Preoperative chemotherapy and corticosteroids: independent predictors of cranial surgical-site infections

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OBJECTIVE Preoperative corticosteroids and chemotherapy are frequently prescribed for patients undergoing cranial neurosurgery but may pose a risk of postoperative infection. Postoperative surgical-site infections (SSIs) have significant morbidity and mortality, dramatically increase the length and cost of hospitalization, and are a major cause of 30-day readmission. In patients undergoing cranial neurosurgery, there is a lack of data on the role of patient-specific risk factors in the development of SSIs. The authors of this study sought to determine whether chemotherapy and prolonged steroid use before surgery increase the risk of an SSI at postoperative Day 30.

METHODS Using the national prospectively collected American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database for 2006–2012, the authors calculated the rates of superficial, deep-incisional, and organ-space SSIs at postoperative Day 30 for neurosurgery patients who had undergone chemotherapy or had significant steroid use within 30 days before undergoing cranial surgery. Trauma patients, patients younger than 18 years, and patients with a preoperative infection were excluded. Univariate analysis was performed for 25 variables considered risk factors for superficial and organ-space SSIs. To identify independent predictors of SSIs, the authors then conducted a multivariate analysis in which they controlled for duration of operation, wound class, white blood cell count, and other potential confounders that were significant on the univariate analysis.

RESULTS A total of 8215 patients who had undergone cranial surgery were identified. There were 158 SSIs at 30 days (frequency 1.92%), of which 52 were superficial, 27 were deep-incisional, and 79 were organ-space infections. Preoperative chemotherapy was an independent predictor of organ-space SSIs in the multivariate model (OR 5.20, 95% CI 2.33–11.62, $p < 0.0001$), as was corticosteroid use (OR 1.86, 95% CI 1.03–3.37, $p = 0.04$), but neither was a predictor of superficial or deep-incisional SSIs. Other independent predictors of organ-space SSIs were longer duration of operation (OR 1.16), wound class of ≥ 2 (clean-contaminated and further contaminated) (OR 3.17), and morbid obesity (body mass index ≥ 40 kg/m²) (OR 3.05). Among superficial SSIs, wound class of 3 (contaminated) (OR 6.89), operative duration (OR 1.13), and infratentorial surgical approach (OR 2.20) were predictors.

CONCLUSIONS Preoperative chemotherapy and corticosteroid use are independent predictors of organ-space SSIs, even when data are controlled for leukopenia. This indicates that the disease process in organ-space SSIs may differ from that in superficial SSIs. In effect, this study provides one of the largest analyses of risk factors for SSIs after cranial surgery. The results suggest that, in certain circumstances, modulation of preoperative chemotherapy or steroid regimens may reduce the risk of organ-space SSIs and should be considered in the preoperative care of this population. Future studies are needed to determine optimal timing and dosing of these medications.

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KEY WORDS surgical-site infection; NSQIP; 30-day readmission; chemotherapy; steroids; predictors of infection

ABBREVIATIONS ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program; ASA = American Society of Anesthesiologists; BMI = body mass index; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; CPT = Current Procedural Terminology; IQR = interquartile range; OR = odds ratio; SIRS = systemic inflammatory response syndrome; SSI = surgical-site infection; WBC = white blood cell.

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EVERY year, more than 100,000 cranial neurosurgical procedures are performed nationally (<http://hcupnet.ahrq.gov>). Patients are frequently prescribed regimens of corticosteroids or chemotherapy for days to weeks preoperatively, depending on the diagnosis. In neurosurgery, neoadjuvant chemotherapy often plays a role in the management of neoplasms, and steroids are very useful in decreasing cerebral edema, inflammation, and symptoms related to increased intracranial pressure.^{8,17,29} However, both therapies may compromise immunity; neutropenia is a well-known complication of chemotherapy, and corticosteroids broadly attenuate the action of leukocytes and inflammatory mediators.^{2-4,10,26} It is less established, however, whether these therapies affect the risk of surgical-site infections (SSIs) in cranial neurosurgery patients after data are controlled for potential confounders.

SSIs are among the most common types of hospital-acquired infections and are responsible for increased mortality, poorer functional outcome, 1 million days in excess hospital stay, and more than \$1.5 billion in additional health care expenditures.⁷ In neurosurgery, SSIs are also a major cause of early hospital readmission within 30 days of discharge.^{5,30} The incidence of cranial SSIs—categorized as superficial, deep incisional, or organ space—ranges between 0.7% and 6.6% in large studies.^{9,18,32} Risk factors for SSIs include operative duration, advanced age, diabetes mellitus, American Society of Anesthesiologists (ASA) class, and wound class.^{19,20,32,33} Knowledge of risk factors as they pertain to neurosurgery is essential in determining ideal timing for preoperative regimens, selecting optimal patients, and guiding appropriate postoperative management.

