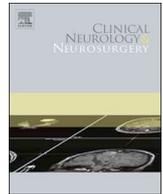




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Cefazolin versus vancomycin for neurosurgical operative prophylaxis – A single institution retrospective cohort study

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ABSTRACT

Objectives: Cefazolin and vancomycin are common choices for neurosurgical antimicrobial prophylaxis. Cefazolin is typically first-line due to its lower toxicity profile and specificity for gram-positives such as skin commensals, while vancomycin is often reserved for patients with cephalosporin or penicillin allergies. However, one randomized clinical trial demonstrated superiority of vancomycin for cerebrospinal fluid (CSF) shunt insertions at a hospital with a high prevalence of methicillin-resistance *Staphylococcus aureus* (MRSA). We aimed to evaluate the association of prophylaxis choice and incidence of surgical site infection (SSI) at our own institution.

Patients and methods: This was a retrospective cohort study of patients who underwent a neurosurgical operation from January 2013 to April 2016 at one particular hospital belonging to our institution. We included patients who received either only cefazolin or only vancomycin as their pre-incisional prophylaxis. Vancomycin was substituted for cefazolin in patients with known penicillin or cephalosporin allergy. Procedures requiring multiple attending surgeons were excluded. We defined a SSI as a confirmed culture isolated from the wound, implant (if pertinent), or CSF (if pertinent) within a year of surgery. Multivariable logistic regression was performed with consideration of antibiotic, operation performed, wound class, and procedure length.

Results: A total of 859 operations met study criteria; 664 patients received Cefazolin, and 195 received Vancomycin. We identified 22 SSIs, with 14 in the cefazolin (2.2%) and 8 in the vancomycin (4.1%) group. Upon logistic regression, there was no significant association of vancomycin substitution with incidence of SSIs between the two groups (odds ratio, 1.59; 95% CI, 0.42–6.00, $p = .49$). In the cefazolin group, 8/14 cultures were positive for *S. aureus* compared to 1/8 of the vancomycin group.

Conclusions: There was no significant difference in neurosurgical site infection incidence when vancomycin prophylaxis was substituted for cefazolin. *S. aureus* was isolated from patients who received cefazolin at a higher rate although this was not statistically significant. At our institution, *S. aureus* makes up 36% of isolated organisms from inpatient and intensive care units. Institutions should consider their own investigations into local antibiograms, SSI rates, and choice of prophylaxis.

1. Introduction

Healthcare-associated infections can be costly to hospitals and dangerous to patients, especially when related to surgery [1]. Surgical site infections (SSI) for patients undergoing neurosurgery are the costliest among the surgical specialties, as each SSI was estimated to cost \$23,755 in 2010 [2]. SSI incidence rates in neurosurgery vary by procedure and location but are estimated occur at a rate of 1–10% [3–8]. Approximately 14 million neurosurgical procedures were performed in 2017, which would equate to anywhere from 140,000 to 1.4 million

neurosurgical patients developing potentially dangerous SSIs [9,10].

A number of different variables have been identified as risk factors for development of SSI in neurosurgical procedures such as surgical duration, wound contamination, and CSF leak [4,5,11]. Although past studies of neurosurgical pre-incisional antibiotic prophylaxis have demonstrated mixed efficacy, general expert consensus, including The United States Center for Disease Control and Prevention (CDC) guidelines for global reduction of SSIs, supports antibiotic prophylaxis [4,12–16].

Recommended prophylactic agents for neurosurgical procedures are

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cefazolin, gentamicin, and vancomycin [17]. Cefazolin is considered to be a reasonable first-line option that covers skin commensals and other organisms frequently implicated in neurosurgical SSI [18]. One Italian study of cerebrospinal fluid (CSF) shunt insertions determined that vancomycin prophylaxis reduced shunt infection rate and mortality compared to cefazolin [19]. Another study from that hospital had previously reported that the majority of infections in neurosurgical patients were caused by *Staphylococcus aureus*, with 39% of those being methicillin-resistant [20]. In this study, we aimed to determine if patients who underwent vancomycin prophylaxis instead of cefazolin prophylaxis experienced a significantly different incidence of SSIs following general neurosurgical procedures.

