a,b]

Variable	Definition	Total Pop. (n = 18 007)	+*C. diff* (n = 346)	−*C. diff* (n = 17 661)	*P* Value[c]
Age, y	18-44	23.4	17.3	23.6	**.001**
	45-54	30.2	25.7	30.3	
	55-64	24.0	27.8	24.0	
	≥65	22.3	29.2	22.2	
Year of admission	2002-2005	37.0	30.6	37.0	**.04**
	2006-2008	31.0	33.0	31.0	
	2009-2011	32.0	36.4	32.0	
Sex	Female	68.7	67.9	68.7	.77
	Male	31.4	32.1	31.3	
Comorbidities	0	22.9	19.1	23.0	<**.001**
	1	34.3	24.9	34.5	
	2	24.7	29.8	24.6	
	≥3	18.1	26.3	17.9	
Payer status	Private	46.4	39.2	46.5	<**.001**
	Medicare	22.7	29.9	22.6	
	Medicaid	14.9	20.6	14.8	
	Self-pay	11.4	7.6	11.5	
	Other	4.6	2.6	4.6	
Intraparenchymal hemorrhage		8.0	13.3	7.9	<**.001**
Sensorium	Coma	4.2	6.9	4.2	**.01**
	Stupor	1.2	1.7	1.1	.30
Mechanical ventilation		37.0	65.3	36.4	<**.001**
Cerebral edema		7.2	7.5	7.2	.84
Herniation		2.8	1.2	2.8	.06
Treatment variables	Ventriculostomy	35.6	54.3	35.2	<**.001**
	Microsurgical clipping	56.1	52.3	56.2	.15
	Decompressive craniectomy	1.1	2.0	1.1	.08
Neurological deficits	Aphasia	5.5	6.7	5.4	.32
	Hemiparesis	11.5	13.3	11.4	.28
Infectious complications	Urinary tract infection	21.1	35.0	20.8	<**.001**
	Pneumonia	21.9	47.4	21.54	<**.001**
	Sepsis	5.3	15.9	5.1	<**.001**
	Meningitis/Ventriculitis	4.3	12.1	4.1	<**.001**
	Other infection	14.6	23.7	14.4	<**.001**
Noninfectious complications	0	28.0	7.8	28.5	<**.001**
	1	29.4	18.8	29.6	
	2	23.6	32.4	23.4	
	≥3	19.0	41.0	18.5	
Hospital region	Northeast	17.8	23.7	17.7	**.002**
	Midwest	21.1	21.4	21.1	
	South	37.7	28.9	37.9	
	West	23.4	26.0	23.3	
Hospital bed size	Small	3.3	3.2	3.3	.68
	Medium	12.3	13.8	12.2	
	Large	84.4	82.9	84.4	
Teaching hospital		87.2	87.1	87.2	.96

[a] *C. diff, Clostridium difficile*; Pop., population.
[b] All data are presented as percentages.
[c] Statistically significant *P* values are boldfaced.

these reports focused on infections that were more prevalent, including catheter-associated blood stream infections and pneumonia.[49] Musa et al[28] evaluated CDI in a single NICU in England, finding a prevalence of 0.6%; SAH was the most common diagnosis among those who developed CDI. Although CDI was treated successfully with antibiotics in most patients in this series, 23.8% patients developed serious complications from CDI, and all-cause mortality for those with CDI was 19%. Although there are limited data on CDI after cranial surgery, Skovrlj et al[23] have reported on the impact of CDI on the