Although substantial evidence has been documented in other surgical specialties,^{16,22,34} less is known about the effects of chemotherapy and steroids—and patient-specific factors in general—on the risk of SSIs in cranial neurosurgery. Therapies that affect immune function may have effects on the risk of SSIs in cranial surgery that differ from those in other surgical fields.^{21,23} Not only does the central nervous system (CNS) have a unique anatomical environment that includes the dura mater, it also has a distinctive immune environment with microglia and relatively few neutrophils. In the limited data that exist on the predictors of SSIs in cranial patients, it was noted in a small single-center study that preoperative chemotherapy trended toward significance in increasing SSI risk.⁶ Somewhat more data exist demonstrating the impact of corticosteroids on the risks of a broad range of postoperative infections in a wide variety of neurosurgical patients, including those who have undergone cranial, spine, or peripheral nerve procedures.²⁵ However, there is the need for a large study that focuses on the risk of SSIs in cranial surgery and controls for factors known to specifically affect SSI risk in neurosurgical patients who undergo cranial procedures.

We hypothesized that preoperative chemotherapy and protracted steroid use increase the incidence of SSIs at postoperative Day 30. In this study, one of the largest of its kind to date, we used the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database to assess the risk of chemotherapy and significant corticosteroid use on superficial and organ-space cranial SSIs.

Methods

Data Source

The ACS NSQIP is a validated, prospectively maintained registry of information obtained from randomly assigned consenting surgical patients from several hundred academic and community hospitals nationwide. The ACS NSQIP database includes information on more than 250 variables, such as demographic information, preoperative characteristics, comorbidities, intraoperative variables, and 30-day morbidity and mortality data in both the inpatient and outpatient settings. There is a 95% success rate in capturing outcomes and greater than 95% interrater reliability in all variables.³¹ Hospitals that participate in ACS NSQIP are required to employ specially trained surgical clinical reviewers, who adhere to strict variable definitions and collection methods.^{13,15} A variety of methods are used to collect data, including medical chart reviews, phone calls, and letters.³¹ Important exclusion criteria were patients younger than 18 years of age and patients treated for trauma. Hospitals are routinely audited to ensure that the data collected are standardized, and previous audits have found near-perfect agreement on the coding of most variables.³¹ Participating hospitals are also provided with risk-adjusted outcomes from ACS NSQIP so that they may use it as a performance measure to compare with national averages.¹⁵ Further details, including lists of inclusion and exclusion criteria in the database and wound classification criteria, are on the ACS NSQIP website (<https://www.facs.org/quality-programs/acs-nsqip>).

Study Population and Primary Outcomes

Prospectively collected data from the years 2006–2012 were obtained from ACS NSQIP. Cases were extracted by querying the data for cases with the primary surgeon's specialty listed as "neurological surgery." As done in previous neurosurgical studies that have queried the ACS NSQIP database,²⁸ all cranial procedures were selected on the basis of ACS NSQIP–used Current Procedural Terminology (CPT) codes: 21137, 21138, 21139, 21175, 21179–21184, 21299, and 61304–62121. Patients were excluded from analysis of organ-space SSIs if they had an infection that was known preoperatively, including if they were undergoing a craniotomy or craniectomy for osteomyelitis (CPT 61501) or an abscess (CPT 61320, 61321, 61514, or 61522). Cases with a wound class of 4 or a "dirty" operative site were also excluded from our analysis of superficial SSIs. Per NSQIP criteria, wounds are classified as "clean" (Class 1), "clean-contaminated" (Class 2), "contaminated" (Class 3), or "dirty" (Class 4). Cases were also grouped into those involving transsphenoidal or ethmoidal sinus penetration (CPT 61548, 61580, or 61581) versus no sinus penetration, and infratentorial (CPT 61305, 61315, 61343, 61345, 61440, 61514, 61519, 61520, 61521, or 61524) versus supratentorial. Overall malignancy and its breakdown into primary versus secondary brain cancer were defined according to pertinent postoperative ICD-9 diagnostic codes.

