Topical vancomycin for neurosurgery wound prophylaxis: an interim report of a randomized clinical trial on drug safety in a diverse neurosurgical population

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OBJECTIVE Postoperative surgical site infections (SSIs) in neurosurgical patients carry a significant risk of increased morbidity and mortality. With SSIs accounting for approximately 20% of nosocomial infections and costing approximately \$1.6 billion USD annually, there is a need for additional prophylaxis to improve current standards of care. Topical vancomycin is increasingly utilized in instrumented spinal and cardiothoracic procedures, where it has been shown to reduce the risk of SSIs. A randomized controlled trial assessing its efficacy in the general neurosurgical population is currently underway. Here, the authors report their initial impressions of topical vancomycin safety among patients enrolled during the 1st year of the trial.

METHODS This prospective, multicenter, patient-blinded, randomized controlled trial will enroll 2632 patients over 5 years. Here, the authors report the incidence of adverse events, the degree of systemic vancomycin absorption in treated patients, and pattern changes of antibiotic-resistant profiles of *Staphylococcus aureus* flora among patients enrolled during the 1st year.

RESULTS The topical vancomycin treatment group comprised 257 patients (514 total enrolled patients), of whom 2 exhibited weakly positive serum levels of vancomycin (> 3.0 mg/dl). *S. aureus* was detected preoperatively in the anterior nares of 35 (18.1%) patients and the skin near the surgical site of 9 (4.7%). Colonization in the nares remained for many patients (71.4%) through postoperative day 30. The authors found a significant association between preoperative *S. aureus* colonization and postoperative colonization. Seven methicillin-resistant isolates were detected among 6 different patients. Two isolates were detected preoperatively, and 5 were de novo postoperative colonization. No adverse responses to treatment have been reported to date.

CONCLUSIONS The authors' data indicate that the use of topical vancomycin is safe with no significant adverse effects and minimal systemic absorption, and no development of vancomycin-resistant microorganisms.

Clinical trial registration no.: NCT02284126 (clinicaltrials.gov)

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KEYWORDS topical vancomycin; neurosurgery; surgical site infection; antibiotics; wound prophylaxis

SURGICAL complications account for a significant portion of healthcare-related morbidity,²⁸ which can greatly inhibit clinicians' efforts to ameliorate patient disease. Nosocomial infections of the surgical wound, or surgical site infections (SSIs), account for the largest portion of operative complications: approximately 13.6% of all US hospital complications²⁸ and approximately 20%

of all healthcare-associated infections in US hospitals.²⁶ Costs have been estimated at \$1.6 billion USD annually.¹⁵

Topical application of vancomycin in the operating room is a longstanding practice; however, evidence supporting the antibiotic's efficacy in reducing SSIs has only been reported in the last decade. Currently, topical application of vancomycin is commonly used for instrumented

ABBREVIATIONS AE = adverse event; CUMC = Columbia University Medical Center; LOS = length of stay; MRSA = methicillin-resistant *Staphylococcus aureus*; SAE = serious adverse event; SSI = surgical site infection; WCMC = Weill Cornell Medical Center.

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spinal procedures, where it has been shown to reduce the incidence of SSIs from 4.7% to 0.7%.^{7,31,32,40,41} A similar benefit was demonstrated in cardiothoracic surgery when vancomycin paste was applied to the edges of the sternum during sternotomy closure.^{5,42} Evidence suggests that vancomycin applied topically might also decrease SSIs among neurosurgery patients receiving standard perioperative care (intravenous cefazolin 1 hour prior to incision). Preoperatively, systemic vancomycin is often used for patients with allergy to cephalosporin or penicillin. Even so, intravenous vancomycin has not demonstrated such benefits over intravenous cephalosporin alone.¹⁸ Intravenous prophylactic antibiotics have variable delivery to the surgical site, which limits their ability to achieve bactericidal concentrations locally with the added risk of adverse systemic effects, including hypersensitivity reactions and renal toxicity. Thus, topical antibiotics may achieve greater local concentration at the surgical site while minimizing systemic toxicity.⁴³

Limited research directly addresses the potential risks of vancomycin among neurosurgical patients when applied topically.^{1,2,30} True allergic reactions to vancomycin are rare and, to our knowledge, no incidence has been reported following topical use. Promotion of antibiotic resistance is of concern for any antimicrobial agent. When applied topically, we believe that the systemic absorption of vancomycin is low. It stands to reason that its effect on the microbiome is minimal and the risk of developing vancomycin-resistant organisms is low. Systemic absorption of topical vancomycin and microbiology profiles of treated patients have not been previously reported.