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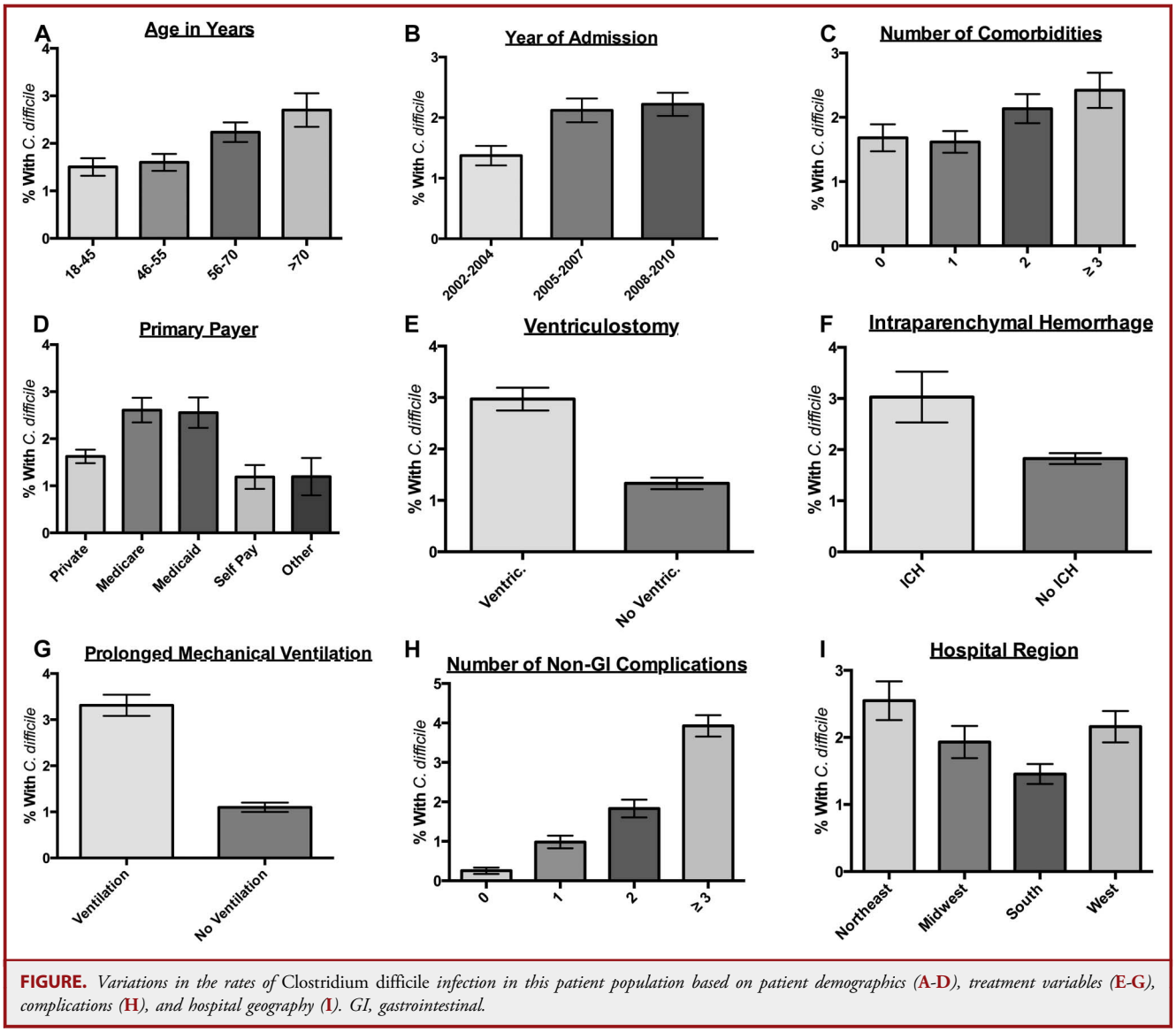

FIGURE. *Variations in the rates of* Clostridium difficile *infection in this patient population based on patient demographics (A-D), treatment variables (E-G), complications (H), and hospital geography (I). GI, gastrointestinal.*

outcomes after elective lumbar spine surgery, finding that CDI was associated with a 36.4-fold increased postoperative mortality. However, no study to date has specifically evaluated CDI in the setting of aneurysmal SAH. Those who have sustained SAH may be a particularly good patient population in which to evaluate CDI, because these patients typically have a comparatively long hospital stay to monitor for hydrocephalus and vasospasm, often in an intensive care unit.

In this nationwide study, 18 007 patients with a diagnosis of SAH who underwent aneurysm repair after SAH were included to evaluate the prevalence of, predictors for, and impact of CDI on outcomes. The prevalence of CDI in this population was found to be 1.9%. In multiple variable logistic regression analyses, Medicaid coverage, ventriculostomy, mechanical ventilation, infectious complications, and noninfectious complications were found to be independently associated with CDI. The frequency of interventional treatment in patients who developed CDI was comparatively low, because only 2.9% underwent colonoscopy (which may be therapeutic if used for colonic decompression or fecal transplantation)[50,51] and 1.5% required gastrointestinal surgery. CDI was not associated with significantly different odds of in-hospital mortality; however, length of hospital stay was longer and the odds of a nonroutine discharge were higher for those who developed CDI.