The primary outcome was development of an SSI by postoperative Day 30. Infectious categories were assigned by ACS NSQIP using Centers for Disease Control guidelines. These consisted of superficial incisional infections

(skin and subcutaneous tissue, excluding stitch abscesses), deep-incisional infections (beneath the subcutaneous tissue until the calvaria), and organ-space infections (including the calvaria down to the brain parenchyma). Only descriptive analysis was performed on deep-incisional SSIs because there was an insufficient number of this category of infections to perform a multivariate predictive analysis. Univariate analysis was performed for 25 variables considered risk factors for superficial and organ-space SSIs. These risk factors were selected on the basis of careful review of prior related SSI literature. Significant corticosteroid use was defined by ACS NSQIP as more than 10 consecutive days of oral or parenteral medication within 30 days prior to the operation. Chemotherapy, which excludes hormonal therapy, was defined as chemotherapy treatment within 30 days preoperatively. Further operational definitions for each of the perioperative risk factors are provided by the ACS NSQIP 2013 user guide (<http://www.aast.org/Assets/fe526f57-5bd3-4700-94bc-497b035551db/635282483441930000/nsqip-definitions-7-1-2013-pdf>). In subsequent multivariate analysis, data were controlled for duration of operation, wound class, white blood cell (WBC) count, and other potential confounders that were significant on the univariate analysis in order to identify independent predictors of superficial-incisional and organ-space SSIs.

Statistical Analyses

Analysis was performed using SPSS version 22 (IBM Corp.). Descriptive statistics are represented as the mean $\pm$ standard deviation and interquartile range (IQR). Initially, univariate analyses were performed on patient demographic characteristics and salient preoperative variables, using the Pearson chi-square test or Fisher exact test when appropriate for categorical data and the Mann-Whitney U-test for continuous variables (e.g., total operation time). Variables with $p \leq 0.20$, as well as factors with a priori clinical significance (chemotherapy, radiotherapy, WBC count, steroids, and malignancy), were entered into a multivariate logistic regression model. We used binary logistic regression with a maximum number of iterations of 20 and significance threshold of $p < 0.05$. Independent predictors of SSIs were identified using this model, and their odds ratios (ORs) and 95% CIs are presented. We employed listwise deletion for subjects missing any of the studied variables. The sample of patients with complete data for each analysis is reported. Goodness of fit for each regression model was assessed via the Hosmer and Lemeshow test, which accomplishes this by testing the null hypothesis that the difference between observed and expected events is zero. The corresponding Pearson chi-square value and p value were then calculated. The predictive power of our model was quantified via receiver operating characteristic (ROC) test C-statistics, which represent the area under an ROC curve and can be used to compare the goodness of fit of regression models.

Results

We identified 8215 patients from the ACS NSQIP database who met the criteria for inclusion. A total of 8098 were included in the analysis of superficial SSIs, after we

excluded an additional 117 patients with a wound class of 4, since ACS NSQIP considers these patients as having a preoperative superficial infection (thus meeting our original exclusion criteria). Seventy-two patients were excluded from the organ-space SSI analysis (leaving a total of 8143) because of the presence of a preoperative abscess, which NSQIP considers a preoperative organ-space infection. Within the total population of 8215 patients, 158 patients (1.92%) developed an SSI; 52 (0.64%) of 8098 patients had a superficial SSI, 27 (0.33%) of 8215 had a deep-incisional SSI, and 79 (0.97%) of 8143 had an organ-space SSI. The mean age of our patients was 55.69 years (SD 16 years, IQR 45–67 years) and 52.4% were female, and our ethnic distribution was consistent with the general US population (see <http://www.census.gov/2010census/data/>) (Table 1).

Organ-Space SSI

Of the 25 factors tested by univariate analysis (Table 2), 12 met our criteria of $p \leq 0.20$ to enter into multivariate analysis to determine independent predictors of an organ-space SSI at postoperative Day 30 (Table 3). Of these 12 factors, 5 were independently significant after controlling for all other covariates (Table 3). Independent predictors of organ-space SSI were preoperative chemotherapy (OR 5.20, 95% CI 2.33–11.62, $p < 0.0001$), chronic corticosteroid use (OR 1.86, 95% CI 1.03–3.37, $p = 0.043$), wound class ($p < 0.0001$), prior operation within 30 days (OR 2.32, 95% CI 1.08–5.02, $p = 0.03$), and operative duration (OR 1.16, 95% CI 1.07–1.26, $p < 0.0001$). Interestingly, leukopenia (defined as WBC count < 4000 cells/ μ l) was not a statistically significant factor ($p = 0.75$), but leukocytosis (defined as WBC count $> 11,000$ cells/ μ l) was associated with decreased odds of SSI (OR 0.31, 95% CI 0.15–0.64, $p = 0.001$). Patients with morbid obesity (body mass index [BMI] ≥ 40 kg/m²) also demonstrated an increased risk of infection (OR 3.05, 95% CI 1.38–6.75, $p = 0.006$). A history of severe chronic obstructive pulmonary disease (COPD) strongly trended toward significance as a predictor of organ-space SSI ($p = 0.06$), but radiation therapy within 90 days of the operation was not a significant predictor ($p = 0.996$). Our binary regression model demonstrated an excellent goodness of fit ($\chi^2 = 8.93$, $p = 0.35$) and predictability ($C = 0.77$).