To date, there has been no report of a prospective, randomized clinical trial assessing the safety or efficacy of topical vancomycin among a neurosurgical population undergoing craniotomy or noninstrumented spinal procedures. Topical Vancomycin for Neurosurgery Wound Prophylaxis is a randomized controlled trial designed to determine whether prophylactic, topical vancomycin applied directly at the site of craniotomy and noninstrumented spinal procedures reduces the incidence of SSI at postoperative day 30. This study is ongoing, and a complete report on the efficacy of topical vancomycin in the neurosurgery setting is forthcoming. In an effort to illustrate whether or not topical application of vancomycin is safe for neurosurgery patients, we report adverse events, drug kinetics, and microbiology profiles from the 1st year of enrollment.

Methods

The Topical Vancomycin for Neurosurgery Wound Prophylaxis study is a prospective, multicenter, randomized, patient-blinded, 2-armed clinical trial (registration no. NCT02284126 [clinicaltrials.gov]). Initial contact and patient recruitment occurs through the outpatient neurosurgical clinics at NewYork-Presbyterian Columbia University Medical Center (CUMC) and NewYork-Presbyterian Weill Cornell Medical Center (WCMC). Outpatients are instructed to use an antibacterial soap, and inpatients are scrubbed below the neck with chlorhexidine preoperatively. To achieve 90% power with a 2-sided test at the 0.05

level, 1316 patients per group (2632 total) are expected to be enrolled over a 5-year period. This interim report includes patients enrolled between October 20, 2014, and October 19, 2015. Enrollment is expected to be ongoing through 2019. The study is funded, beginning in February 2014, by the Agency for Healthcare Research and Quality (AHRQ), which is part of the US Department of Health and Human Services.

Patients older than 18 years undergoing craniotomy with planned complete dural or dural-substitute closure or a noninstrumented spinal procedure are screened, provide consent, and are randomized in a 1-to-1 ratio through the Research Electronic Data Capture (REDCap), a secure, Web-based data management system.²² Patients are randomized to receive either standard prophylaxis or topical vancomycin at the surgical site in addition to standard prophylaxis. Standard prophylaxis includes intravenous cefazolin 1 hour prior to incision. Attending surgeons may use intravenous vancomycin as standard prophylaxis for patients randomized to the control arm with a cephalosporin or penicillin allergy (positive control group). Otherwise, patients in the control arm receive no vancomycin, topical or intravenous.

Patients undergoing instrumented spinal procedures are excluded from the trial because topical vancomycin is already indicated for this population.^{7,31,32,40,41} In addition, patients are excluded if they have evidence of renal insufficiency, allergy to vancomycin including dermatological manifestations, dizziness, or subjective hearing loss (see Table 1 for a full list of inclusion and exclusion criteria).

Adverse Event Reporting

Phone interviews were conducted between 14 and 30 days after surgery to assess infections, poor recovery concomitant with wound healing, and adverse events (AEs).

Using a comprehensive checklist, patients were ascertained for signs and symptoms of infection, including fe-

TABLE 1. Summary of study enrollment criteria

Inclusion criteria
Age >18 yrs
Patient undergoing craniotomy, craniectomy, or noninstrumented spinal procedures
Exclusion criteria
Admission creatinine >1.5 mg/dl or documented renal insufficiency
Allergy to vancomycin, including rashes, dizziness, &/or subjective hearing loss
Preexisting infection at or adjacent to operative site
Planned neurosurgical procedure for vestibular schwannoma, carotid endarterectomy, transsphenoidal approach
Cannot obtain informed consent from subject, representative, or surrogate
Lack of clinical equipoise for use of vancomycin, as determined by operating surgeon
Possible same-day discharge following surgical procedure
Instrumented spinal surgery for which vancomycin powder is currently used as standard of care

ver or chills, increased pain, redness, swelling or warmth around the surgical site, and drainage fluid, discharge, or pus from the incision. In addition, patients were screened for AEs, including hearing loss and local or systemic allergic reactions. All AEs were reported to the Data and Safety Monitoring Board (DSMB) within 24 hours and collectively reviewed and adjudicated among the DSMB members and principal investigators each quarter.