Given the association between antibiotic use and CDI, it is not surprising that multiple infectious complications, including urinary tract infections, pneumonia, sepsis, and meningitis/ventriculitis, were independently associated with developing

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TABLE 2. Univariate Logistic Regression Evaluating Potential Predictors of Developing *C. difficile* After Aneurysm Repair Following SAH[a]

Variable	OR	95% CI	*P* Value[b]
Age, y			
18-44	*Ref.*	—	—
45-54	1.12	0.79-1.57	.53
55-64	1.53	1.12-2.10	**.008**
≥65	1.75	1.27-2.42	**.001**
Year of admission			
2002-2005	*Ref.*	—	—
2006-2008	1.23	0.93-1.65	.15
2009-2011	1.35	0.98-1.85	.06
Sex			
Male	*Ref.*	—	—
Female	0.98	0.78-1.22	.83
Comorbidity			
AIDS	—	—	—
Alcohol abuse	1.07	0.67-1.71	.28
Anemia	1.49	1.17-1.90	**.001**
Arthritis (rheumatoid)/ collagen disease	0.68	0.21-2.24	.53
Chronic blood loss anemia	0.84	0.26-2.71	.77
CHF	1.53	1.04-2.27	**.03**
Chronic pulmonary disease	1.43	1.08-1.88	**.01**
Coagulopathy	1.66	1.09-2.52	**.02**
Diabetes mellitus (uncomplicated)	1.10	0.77-1.57	.59
Diabetes mellitus (chronic complications)	2.17	0.89-5.26	.09
Drug abuse	1.04	0.66-1.64	.87
Hypertension	1.01	0.81-1.27	.92
Hypothyroidism	0.80	0.47-1.37	.42
Liver disease	1.77	0.87-3.62	.12
Metastatic cancer	1.26	0.17-9.18	.82
Obesity	0.88	0.53-1.47	.63
Peripheral vascular disorders	1.55	1.03-2.34	**.04**
Pulmonary circulation disorder	2.63	1.44-4.81	**.002**
Renal failure	1.97	1.02-3.80	**.04**
Solid tumor without metastasis	2.49	1.02-6.08	**.04**
Valvular disease	1.16	0.61-2.21	.64
Weight loss	2.74	1.97-3.80	**<.001**
Primary payer			
Private	*Ref.*	—	—
Medicare	1.57	1.22-2.01	**.001**
Medicaid	1.63	1.25-2.12	**<.001**
Self-pay	0.77	0.49-1.20	.25
Other	0.69	0.30-1.57	.37
Intraparenchymal hemorrhage	1.79	1.27-2.53	**.001**
Sensorium			
Coma	1.76	1.19-2.60	**.004**
Stupor	1.53	0.60-3.91	.37
Mechanical ventilation	3.26	2.59-4.12	**<.001**
Cerebral edema	1.07	0.72-1.60	.74
Herniation	0.40	0.15-1.09	.07
Treatment variables			
Ventriculostomy	2.20	1.75-2.71	**<.001**
Microsurgical clipping	0.87	0.71-1.07	.18
Decompressive craniectomy	1.96	0.94-4.08	.07
Neurological deficits			
Aphasia	1.26	0.83-1.91	.27
Hemiparesis	1.19	0.87-1.64	.28
Infectious complications			
Urinary tract infection	2.03	1.62-2.55	**<.001**
Pneumonia	3.27	2.64-4.04	**<.001**
Sepsis	3.54	2.63-4.77	**<.001**
Meningitis/ventriculitis	3.13	2.24-4.36	**<.001**
Other infection	1.85	1.41-2.44	**<.001**
Noninfectious complications			
0	*Ref.*	—	—
1	2.34	1.51-3.63	**<.001**
2	5.02	3.23-7.81	**<.001**
≥3	7.97	5.23-12.1	**<.001**
Hospital region			
Northeast	*Ref.*	—	—
Midwest	0.74	0.53-1.04	.08
South	0.56	0.40-0.79	**.001**
West	0.82	0.58-1.15	.25
Teaching hospital	1.02	0.73-1.43	.90
Hospital bed size			
Small	*Ref.*	—	—
Medium	1.16	0.60-2.25	.66
Large	1.00	0.56-1.79	1.00

[a]AIDS, acquired immunodeficiency syndrome; CHF, congestive heart failure; CI, confidence interval; OR, odds ratio; Ref., reference; SAH, subarachnoid hemorrhage.
[b]Statistically significant *P* values are boldfaced.