In a secondary analysis, malignancy was further categorized as primary brain cancer or secondary brain cancer.

TABLE 1. Demographic characteristics of the study population

Characteristic	Value
Sex: male	3907 (47.60%)
Age in yrs	
Mean	55.69
SD	16.21
IQR	45.00–67.00
Race	
White	5578 (78.40%)
Asian	210 (3.00%)
Black	770 (10.80%)
American Indian	22 (0.30%)
Hispanic	524 (7.40%)

TABLE 2. Univariate analysis of factors for superficial and organ-space SSIs at postoperative Day 30

Variable	Superficial SSI			Organ-Space SSI		
	No. of Pts (%)	Frequency	p Value	No. of Pts. (%)	Frequency	p Value
WBC count			0.18			0.03
Normal	5887 (72.7%)	0.5%		5917 (72.7%)	1.1%	
<4 cells/ μ l	270 (3.33%)	1.1%		272 (3.34%)	1.1%	
>11 cells/ μ l	1941 (24.0%)	0.9%		1954 (24.0%)	0.5%	
BMI (kg/m ²)			0.29			0.04
<18.5	509 (5.59%)	0.6%		518 (6.36%)	0.8%	
18.5–24.99	2318 (28.6%)	0.6%		2326 (28.6%)	1.2%	
25–29.99	2675 (33.0%)	0.6%		2689 (33.0%)	0.7%	
30–34.99	1522 (18.8%)	0.7%		1527 (18.8%)	1.2%	
35–40	643 (7.94%)	0.6%		650 (7.98%)	0.8%	
>40	431 (5.32%)	0.9%		433 (5.32%)	2.3%	
Age in yrs			0.12			0.15
18–40	1515 (18.7%)	0.8%		1897 (23.3%)	1.4%	
41–65	4185 (51.7%)	0.7%		4208 (51.7%)	1.0%	
66–79	1888 (23.3%)	0.4%		1525 (18.7%)	0.6%	
80–89	466 (5.75%)	0%		469 (5.76%)	0.6%	
$\geq$ 90	44 (0.54%)	1.9%		44 (0.54%)	0.00	
Current smoker			0.12			0.47
Yes	1767 (21.8%)	0.9%		1797 (22.1%)	1.1%	
No	6331 (78.2%)	0.6%		6346 (77.9%)	0.9%	
>2 ETOH drinks/2 wks preop			0.57			1.00
Yes	340 (4.20%)	0.9%		346 (4.25%)	0.9%	
No	7758 (95.8%)	0.6%		7797 (95.8%)	1.0%	
Severe COPD			0.87			0.15
Yes	348 (4.30%)	0.6%		349 (4.29%)	1.7%	
No	7750 (95.7%)	0.6%		7794 (95.7%)	0.9%	
Disseminated cancer			0.31			0.23
Yes	798 (9.85%)	0.5%		805 (9.89%)	0.9%	
No	7300 (90.1%)	0.7%		7338 (90.1%)	1.4%	
Malignancy			0.51			0.13
None	5856 (72.3%)	0.7%		5895 (72.4%)	0.8%	
Primary brain	1402 (17.3%)	0.4%		1403 (17.2%)	1.4%	
Secondary	840 (10.4%)	0.6%		845 (10.4%)	1.1%	
Chronic steroids			0.97			0.004
Yes	921 (11.4%)	0.7%		916 (11.2%)	1.9%	
No	7177 (88.6%)	0.6%		7227 (88.8%)	0.9%	
>10% body weight loss 6 mos preop			0.62			0.67
Yes	147 (1.82%)	0.6%		153 (1.88%)	1.3%	
No	7951 (98.2%)	0.7%		7990 (98.1%)	1.0%	
Transfusion >4 units PRBCs 72 hrs preop			0.29			1.00
Yes	52 (0.64%)	1.9%		53 (0.65%)	0.00%	
No	8046 (99.4%)	0.6%		8090 (99.3%)	1.0%	
Intra/postop transfusion			0.77			0.68
Yes	520 (6.42%)	0.4%		537 (6.59%)	1.0%	
No	7578 (93.6%)	0.7%		7606 (93.4%)	1.1%	

Continued

TABLE 2. Univariate analysis of factors for superficial and organ-space SSIs at postoperative Day 30 (continued)