Serum Analysis

Systemic absorption of topical vancomycin was monitored using serum vancomycin levels drawn at 6 and 20 hours after wound closure, as vancomycin levels have been shown to peak within the first 24 hours postoperatively.⁴¹ Serum levels of vancomycin were measured in all study patients who received intravenous or topical vancomycin. An undetectable vancomycin level was defined by the central laboratory as ≤ 3.0 mg/dl (CUMC) or ≤ 3.5 mg/dl (WCMC).

Microbiology Analyses

Microbe cultures were obtained from the anterior nares and surgical site preoperatively before draping occurred, within 48 hours of wound closure, and again at 2 weeks and 3 months following surgery with premoistened culturette rayon-tipped swabs (Becton Dickinson). Patient mailers were used to obtain 2-week and 3-month swabs remotely. Cultures were initially stored at 4°C and later were incubated in 6% sodium chloride-supplemented tryptic soy broth at 37°C overnight for supported *S. aureus* growth. The samples were then plated on mannitol salt agar (Becton Dickinson), which selected for *Staphylococcal* species^{20,37} for 48 hours at 35°C. Colonies of *S. aureus* that altered mannitol agar from pink to yellow were then streaked onto sheep blood agar and incubated for 24 hours. The presence of *S. aureus* was then fully ascertained using the Murex StaphAurex rapid latex agglutination test (Remel).

Vancomycin susceptibility testing was completed using Etest, and DNA sequencing was utilized to identify known genes of resistance (i.e., the *mec* gene complex that is responsible for methicillin resistance³). Genotyping of the variable-repeat region of protein A (*spa*) gene was used to determine clonal lineage of *S. aureus*, and *spa* types were assigned using StaphType software (version 2.2.1, Ridom).

Statistical Analyses

Standard univariate analyses were performed using Pearson's chi-square test for categorical variables and the Student t-test for continuous variables, as appropriate. Odds ratios with 95% confidence intervals were computed for the outcomes of interest. Frequency of serious adverse event (SAEs), AEs, and hearing changes were assessed between treatment groups.

Serum vancomycin was classified as either detectable or nondetectable. Frequency of detectable serum vancomycin was assessed between patients who received topical vancomycin without intravenous vancomycin and those who received intravenous vancomycin alone (positive control) using standard contingency table comparison. The means

and standard deviations were calculated for serum vancomycin concentration among those with detectable values and compared positive control patients who received intravenous vancomycin using the Student t-test. Additionally, a Passing-Bablok regression was performed to determine statistical agreement of "detectable" and "nondetectable" values between hospitals.

Microbiology cultures were evaluated based on frequency of pre- and postoperative *S. aureus* colonization of the anterior nares and skin. The treatment and control groups were compared. Differences in colonization according to race/ethnicity (classified as Caucasian, Hispanic, Asian, and African American, among others) were compared using standard contingency table analysis. The mean length of stay (LOS) and BMI were compared between those with and without pre- and postoperative colonization using the Student t-test. Frequency of methicillin-resistant *S. aureus* (MRSA) colonization was compared between treatment groups by contingency table analysis.

Results

Patient Population

Patient enrollment began October 21, 2014, at Columbia University Medical Center (CUMC) and January 7, 2015, at Weill Cornell Medical Center (WCMC). During the 1st year, 514 patients were enrolled, including 257 patients in each of the treatment and control groups. Two hundred eighty of 514 (54.5%) patients were female, and the mean age was 55 ± 16.87 years. One patient withdrew from the study for unknown reasons, and 4 cases were rescheduled or canceled after randomization. See Table 2 for a full description of patient demographics.

Adverse Events

Seven of 514 patients experienced an SAE. SAEs were reported in 2 of 257 (0.8%) patients in the treatment group and 5 of 257 (1.9%) patients in the control group (OR 2.53, 95% CI 0.54–12.8; $p = 0.45$). Overall, 114 of 514 (22.2%) patients experienced AEs. AEs were reported in 60 of 257 (23.3%) patients in the treatment group and 54 of 257 (21.0%) patients in the control group. We found no difference in the frequency and type of AEs between the 2 groups (OR 0.87, 95% CI 0.58–1.31; $p = 0.60$). Table 3 provides a summary of AE occurrences.

Due to uncertainty in the literature regarding the ototoxicity of vancomycin, we regularly assessed for postoperative hearing changes. Twenty-four of 209 (11.4%) patients in the treatment group and 15 of 212 (7.1%) patients in the control group reported hearing changes (OR 1.62, 95% CI 0.82–3.10; $p = 0.18$). The remaining patients were lost to hearing follow-up (48 [18.7%] in the treatment group and 45 [17.5%] in the control group).