2. Patients and methods

In this retrospective cohort study, we reviewed the records of patients who underwent a neurosurgical operation between January of 2013 and April of 2016 in one particular hospital. In mid-April 2016, surgeries were relocated to a newer hospital. Patients were included if they were not incarcerated and underwent a procedure by one of the three attending neurosurgeons who were continuously employed during the study period. We excluded cases in which the prophylactic antibiotic administered was neither exclusively cefazolin nor vancomycin. We also excluded cases that involved multiple attending surgeons as many of these cases reflected necessary intervention by a general surgeon for abdominal exploration.

At our institution, cefazolin is generally the prophylactic antibiotic of choice for neurosurgical operations. Cefazolin is considered safe, while vancomycin is associated with a relatively increased incidence of drug-related adverse effects, necessitating periodic monitoring of serum vancomycin trough levels [21–23]. Cross-reactivity rates between penicillins and cephalosporins have long been reported in the literature, but the actual incidence has been debated, with numbers anywhere between 0% and 20% [24–27]. However, to minimize any risk associated with the possibility of allergic cross-reactivity, vancomycin substitution is our institution's second-line neurosurgical prophylaxis of choice for patients who report penicillin or cephalosporin allergies. One of the attending neurosurgeons additionally transitioned from cefazolin prophylaxis for shunt operations to vancomycin prophylaxis in late 2014 as previous research has shown decreased SSI incidence at hospitals with a high prevalence of *S. aureus* [19]. All patients underwent skin pre-preparation with chlorhexidine and preparation with iodine-based solution. All neurosurgical antibiotic prophylaxis was administered within 60 min of skin incision. Cefazolin was dosed at 2 g intravenously for patients less than 120 kg and at 3 g for those 120 kg or greater. Vancomycin was dosed at 1 g intravenously.

Association of antibiotic prophylaxis with incidence of SSI was analyzed using the standard superficial SSI definitions of purulent drainage, aseptically-obtained positive culture, intentionally re-opened incision by a surgeon, or clinical diagnosis by an attending physician occurring within 30 days of a procedure [28]. The standard deep SSI definitions were also utilized. For the purpose of antimicrobial analysis in this study, a surgical site infection was separately defined (hereby referred to as the study SSI or study-defined SSI) as clinical suspicion of an infection in addition to a positive histological diagnosis, such as gram stain revealing hyphae, or culture within one year of surgery from a swab of expressed content, an aspirate, or an implant from the surgical site. Cerebrospinal fluid cultures were also considered for cases involving intentional durotomy, but careful comparison against blood cultures, catheter cultures, and clinical documentation was conducted to ensure the primary source of infection was related to the surgical incision. If a patient received multiple operations in the year prior to development of SSI, only the most immediate prior surgery was considered to be associated with the infection.

Variables of interest included patient age and sex, identity of the attending neurosurgeon, procedure performed, procedure length, pre-

Table 1

Patient demographics, descriptive statistics, and Mann-Whitney U test (for continuous variables) or Fisher-Freeman-Halton statistic (for categorical variables) of operations in which either cefazolin or vancomycin were administered as the sole prophylactic antibiotic.

	Cefazolin (n = 664)	Vancomycin (n = 195)	p-value
Age, mean (SD)	48.7 (21.9)	41.5 (25.7)	< .01
Male, n (%)	360 (54.2)	88 (45.1)	.03
Region of Procedure, n (%)			< .01
Cranial Procedures	326 (49.1)	119 (61.0)	
Spinal Procedures	329 (49.5)	76 (38.9)	
Peripheral Procedures	9 (1.4)	0 (0)	
Shunt Procedures, n (%)	56 (8.4)	73 (37.4)	< .001
Shunt Insertion	28 (4.2)	27 (13.8)	
Shunt Revision	27 (4.0)	41 (21.0)	
Shunt Removal	1 (0.2)	5 (2.6)	
Patient Classification, n (%)			< .01
Day Surgery	317 (47.7)	69 (35.4)	
Inpatient	313 (47.1)	119 (61.0)	
Emergency	34 (5.1)	7 (3.6)	
Wound Class, n (%)			< .001
Clean	635 (95.6)	173 (88.7)	
Clean, contaminated	22 (3.3)	13 (6.7)	
Dirty	7 (1.1)	9 (4.6)	
Pre-Operative Length-of-Stay, mean (SD)	1.8 (5.5)	6.2 (20.0)	< .001
Total Procedure Length, mean (SD) ^a	155.7 (91.7)	134.1 (106.1)	< .001
Procedure Within Previous Year, n (%)	48 (7.2)	51 (26.2)	< .001
Surgical Site Infections, n (%)			
Standard Definition	18 (2.7)	5 (2.6)	1.00
Study Definition	14 (2.1)	8 (4.1)	.13