Variable	Superficial SSI			Organ-Space SSI		
	No. of Pts	Frequency	p Value	No. of Pts	Frequency	p Value
Chemo <30 days preop			0.20			<0.0001
Yes	240 (2.96%)	1.2%		242 (2.95%)	3.7%	
No	7858 (97.0%)	0.6%		7901 (97.0%)	0.9%	
RT w/in 90 days preop			0.20			
Yes	129 (1.58%)	1.6%		131 (1.61%)	0.00%	
No	7969 (98.4%)	0.6%		8012 (98.4%)	1.0%	
Preop sepsis			0.04			0.76
None	7493 (92.5%)	0.6%		7506 (92.2%)	1.00%	
SIRS	533 (6.58%)	0.9%		543 (6.67%)	0.70%	
Sepsis	53 (0.65%)	1.9%		69 (0.85%)	0.00%	
Septic shock	19 (0.23%)	5.3%		25 (0.31%)	0.00%	
Prior op w/in 30 days			0.36			0.06
Yes	430 (5.28%)	0.9%		439 (5.39%)	1.8%	
No	7668 (94.7%)	0.6%		7704 (94.6%)	0.9%	
Emergency case			0.63			0.61
Yes	1357 (16.8%)	0.7%		1398 (17.2%)	1.1%	
No	6741 (83.2%)	0.6%		6745 (8.28%)	0.9%	
Wound class			0.08			0.001
1 (clean)	7626 (94.2%)	0.6%		7606 (93.4%)	0.9%	
2 (clean-contaminated)	388 (4.79%)	0.8%		387 (4.75%)	1.6%	
3 (contaminated)	84 (1.04%)	3.6%		80 (0.98%)	5.0%	
4 (dirty)	N/A	N/A	0.08	70 (0.86%)	1.4%	
ASA class						0.31
1	106 (1.28%)	1.9%		108 (1.33%)	0.0%	
2	2052 (25.3%)	0.3%		2067 (25.4%)	0.7%	
3	4445 (54.9%)	0.8%		4489 (55.1%)	1.1%	
4	1353 (16.7%)	0.4%		1385 (17.0%)	1.2%	
5	142 (1.75%)	0.1%		147 (1.81%)	0.0%	
Hematocrit						0.39
Normal (35–55%)	6588 (81.4%)	0.6%		6600 (81.1%)	0.9%	
<35%	1353 (16.7%)	0.7%		1379 (16.9%)	1.1%	
>55%	157 (1.94%)	0.6%		164 (2.01%)	1.9	
Infratentorial			0.02			0.34
Yes	680 (8.40%)	1.3%		688 (8.45%)	1.3%	
No	7418 (91.6%)	0.6%		7455 (91.6%)	0.9%	
Sphenoid sinus penetration			0.52			0.12
Yes	416 (5.14%)	0.2%		419 (5.15%)	0.2%	
No	7682 (94.9%)	0.7%		7724 (94.9%)	1.0%	
Diabetes			0.44			0.82
No	7099 (87.7%)	0.7%		7132 (87.6%)	1.0%	
Oral meds	197 (2.43%)	0%		198 (2.43%)	0.5%	
Non-insulin meds	423 (5.22%)	0.2%		428 (5.26%)	0.9%	
Insulin	379 (4.68%)	0.5%		385 (4.73%)	1.3%	
Dialysis			1.00			0.53
Yes	56 (0.69%)	0%		58 (0.71%)	1.8%	
No	8042 (99.3%)	0.6%		8085 (99.3%)	1.0%	

Chemo = chemotherapy; ETOH = ethanol; meds = medication(s); PRBCs = packed red blood cells; Pts = patients; RT = radiotherapy.