Serum Analysis

Serum vancomycin levels within 24 hours after surgery were recorded in 123 of 514 patients (114 of 257 [44%] patients from the treatment group and 9 of 257 [3.5%] patients from the control group). Serum vancomycin levels were positive in 2 of 101 (2%) treatment patients who did not receive intravenous vancomycin prior to surgery and

TABLE 2. Study demographic summary

Characteristic	Value
No. of patients	514 (100)
Study site CUMC	362 (70.4)
Randomized to treatment	257 (50.0)
Female sex	280 (54.5)
Race/ethnicity	
African American (black)	41 (8.0)
Asian	22 (4.3)
Caucasian (white)	335 (65.2)
Hispanic (Latino/a)	58 (11.3)
Middle Eastern	7 (1.4)
Mixed or other	15 (2.9)
Native American	1 (0.2)
Pacific Islander	1 (0.2)
Unknown	34 (6.6)
Mean age, yrs	55.09 (16.87)
Mean BMI, kg/m ²	27.48 (8.51)

Values are presented as the number of patients (%) unless stated otherwise. Mean values are presented as the mean (SD).

12 of 13 (92%) treatment patients who received intravenous vancomycin prior to surgery ($\chi^2 = 6.62$, $p < 0.001$). Among the 9 patients from the control group, serum vancomycin levels were positive in 0 of 3 (0%) patients who did not receive intravenous vancomycin prior to surgery and 6 of 6 (100%) patients who received intravenous vancomycin prior to surgery ($\chi^2 = 1.58$, $p = 0.114$). The mean positive serum vancomycin level in those who received topical vancomycin with no intravenous vancomycin was 6.3 ± 1.8 $\mu\text{g/ml}$ compared with 10.7 ± 3.1 $\mu\text{g/ml}$ in the control group ($p = 0.08$). A Passing-Bablok regression showed very good agreement between serum vancomycin assays performed at the clinical specimen laboratories of CUMC and WCMC ($R^2 = 0.9868$).

Microbiology Analyses

We collected preoperative (on the surgery day) and postoperative microbiology cultures from the anterior nares, collected on postoperative days 1–2 in 193 (37.5%) and the skin in 270 (52.5%) of the 514 patients enrolled. Preoperative colonization of *S. aureus* was observed in the anterior nares for 35 of 193 (1.8%) and skin for 9 of 270 (3.3%) patients. Preoperative colonization of the nares was observed in 16 of 99 (16.2%) and 19 of 94 (20.2%) patients in the treatment and control groups, respectively (OR 0.76, 95% CI 0.36–1.54; $p = 0.58$). Preoperative colonization of the skin was observed in 5 of 142 (3.5%) and 4 of 128 (2.3%) patients in the treatment and control groups, respectively (OR 1.13, 95% CI 0.30–4.31; $p = 0.85$).

Postoperative colonization of *S. aureus* was observed in the anterior nares for 37 of 193 (19.2%) patients. Postoperative colonization of *S. aureus* was observed on the skin for 26 of 270 (9.6%) patients. Postoperative colonization of the nares was observed in 18 of 99 (18.1%) and 19 of 94 (20.2%) patients in the treatment and control groups, re-

TABLE 3. Summary of adverse events (n = 162)

AE	No. of AEs (%)		Probability of No Association w/ Randomization
	Control	Treatment	
Fever	5 (3.1)	5 (3.1)	1
Gastrointestinal	14 (8.6)	7 (4.3)	0.1
Pulmonary	2 (1.2)	2 (1.2)	1
Urinary tract infection	11 (6.8)	8 (4.9)	0.48
Allergy or dizziness	20 (12.3)	22 (13.6)	0.75
Edema	3 (1.9)	3 (1.9)	1
Wound care	4 (2.5)	7 (4.3)	0.36
Other	19 (11.7)	30 (18.5)	0.1

spectively (OR 0.88, 95% CI 0.44–1.75; $p = 0.85$). Postoperative colonization of the skin was observed in 11 of 142 (7.7%) and 15 of 128 (11.7%) patients in the treatment and control groups, respectively (OR 0.63, 95% CI 0.29–1.37; $p = 0.31$).