Abbreviations: n, sample size; SD, standard deviation.

^a Total procedure length was defined as time from skin incision to finishing of closure.

operative length-of-stay, patient classification (day surgery, inpatient, or emergency), wound class, and whether surgery had been performed in the previous year. However, if a particular procedure was not performed more than four times during the study period, it was excluded from analysis. A two-tailed Fisher's exact test was performed to examine whether there was a significant difference in incidence of SSI between the antibiotic groups, without controlling for other factors. Multivariable logistic regression was performed to control for the possibility of confounding variables in analysis of antibiotic prophylaxis choice on subsequent development of SSI. R-3.4.2 was used for all statistical analysis. An acceptable alpha of 0.05 was determined a-priori for Fisher's exact test and multivariable regression. Any analysis of culture data utilized the study SSI definition only.

This study was approved by the Institutional Review Board of the University of Texas Medical Branch (Galveston, Texas; IRB 18-0046).

3. Results

A total of 859 operations met the study criteria; 664 patients received cefazolin, and 195 received vancomycin. Patient demographic data and other descriptive statistics can be found in Table 1. Using the standard SSI definition, there were 23 (3.4%) SSIs, with 18 (2.7%) in the cefazolin group and 5 (2.6%) in the vancomycin group. Of these SSIs, 22 had a confirmed culture or histological diagnosis, and 4 were clinically diagnosed. Using the study SSI definition, there were 22 (2.6%), with 14 (2.1%) in the cefazolin group and 8 (4.1%) in the vancomycin group (Table 2). Of patients with study-defined SSIs, 16 required a subsequent operation. The result of Fisher's exact test demonstrated no significant difference in standard SSI risk (odds ratio (OR), 1.06; 95% CI, 0.37–3.70; p = 1.00) for patients who received cefazolin prophylaxis compared to vancomycin. The result of Fisher's

Table 2
 Information about cases complicated by a surgical site infection (as defined by study criteria) including procedure, prophylactic antibiotics, patient class (inpatient, day surgery, emergency), where the patient was admitted from prior to surgery, where the patient was when the positive culture was taken, wound class, history of surgery within the previous year, organism isolated, whether the organism was resistant to cephalosporins, whether the surgical site infection also met the standard surgical site infection definition, and what treatment regimen was employed following a positive identification.