CDI in this study. The fact that UTIs remained an independent predictor of CDI despite including other infectious complications in the multivariate model emphasizes the importance of minimizing the risk of developing UTIs in this patient population. Meticulous sterile technique during placement, securing the catheter to the leg, and early discontinuation of catheters have been shown in neurosurgical patients to decrease the incidence of UTIs.[52] Ventriculostomy was also found to be associated with CDI. Although the usage of antibiotic-impregnated ventricular catheters is increasing,[53] patients with an external ventricular drain often receive periprocedural antibiotic administration, and some patients may also undergo continued antibiotic prophylaxis while the drain is in place. Previous studies have found that discontinuing antibiotic prophylaxis while external ventricular drains are in place was associated with a decrease in the incidence of CDI.[54]

Although the association between CDI and infectious complications is not surprising, it is notable that a greater burden of noninfectious complications was also found to be an independent predictor of CDI in this study. Patients who have developed noninfectious complications may have greater exposure to health care providers and thus higher colonization pressure; they may also have a dampened immunologic response to the stress of CDI

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TABLE 3. Multivariate Logistic Regression Evaluating the Predictors of Developing *C. difficile* Infection After Aneurysmal SAH[a]

Variable	OR	95% CI	*P* Value[b]
Age, y			
18-44	*Ref.*	—	—
45-54	0.99	0.70-1.40	.97
55-64	1.24	0.90-1.72	.19
≥65	1.02	0.66-1.57	.93
Year of admission			
2002-2005	*Ref.*	—	—
2006-2008	1.08	0.81-1.44	.59
2009-2011	1.08	0.79-1.49	.63
Comorbidity			
Anemia	0.88	0.66-1.17	.38
Congestive heart failure	0.83	0.55-1.26	.39
Chronic pulmonary disease	1.18	0.88-1.60	.27
Coagulopathy	0.93	0.61-1.44	.72
Diabetes mellitus (chronic complications)	1.29	0.52-3.21	.58
Peripheral vascular disease	1.26	0.83-1.92	.28
Pulmonary circulation disorder	1.32	0.73-2.39	.36
Renal failure	1.35	0.68-2.66	.39
Tumor	**2.55**	**1.05-6.22**	**.04**
Weight loss	1.42	0.99-2.05	.06
Primary payer			
Private	*Ref.*	—	—
Medicare	1.24	0.86-1.78	.26
Medicaid	**1.49**	**1.14-1.95**	**.004**
Self-pay	0.94	0.59-1.50	.79
Other	0.77	0.34-1.78	.54
Intraparenchymal hemorrhage	1.30	0.90-1.90	.17
Sensorium			
Coma	1.07	0.70-1.64	.74
Mechanical ventilation	**1.57**	**1.19-2.08**	**.001**
Herniation	**0.22**	**0.08-0.62**	**.004**
Treatment variables			
Ventriculostomy	**1.35**	**1.06-1.72**	**.02**
Decompressive craniectomy	1.31	0.60-2.88	.49
Infectious complications			
Urinary tract infection	**1.51**	**1.18-1.92**	**.001**
Pneumonia	**1.69**	**1.32-2.15**	**<.001**
Sepsis	**1.65**	**1.17-2.33**	**.005**
Meningitis/ventriculitis	**2.00**	**1.35-2.96**	**.001**
Other infection	1.10	0.82-1.49	.53
Non-infectious complications			
0	*Ref.*	—	—
1	1.55	0.99-2.43	.06
2	**2.43**	**1.49-3.97**	**<.001**
≥3	**3.09**	**1.85-5.16**	**<.001**
Hospital region			
Northeast	*Ref.*	—	—
Midwest	0.74	0.52-1.06	.10
South	**0.65**	**0.46-0.92**	**.02**
West	0.80	0.55-1.17	.25

[a]CI, confidence interval; OR, odds ratio; Ref., reference; SAH, subarachnoid hemorrhage.
[b]Statistically significant *P* values are boldfaced.

colonization. Additionally, mechanical ventilation was associated with CDI and there was a trend toward significance for premorbid weight loss. This suggests that overall nutritional status and integrity of the immune system may also be important for the development of CDI. Ensuring adequate caloric intake, optimizing nutritional status, and resuming enteral feeding when logistically feasible may be important to maintain normal gastrointestinal flora.