Among the 35 patients with preoperative colonization in the nares, postoperative *S. aureus* colonization of the skin was observed in 6 (17.1%; 2 treatment vs 4 control) patients. Postoperative *S. aureus* colonization of both the anterior nares and skin was observed in 3 of 35 (1.6%; 0 treatment vs 3 control) patients preoperatively colonized in the nares. From the 9 patients preoperatively colonized on the skin with *S. aureus*, 1 (0 treatment vs 1 control) patient remained colonized after surgery.

Preoperative *S. aureus* colonization of the anterior nares was significantly associated with postoperative colonization of the nares (OR 16.01, 95% CI 6.84–35.3; $p < 0.001$). However, preoperative colonization of the skin near the surgical site was not associated with postoperative colonization of the skin (OR 1.18, 95% CI 0.10–8.47; $p = 0.88$). Additionally, preoperative colonization of the nares was not associated with postoperative colonization of the skin (Table 4).

There was no observed difference between the treatment and control groups in the likelihood of persistence of preoperative colonization of the nares (OR 1.27, 95% CI 0.28–5.76; $p = 0.99$) or skin (OR 1.67, 95% CI 0.07–37.27; $p = 0.99$). Similarly, there was no observed difference between the treatment and control groups in the likelihood of de novo postoperative colonization of the nares (OR 0.78, 95% CI 0.27–2.37; $p = 0.77$) or skin (OR 1.46, 95% CI 0.65–3.17; $p = 0.41$).

There was no difference observed in postoperative colonization rates based on elective or inpatient status. Postoperative *S. aureus* colonization of the nares was observed in 24 of 132 (18.2%) elective cases and 13 of 61 (21.3%) inpatient cases (OR 0.82, 95% CI 0.39–1.75; $p = 0.61$). Postoperative *S. aureus* colonization of the skin was observed in 19 of 183 (10.4%) elective cases and 7 of 87 (8.0%) inpatient cases (OR 1.32, 95% CI 0.53–3.28; $p = 0.54$).

There was no significant difference observed in the comparison of preoperative colonization of the nares ($\chi^2 = 6.54$; $p = 0.140$) or skin ($\chi^2 = 3.25$; $p = 0.517$) when categorized by race/ethnicity. On subgroup analysis, however,

TABLE 4. Preoperative and postoperative cultures from the anterior nares and skin in 463 patients

	Preop Nares Colonization		No Preop Nares Colonization		Preop Skin Colonization		No Preop Skin Colonization	
	Postop Nares Colonized	No Postop Nares Colonized	Postop Nares Colonized	No Postop Nares Colonized	Postop Skin Colonized	No Postop Skin Colonized	Postop Skin Colonized	No Postop Skin Colonized
Randomization								
Control	14	5	5	70	1	3	14	110
Treatment	11	5	7	76	0	5	11	126
Total	25	10	12	146	1	8	25	236
Procedure								
Elective/outpatient	17	9	7	99	1	6	18	158
Inpatient	8	1	5	47	0	2	7	78
Total	25	10	12	146	1	8	25	236
Race								
African American (black)	1	0	1	4	0	0	2	12
Asian	3	2	2	6	0	0	3	12
Caucasian (white)	17	8	5	97	1	5	14	147
Hispanic (Latino/a)	1	0	2	15	0	1	2	26
Middle Eastern	0	0	0	2	0	0	0	5
Native American	0	0	0	0	0	0	0	0
Pacific Islander	0	0	0	1	0	0	0	1
Mixed or other	1	0	0	7	0	0	1	9
Declined or unknown	2	0	2	14	0	2	3	24
Total	25	10	12	146	1	8	25	236

we did observe that patients of Asian race were more likely to present with preoperative colonization of the nares than those of non-Asian race, observed in 5 of 13 (38.5%) Asian patients versus 30 of 180 (16.7%) non-Asian patients (OR 3.13, 95% CI 1.07–9.36; $p = 0.049$).

No significant difference in LOS or BMI was found based on pre- or postoperative *S. aureus* colonization of the nares or skin compared with those without colonization (Table 5).

Seven culture swabs for 6 different patients contained MRSA strains. Table 6 provides a summary of each sample that was positive for methicillin resistance. We found no differences in rates of MRSA between treatment groups, collection site, or the time of collection. We did not detect vancomycin-resistant strains of *S. aureus* in any of the study patients.