TABLE 3. Multivariate analysis of predictors of organ-space SSI

Variable	p Value	OR	95% CI Bounds	
			Lower	Upper
Operative duration (hrs)	<0.0001	1.159	1.070	1.255
Length of hospitalization (days)	0.189	1.006	0.997	1.015
History of severe COPD	0.060	2.349	0.966	5.713
Corticosteroid use	0.041	1.859	1.026	3.371
Chemo	<0.0001	5.201	2.328	11.620
Prior op w/in 30 days	0.032	2.324	1.076	5.021
Wound Class 1 (clean)	<0.0001			
Wound Class 2 (clean-contaminated)	0.012	3.232	1.288	8.109
Wound Class 3 (contaminated)	<0.0001	8.038	2.641	24.460
Wound Class 4 (dirty)	0.474	2.095	0.276	15.886
Sinus penetration	0.061	0.136	0.017	1.100
No malignancy	0.495			
Primary brain cancer	0.275	1.368	0.779	2.405
Secondary brain cancer	0.903	0.951	0.425	2.129
Normal WBC count (4000–11,000 cells/ μ l)	0.006			
WBC count <4000 cells/ μ l	0.754	0.825	0.248	2.746
WBC count >11,000 cells/ μ l	0.001	0.312	0.152	0.639
Normal BMI (18.5–24.9 kg/m ²)	0.047			
Underweight (BMI <18.5 kg/m ²)	0.338	1.586	0.617	4.075
Overweight (BMI 25–29.9 kg/m ²)	0.897	0.958	0.503	1.827
Obese (BMI 30–34.9 kg/m ²)	0.128	1.660	0.865	3.188
Very obese (BMI 35–39.9 kg/m ²)	0.986	1.009	0.371	2.748
Morbidly obese (BMI >40 kg/m ²)	0.006	3.049	1.377	6.753
Age 16–40 yrs	0.307			
Age 41–65 yrs	0.123	0.655	0.382	1.122
Age 66–79 yrs	0.035	0.448	0.212	0.945
Age 80–89 yrs	0.420	0.600	0.174	2.077
Age $\geq$ 90 yrs	0.998	0.000	0.000	0.000
RT w/in 90 days of op	0.996	0.000	0.000	0.000

Neither were independent predictors of SSIs (primary: OR 1.37, 95% CI 0.78–2.41, $p = 0.28$; secondary: OR 0.95, 95% CI 0.43–2.13, $p = 0.90$), and our results were unchanged (chemotherapy: $p < 0.0001$, OR 5.20, 95% CI 2.33–11.62; steroids: $p = 0.041$, OR 1.86, 95% CI 1.03–3.37; WBC < 4: $p = 0.754$, OR 0.83, 95% CI 0.25–2.75; WBC > 11: $p = 0.001$, OR 31, 95% CI 0.15–0.64).

Superficial SSI

Of the 25 variables that were tested in the univariate analysis (Table 2), 9 met our criteria of $p < 0.20$ to enter into the multivariable analysis to determine independent predictors of a superficial SSI at postoperative Day 30 (Table 4). These were operative duration, current smoker, preoperative radiation therapy within 90 days, preoperative chemotherapy within 30 days, wound class, ASA class, infratentorial cases, age, and preoperative manifestations of systemic inflammatory response syndrome (SIRS) or sepsis.

Preoperative chemotherapy, although predictive for organ-space SSIs, was not a predictor of superficial SSIs

in multivariate regression (OR 1.88, 95% CI 0.43–8.22, $p = 0.40$), and neither was a protracted course of steroids ($p = 0.73$, OR 0.85, 95% CI 0.34–2.14). Low, normal, or high WBC count was not a significant factor in superficial SSI ($p = 0.39$). The only independent predictors of superficial infection were operative duration (OR 1.13, 95% CI 1.02–1.25, $p = 0.02$), infratentorial case (OR 2.20, 95% CI 1.04–4.67, $p = 0.04$), and wound class ($p = 0.01$). Our model demonstrated good predictability ($C = 0.72$) and fit ($\chi^2 = 4.24$, $p = 0.84$).

Postinfection Outcomes

The majority of superficial, deep-incisional, and organ-space SSIs occurred after discharge (82.4%, 61.5%, and 74.1%, respectively). Although there was no significant difference in the frequency of postoperative death between patients with and those without an organ-space SSI (6.0% vs 4.8%, $p = 0.818$, respectively), patients with an organ-space SSI were far more likely to have postoperative sepsis (34.9% vs 3.3%, $p < 0.0001$) and septic shock (8.4% vs 1.2%, $p < 0.0001$).

Similar to organ-space SSIs, superficial SSIs did not lead to increased fatality (6.0% vs 1.9%, $p = 0.372$), although both were associated with poorer outcomes. Compared with patients without superficial SSIs, patients with superficial SSIs were significantly more likely to experience sepsis (9.6% vs 3.6%, $p = 0.021$) and require reoperation (28.8% vs 7.8%, $p < 0.0001$). There was a trend toward an increased frequency of septic shock (3.8% vs 1.3%, $p = 0.14$) in patients with superficial SSIs, and these patients had disproportionately more sepsis and septic shock than patients who developed organ-space SSIs.

Discussion

In this study we examined whether chemotherapy and prolonged use of steroids predict superficial or organ-space SSIs. After controlling for many previously identified covariates—including WBC count, wound class, and operative duration—preoperative chemotherapy and corticosteroid use were independent predictors of organ-space SSIs, but neither were significant risk factors for superficial SSIs.