Procedure	Prophylaxis	Patient Class	Admit From	Location Diagnosed	Wound	Prior Surg	Organism	Resistant ^a	Standard SSI?	Post-Diagnosis Treatment
Craniotomy for meningioma resection	Cefazolin	Day Surg	Day Surg	ED	Clean	N	MRSA	Y	Y	Debridement + Vancomycin + Lifelong Doxycycline
Craniotomy for hematoma evacuation	Cefazolin	Inpatient (ICU)	ED	Same Admit	Clean	N	Morganella morganii	Y	Y	Debridement + Cefepime
Craniotomy for hematoma evacuation	Cefazolin	Inpatient (ICU)	ED	Same Admit	Clean	Y	Enterobacter aerogenes	Y	Y	Debridement + Meropenem
Endoscopic synostectomy	Cefazolin	Inpatient (NICU)	N/A ^d	NSGY Clinic	Clean	N	Enterobacter cloacae	Y	Y	Debridement + Ceftriaxone
L3-5 Hemilaminectomy	Cefazolin	Day Surg	Day Surg	Inpatient (ICU)	Clean	N	MSSA	N	Y	Debridement + Nafticillin
L3 Hemilaminectomy	Cefazolin	Emergency	ED	ED	Clean	N	MSSA	Y	Y	Debridement + Nafticillin
T3 and T4 to T7 and T8 Minimally Invasive Posterior Instrumentation	Cefazolin	Emergency	ED	ED	Clean	N	Enterobacter cloacae, Staphylococcus epidermidis	Y	Y	TMP-SMX
L4-5 laminectomy	Cefazolin	Day Surg	Day Surg	Inpatient (Wards)	Clean	Y	Coagulase-negative Staphylococcus	N	Y	Debridement + Vancomycin followed by Doxycycline + Ciprofloxacin
L3-4 laminectomy	Cefazolin	Day Surg	Day Surg	ED	Clean	N	MSSA	N	Y	Debridement + Nafticillin
T12-L1 laminectomy	Cefazolin	Inpatient (ICU)	ED	ED	Clean	N	MSSA	N	Y	Wound packing + Doxycycline
L4-5 laminectomy	Cefazolin	Day Surg	Day Surg	Inpatient (Wards)	Clean	N	MSSA	N	Y	TMP-SMX
T1-4 laminectomy	Cefazolin	Inpatient (Wards)	OSH	OSH	Clean	N	MSSA, Klebsiella pneumoniae, Enterobacter cloacae	Y	Y	Debridement + Vancomycin + Piperacillin / Tazobactam
Suboccipital craniotomy for cerebellopontine angle tumor resection	Cefazolin	Day Surg	Day Surg	Same Admit	Clean, contaminated	N	Enterobacter cloacae	Y	Y	Debridement + Meropenem
Suboccipital decompression	Cefazolin	Day Surg	Day Surg	ED	Clean	N	MSSA	N	Y	Nafticillin
Craniotomy for skull base brain tumor resection	Vancomycin	Inpatient (Pediatric Wards)	ED	Operating Room from Inpatient (PICU)	Clean	Y	Septate hyphae ^b	N/A ^b	N	Shunt removal + Amphotericin
CSF shunt insertion	Vancomycin	Inpatient (NICU)	N/A ^d	ED	Clean	N	Staph epidermidis	Y	N	Shunt removal + Vancomycin
CSF shunt insertion	Vancomycin	Inpatient (NICU)	N/A ^d	NSGY Clinic	Clean	N	MSSA	N	N	Mupirocin
CSF shunt revision	Vancomycin	Emergency	ED	Inpatient (Pediatric Wards)	Clean	Y	Enterobacter cloacae	Y	Y	Shunt removal + Ceftriaxone + Gentamicin

(continued on next page)

Table 2 (continued)

Procedure	Prophylaxis	Patient Class	Admit From	Location Diagnosed	Wound	Prior Surg	Organism	Resistant ^d	Standard SSI?	Post-Diagnosis Treatment
CSF shunt revision	Vancomycin	Day Surg	Day Surg	NSGY Clinic	Clean	Y	Coagulase-negative Staphylococcus	N/A ^c	Y	Shunt removal + Vancomycin
Lumbar peritoneal shunt insertion	Vancomycin	Inpatient (ICU)	OSH	Same Admit	Clean	Y	Staphylococcus epidermidis	Y	Y	Shunt removal + Vancomycin
S1 pedicle screw revision	Vancomycin	Day Surg	Day Surg	OSH	Clean, contaminated	Y	Staphylococcus epidermidis	N/A ^c	Y	Debridement + Vancomycin + Aztreonam
Suboccipital decompression	Vancomycin	Inpatient (NICU)	N/A ^b	Same Admit	Clean	Y	Enterobacter cloacae	Y	Y	Gentamicin + Cefotaxime

Abbreviations: CSF, cerebrospinal fluid; ED, emergency department; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; N, no; N/A, not applicable; NICU, neonatal intensive care unit; NSGY, neurosurgery; PICU, pediatric intensive care unit; OSH, outside hospital; SSI, surgical site infection; TMP-SMX, trimethoprim-sulfamethoxazole, Y, yes.