In addition to patient variables, insurance status and hospital geography were found to be associated with the development of CDI; these associations have been previously reported in patients undergoing cardiac and vascular surgery. Regional variation in the incidence of CDI has been previously reported and at least partially attributable to differential colonization of health care facilities and workers with the pathogen.[19] Previous studies have shown that hospital and regional initiatives (including antibiotic stewardship programs) can decrease the incidence of CDI, and should be pursued when the incidence of CDI is found to be high.[26] Differential rates of CDI by payer status have been previously reported in surgical populations, hypothesized to be due to poor baseline heath because of decreased access to primary care.[19]

CDI was not found in this population to be associated with differential mortality. The odds of undergoing colonoscopy or gastrointestinal surgery during the hospitalization were higher for patients with CDI, which is not surprising, because there are relatively few reasons why patients would require these interventions after cerebral aneurysm repair. Nonetheless, the absolute rates of these interventional treatments in this patient population were relatively low, suggesting that medical treatment alone may be sufficient in most patients with SAH. However, inferior outcomes were found for those with CDI in terms of longer length of stay and increased odds of a nonroutine hospital discharge in multivariate analyses including both infectious and noninfectious complications, as well as other demographics and severity adjustment markers as covariates, which emphasizes the importance of CDI on the outcomes and efficiency of care after SAH.

Limitations

There are many notable limitations to this study. As with any study based on ICD-9 identifiers, there may be coding errors, and

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TABLE 4. The Impact of *C. difficile* Infection on the Outcomes After Aneurysmal Subarachnoid Hemorrhage[a]

Definition	Total Pop. (n = 18 007)	+*C. diff* (n = 346)	−*C. diff* (n = 17 661)	OR	95% CI	*P* Value[b]	C-Statistic
In-hospital mortality	11.2	7.5	11.2	0.93	0.53-1.63	.80	0.92
Length of stay ≥ 24 d	27.5	70.3	26.6	3.16	2.32-4.29	**<.001**	0.86
GI surgery	0.2	1.5	0.2	3.94	1.36-11.42	**.01**	0.85
Colonoscopy	0.2	2.9	0.2	12.09	5.29-27.64	**<.001**	0.88
Nonroutine discharge	55.3	83.4	54.7	1.64	1.13-2.39	**.01**	0.84

[a]*C. diff, Clostridium difficile*; CI, confidence interval; GI, gastrointestinal; OR, odds ratio; Pop., population.
[b]Statistically significant *P* values are boldfaced.

as with any study based on the NIS, there are limited outcomes available and data are only available from hospitals that partake in the Healthcare Cost and Utilization Project. Because clinical data are only available if there is a corresponding ICD-9 code, data on antibiotic administration and duration, acid-suppressive medication usage, the method of detection of CDI, and the severity of CDI upon diagnosis could not be evaluated. Likewise, validated measures of severity of aneurysmal SAH including Hunt-Hess grade and Fisher grade, as well as aneurysm location, could not be ascertained; thus, severity adjustment was estimated with other clinical variables including ventriculostomy, mechanical ventilation, and modality selected for aneurysm repair. The time between specific complications and CDI could not be evaluated. Therefore, it is difficult to ascertain which infectious complications preceded CDI, and only the association between these infections and CDI, and not causality, could be assessed. The cause of death is not listed in the NIS, and therefore it is impossible to ascertain in how many patients in-hospital mortality was attributed to complications related to CDI. Moreover, the true prevalence of CDI after cerebral aneurysm repair may be underestimated by the NIS, because this database only follows patients during the hospital stay and does not include data on patients who developed CDI after the index hospitalization.

CONCLUSION

There are also many important advantages to the use of a nationwide data set to evaluate the association between CDI and cerebral aneurysm repair after SAH. The NIS includes a broad patient population including those from a large geographic area and a breadth of institutions. This decreases the bias of patients treated at large, academic medical centers, or the publication bias of institutions that may report their experience with CDI after several untoward events. In addition, the NIS provides a large sample size providing statistical power to assess patient- and hospital-level predictors of developing CDI after SAH. The fact that CDI had a profound association with length of hospital stay and nonroutine hospital discharge disposition highlights the importance of CDI after SAH. Additional studies, particularly with prospective data, are needed to design and evaluate the implementation of programs to decrease the incidence of CDI in NICUs.

Disclosures

Dr Aziz-Sultan is a proctor for Covidien and Codman; teaches courses and physicians. Dr Gormley: Codman. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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