Although the impact of oral or parenteral chemotherapy on immunity—and theoretically, the ability to fight infection—may be intuitively expected, its effect on postoperative infections has not been well described, particularly in neurosurgical patients.⁶ In one small study, Chiang et al.⁶ demonstrated an increased risk of SSIs on bivariate analysis, but there were only 6 patients on chemotherapy in the study. Other studies have shown an increased risk of SSIs with locally applied carmustine wafers.²⁴ Our study is among the largest to date demonstrating an increased risk of organ-space infections—such as meningitis—specifically among neurosurgical patients treated with preoperative or neoadjuvant chemotherapy.

Since the effects of chemotherapy on organ-space SSIs remained significant even when controlling for potentially strong confounders—including malignancy, preoperative radiotherapy, operative duration, and WBC count (Table 3)—our findings suggest that chemotherapy affects the risk of organ-space SSIs in ways that are not readily identifiable in the clinical setting. Most notably, chemotherapy was an independent predictor even in the absence of leukopenia (WBC count < 4000 cells/ μ l). In light of standard practice guidelines, according to which patients undergoing chemotherapy are generally considered to be at a higher risk of infection if they have associated leukopenia (and specifically neutropenia),¹⁰ our results suggest that even with an otherwise normal WBC count, neurosurgical patients who receive chemotherapy before undergoing cranial surgery are still at an increased risk of serious organ-space SSIs. Unlike the results of studies outside of neurosurgery, our finding that leukopenia was not predictive of organ-space SSIs in the multivariate model suggests that standard clinical tests, such as a complete blood count, may not sufficiently assess the risk of postoperative CNS organ-space infections in patients receiving chemotherapy.

Our finding that significant preoperative corticosteroid use increases the risk of an organ-space SSI may follow the similar logic that immunocompromising therapies are associated with an increased risk of SSIs. Specifically, our study focused on more than 10 days of corticosteroid use within the 30 days immediately preceding surgery, which

TABLE 4. Multivariate analysis of predictors of superficial SSI

Variable	p Value	OR	95% CI Bounds	
			Lower	Upper
Operative duration (hrs)	0.018	1.130	1.021	1.251
Current smoker	0.282	1.400	0.758	2.585
Chemo	0.399	1.884	0.432	8.223
RT w/in 90 days of op	0.379	2.186	0.383	12.480
No sepsis, SIRS, or septic shock	0.297			
SIRS	0.441	1.491	0.539	4.122
Sepsis	0.418	2.388	0.290	19.648
Septic shock	0.084	6.995	0.768	63.729
Wound Class 1 (clean)	0.010			
Wound Class 2 (clean-contaminated)	0.582	1.397	0.426	4.584
Wound Class 3 (contaminated)	0.003	6.893	1.964	24.196
ASA Class 1	0.064			
ASA Class 2	0.034	5.705	1.144	28.450
ASA Class 3	0.031	2.494	1.086	5.730
ASA Class 4	0.856	1.116	0.342	3.646
ASA Class 5	0.631	1.712	0.190	15.412
Infratentorial location	0.040	2.202	1.038	4.672
Age 16–40 yrs	0.476			
Age 41–65 yrs	0.975	0.989	0.491	1.993
Age 66–79 yrs	0.399	0.664	0.257	1.719
Age 80–89 yrs	0.993	0.000	0.000	0.000
Age ≥ 90 yrs	0.154	4.739	0.559	40.171
Normal WBC count (4000–11,000 cells/ μ l)	0.390			
WBC < 4000 cells/ μ l	0.331	1.838	0.539	6.271
WBC $> 11,000$ cells/ μ l	0.265	1.451	0.754	2.792
Corticosteroid use	0.730	0.850	0.338	2.138
Malignancy	0.393			
Primary brain cancer	0.192	0.547	0.221	1.353
Secondary brain cancer	0.503	0.704	0.252	1.968

is generally longer than the shorter-term regimens that are frequently prescribed preoperatively for a variety of cranial procedures.^{8,29} Our data suggest, in effect, that patients who are prescribed longer courses of steroids as a preoperative measure, or those who take corticosteroids for other reasons, such as rheumatologic disorders, have a higher risk of an organ-space SSI at 30 days after surgery. Our results are consistent with one of the few previous studies examining the risk of infection in neurosurgical patients on protracted corticosteroid therapy.²⁵ In this larger study by Merkler et al.,²⁵ which broadly assessed the risks of many types of postoperative infections—including pneumonia, SSIs, and urinary-tract infections—after neurosurgical procedures, the authors found that corticosteroid use was associated with an increased risk of an organ-space SSI (OR 3.95, CI 2.29–6.79, $p < 0.001$). They assessed this risk in neurosurgery in a broad sense, however, with limited classification of subgroups. Indeed, organ-space SSIs are not necessarily comparable among the varying cra-

nial, spine, and peripheral nerve surgeries. In addition, the authors did not control for certain factors, such as WBC count and duration of operation, so the effects of these potential confounders is unclear.