^a Yes if any of the isolated organisms are resistant to first generation cephalosporins.
^b No culture was obtained.
^c Sensitivity analysis was not completed.
^d Patient was not admitted as procedure performed after birth and before discharge to home.

Table 3

Adjusted odds ratios for development of surgical site infection using both the standard and study-specific definitions.

Variable	Study-Defined SSI			Standard Definition SSI		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	0.99	0.96–1.02	.48	1.00	0.97–1.03	.91
Male Sex	1.45	0.53–3.96	.47	1.34	0.60–4.13	.36
Patient Classification						
Day Surgery	Ref	–	–	Ref	–	–
Inpatient	0.75	0.23–2.48	.64	0.80	0.26–2.46	.69
Emergency	1.82	0.25–13.31	.55	1.67	0.24–11.91	.61
Wound Class						
Clean	Ref	–	–	Ref	–	–
Clean, contaminated	1.41	0.18–10.79	.74	1.78	0.27–11.85	.55
Dirty ^a	0	0–Inf	1.00	0	0–Inf	1.00
Pre-Operative LOS	1.02	0.99–1.04	.17	1.00	0.95–1.06	.96
Total Procedure Length	1.00	0.99–1.01	.58	0.98	0.99–1.00	.52
Procedure in Past Year	4.90	1.23–19.54	.02	6.14	1.48–25.51	.01
Vancomycin Prophylaxis	1.59	0.42–6.00	.49	0.56	0.13–2.40	.44

Abbreviations: CI, confidence interval; Inf, infinity; LOS, length of stay; OR, odds ratio; Ref, reference; SSI, surgical site infection.

^a None of the 16 patients with a dirty wound class developed a surgical site infection.

exact test for study SSI risk was also non-significant (OR, 0.50; 95% CI, 0.19–1.41; p = .13). Multivariable logistic regression using both the standard and study SSI definitions also revealed no association between vancomycin substitution and risk of SSI. The results of the logistic regressions can be found in Table 3. Among all variables analyzed, only a history of neurosurgical operation at the same incision site or at an adjacent site within the previous year was significantly associated with a difference in incidence of SSI (standard SSI: OR, 6.14; 95% CI, 1.48–25.51; p = .01; study SSI: OR, 4.90; 95% CI, 1.23–19.54; p = .02).

In the cefazolin group, 8/14 operations produced cultures positive for *S. aureus*, one of which was methicillin-resistant, compared to 1/8 of the vancomycin group, which was methicillin-sensitive. Result of Fisher’s exact test for proportion of infections caused by *S. aureus* was not significant (p = .07). Additionally, of all operations with positive cultures in the cefazolin group, 8/14 operations produced at least one organism resistant to cephalosporins. Sensitivity analysis was only performed for 5/8 of the operations complicated by SSI in the vancomycin group, of which 4/5 had cephalosporin-resistant organisms.

Staphylococcus aureus cultures made up 9/24 organisms isolated. The second most commonly-isolated genus was Enterobacter, which was positive in 5/14 operations in the cefazolin group and 2/8 operations in the vancomycin group. The treatment for these patients varied, with one patient also producing methicillin-sensitive *S. aureus* and *Klebsiella pneumoniae* in their cultures. Half of the operations complicated by SSI in the vancomycin group involved coagulase-negative Staphylococcus, with 3/4 identified as *S. epidermidis*. The other culture was not further identified. All four patients in the vancomycin prophylaxis group with coagulase-negative Staphylococcus were successfully treated by vancomycin after pathogen identification. Additional information regarding organisms isolated and treatments can be found in Table 2.

4. Discussion

Using both the standard SSI definition and our modified definition, which expands the analysis to one year after the operation and requires a histologically-confirmed or culture-confirmed diagnosis, our results demonstrated no difference in incidence of SSIs between patients who

received solely cefazolin compared to vancomycin for neurosurgical prophylaxis. The incidence rate of SSIs (2.6–3.4%) at our institution was consistent with previously reported statistics [3–8]. The only variable significantly associated with increased risk of infection in our study was having had surgery at the same (or an adjacent) surgical site within the previous year. A similar result has been previously reported in the literature: patients who underwent CSF shunt revisions or revisions for spinal surgery developed SSIs at increased rates [29–31].