Merkler et al. did, however, find that while corticosteroid treatment increased the risk of organ-space SSIs in the general neurosurgical population, it did not increase the risk of superficial SSIs, a finding that is consistent with our analysis of corticosteroid use as well as for chemotherapy. In effect, these therapies appear to increase the risk of deeper SSIs largely occurring in the brain parenchyma, but not superficial SSIs of the skin and subcutaneous tissue. The underlying reason for this distinction, although unclear, may be that there are 2 separate disease processes, which not only affect different tissues but are also divided by multiple layers, including the dura, bone, and galea. In addition, the CNS has a privileged immune environment¹⁴ that is distinct from the systemic myeloid cells in the skin and subcutaneous tissue of the scalp. For example, the CNS is relatively devoid of neutrophils and instead has microglia,²⁷ which are largely not derived from the bone marrow¹² and have a lower turnover rate.^{11,21} In effect, there are a variety of potential reasons that may explain our findings that systemic chemotherapy and corticosteroids significantly impact the risk of organ-space SSIs, but not superficial SSIs, in cranial neurosurgery.

In addition to our findings regarding chemotherapy and corticosteroids, we found other independent predictors of organ-space and superficial SSIs that are consistent with previous studies, including wound class, ASA class, and operative duration. An infratentorial location was also an independent predictor of a superficial SSI, a result also consistent with previous studies.³³ Interestingly, a WBC count above 11,000 cells/ μ l was associated with decreased odds of organ-space SSI. Although interpretation of this finding is limited by the nature of the database, it may be attributable to a population with a high-normal WBC count due to normal variation. Our finding that morbid obesity (BMI ≥ 40 mg/m²) is an independent predictor of organ-space SSIs has not been previously found in cranial neurosurgery, although this condition has been described as a risk factor in other surgical specialties.¹ We did not find diabetes mellitus, radiation therapy within 90 days, intra- or preoperative transfusions, smoking, or advanced age (> 65 years) to be predictive of organ-space or superficial SSIs.

Certain limitations in our study should be noted. Although the ACS NSQIP database is a highly valuable resource that contains detailed guidelines on how to record patient characteristics and surgical outcomes, we were limited by some of the database's definitions. We could not include certain details in our analysis, including the specific type or dose of chemotherapy, corticosteroids, or radiation. We were able to categorize steroid use as "significant" because the database included a separate category for patients undergoing steroid therapy for more than 10 days. However, the database did not provide information about short-term steroid use. For chemotherapy, we were unable to assess the impact of less-common, alternative deliveries of chemotherapy. We were also unable to control for the presence or absence of preoperative antibiotics, confounding medications possibly associated with poor

wound healing, or patients with acquired immunodeficiencies such as HIV infection. Other information that cannot be obtained from the database includes information about the pathogens responsible for each SSI, the WBC differential, and certain hospital characteristics (e.g., case volume, academic setting). Although surgical clinical reviewers adhere to strict ACS NSQIP variable definitions and collection methods with interrater reliability greater than 95%,^{13,15,31} to some degree our study may have been affected by variations in data entry or missing data. As with any large database, there are limitations to analyzing CPT codes, although we did our best to select the appropriate codes that have been used in previous ACS NSQIP studies.²⁸ Due to the overall low incidence of SSI events in ACS NSQIP coupled with the limits of inferring clinical information from CPT codes, we did not feel that we would be able to run a reliable statistical analysis that takes into account a variety of indications for cranial neurosurgery. Also, the CPT codes for preoperative infections (e.g., abscess) are assigned immediately prior to surgery, so if an abscess were only discovered intraoperatively, it could have been included in our analysis despite actually having been present preoperatively. Although ACS NSQIP is pioneering in that it captures 30-day outcomes with minimal loss to follow-up, it does not provide us with outcomes after 30 days.

In conclusion, we report one of the first and largest analyses showing that preoperative chemotherapy and corticosteroids are independent predictors of an organ-space SSI at 30 days following cranial neurosurgery, a finding that may be related to impaired immunity in these subgroups. Our results suggest that commonly prescribed preoperative steroids and chemotherapy regimens should be optimized to provide their necessary therapeutic effect while also minimizing the risk of dangerous organ-space SSIs. Future studies may help determine the specific duration, dose, and type of chemotherapy or corticosteroids that may significantly affect the incidence of postoperative infectious complications.

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