Interestingly, all the patients in the cefazolin group of our study who developed study-defined SSIs did so within the first 30 days after surgery. Of the three patients in the vancomycin group who developed SSIs after the first 30 days, two patients had undergone CSF shunt insertion. Delayed shunt infections have been described in the literature as occurring up to 11 years after surgery, so it is possible the difference in SSIs occurring after 30–90 days is not attributable to choice of prophylaxis [32].

Although overall infection rates were not different between the two groups, there is a possibility that the study was underpowered given the low incidence of SSIs. There was a near absence of *S. aureus* infections in the vancomycin group. Furthermore, the results of the study by Tacconelli et al. supported substitution of vancomycin for cefazolin in CSF shunt surgeries at an institution with high *S. aureus* prevalence as the majority of isolates from neurosurgical SSIs at their institution were *S. aureus* [19]. However, in our study, *S. aureus* was isolated in less than half (9/22, 40.9%) of SSIs, with three SSIs producing polymicrobial cultures. Furthermore, review of antibiograms from the years 2013 and 2014 for the same hospital at which these procedures were performed revealed that 63.1% (1994/3160) of gram-positive isolates, which contribute to less than half of the all isolates, from the emergency room, adult inpatient, adult intensive care unit, and adult outpatient clinics were *S. aureus* and 46.7% (932/1994) of these were methicillin-resistant [33,34]. Therefore, although cefazolin remains a reasonable choice while *S. aureus* contributes to less than half of neurosurgical SSI isolates, there is a real possibility that the increasing incidence of methicillin-resistant *S. aureus* infections will necessitate substitution with vancomycin [35,36].

It is additionally important to note that the cefazolin and vancomycin group characteristics were significantly different (Table 1). These differences were controlled for in the logistic model, but recognition of differences between the groups is important. As an example, over one-third of the surgeries performed in the vancomycin group were shunt-related. As a result, the variety of operations involving vancomycin prophylaxis was limited compared to those of the cefazolin group. Although the logistic model did not demonstrate a statistically significant association between operation performed or choice of prophylactic antibiotic, there is a possibility of confounding or bias.

We believe that choice of antibiotic prophylaxis should be guided by individual institutions' microbiomes and that basis upon results of antibiogram analysis is both a necessity and responsibility. Vancomycin has demonstrated significant superiority in reduction of methicillin-resistant *S. aureus* [37]. Additionally, institutions can consider screening patients for intranasal *S. aureus* as methicillin-resistant *S. aureus* colonization has been shown increase the risk of developing a SSI – a risk that is reduced by proper perioperative care [38].

There are, however, some important limitations to note. The retrospective nature of this study and the criteria for vancomycin substitution limit the conclusions that can be made. Additionally, the limited number of patients who received exclusive vancomycin prophylaxis resulted in a low number of SSIs in that group for study comparison. Furthermore, the three neurosurgeons included in the study had roughly the same amount of experience and performed many of the same procedures, which limits the generalizability of our study. Another consideration is that although the surgeons followed general guidelines, their clinical judgment in assessing other variables may have led to a decision to substitute vancomycin for cefazolin, which was not controlled for in this study. A multicenter randomized, controlled

trial should be conducted with consideration of the institutional microbiomes in order to make more generalizable recommendations. Prospective trials should also consider studying combination treatments such as both cefazolin and vancomycin versus either antibiotic alone.

5. Conclusion

Choice of cefazolin versus vancomycin prophylaxis was not significantly associated with a difference in rates of SSI development. Previous incision at or near the surgical site within the previous year was associated with increased risk of developing a wound infection. Although our study did not demonstrate statistical significance, patients who receive cefazolin prophylaxis may be more likely to have *S. aureus* isolated from wound cultures. Institutions should carefully review antibiogram results and consider vancomycin prophylaxis if there is a high prevalence of *S. aureus*, especially methicillin-resistant strains, and institutions with microbial profiles and case logs similar to our institution's would not be expected to have a higher incidence of SSI in patients with penicillin or cephalosporin allergies.

Conflicts of interest

The authors report that there are no conflicts of interest or financial relationships to report.

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