Discussion

Surgical site infections are a significant cause of mor-

bidity, mortality, and cost burden in neurosurgery.^{9,11,15,16,19,23,39} Our study was designed to determine whether vancomycin powder applied topically to the wound closure further reduces SSIs. Caution has been raised against implementing the widespread prophylactic use of topical vancomycin due to concerns for breeding antibiotic-resistant *S. aureus*. However, among surgical specialties currently utilizing topical vancomycin antibiotic prophylaxis, this treatment is warranted for operational areas in which SSI carries significant morbidity and mortality concerns.¹¹ A 2010 report of 2630 consecutive craniotomies for intracranial tumors revealed institutional morbidity and mortality rates due to deep SSI.²⁷ Minor additional disabilities were observed in 12.8% of patients with SSI while major additional disabilities were observed in 7.7% and death in 5.1%.²⁷ Although these rates are not directly indicative of the entire US neurosurgical SSI population, they indicate that the morbidity and mortality associated with neurosurgical SSIs necessitate the exploration of efficacy and safety of topical vancomycin prophylaxis in neurosurgery.

TABLE 5. LOS and BMI based on *S. aureus* colonization status

Colonization Group	Mean (SD) LOS, Days	p Value (vs no colonization)	Mean (SD) BMI, kg/m ²	p Value (vs no colonization)
Preop colonization of nares	9.3 (28.1)	0.14	26.8 (5.3)	0.76
Postop colonization of nares	9.3 (27.2)	0.13	27.4 (4.4)	0.12
Preop colonization of skin	7.2 (3.3)	0.72	24.75 (2.1)	0.65
Postop colonization of skin	4.2 (3.9)	0.15	28.01 (6.9)	0.9

TABLE 6. Summary of MRSA-positive cultures

Collection Site	Study Arm	Time of Collection
Anterior nares*	Treatment	>30 days postop
Incision site*	Treatment	>30 days postop
Anterior nares	Treatment	>30 days postop
Incision site	Control	>30 days postop
Anterior nares	Treatment	Preop
Anterior nares	Treatment	Preop
Incision site	Control	<30 days postop

* Same patient.

Data from neurosurgical patients suggest that those identified with MRSA colonization may benefit from specific perioperative care with vancomycin.³ *Staphylococcus aureus* colonizes the anterior nares and skin in more than one-third of hospitalized patients, with 1%–5% colonized by MRSA; colonization at admission is associated with an increased risk of postoperative *S. aureus* infections.^{14,21} Due to the significant number of SSIs resulting from MRSA and methicillin-sensitive strains of *S. aureus*,¹² the previously reported efficacy of topical vancomycin is logical.

Prolonged systemic antibiotic prophylaxis increases the risk of developing resistant organisms in the central nervous system after implantation of medical devices.¹⁰ Consequently, shorter perioperative courses of antibiotics are recommended.¹⁰ A single topical application of vancomycin is expected to provide needed local prophylaxis for the surgical site while minimizing unnecessary systemic exposure. We observed only 2 patients treated with topical vancomycin who exhibited slightly positive vancomycin serum levels (6.3 µg/ml), compared with those who received intravenous vancomycin (10.7 µg/ml). The difference in serum vancomycin levels was not significantly different; however, the frequency at which systemic absorption was observed suggests that topical vancomycin has minimal systemic effect.

Adverse reactions to intravenous vancomycin include hypotension, phlebitis, chills, skin rash, eosinophilia, neutropenia, flushing of the face and neck, and, in rare cases, drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, ototoxicity, renal failure, Stevens-Johnson syndrome, thrombocytopenia, and vasculitis.²⁹ Additional gastrointestinal reactions are associated with oral administration of vancomycin.³³ Limited reports are available regarding topical application; however, previous studies of topical vancomycin in the setting of instrumented spine and cranial procedures have reported no association of vancomycin-related AEs with topical treatment.^{1,2,4,35,36} To our knowledge, this study is the first randomized controlled trial to validate a lack of adverse response to topical vancomycin, specifically no significant postoperative hearing changes.

The most common postoperative infectious organism in cranial surgery is *S. aureus*,¹³ of which methicillin-resistant strains confer a great risk for mortality.¹⁷ Monitoring pre- and postoperative *S. aureus* colonization provides a means for evaluating potential risk for infection and changes in patients' natural flora. As expected, we found that preoperative *S. aureus* colonization of the anterior nares was

significantly associated with postoperative colonization of the same site, while preoperative *S. aureus* colonization of the skin was not significantly associated with postoperative colonization of the same site. This supports that current standards of surgical preparation are, to some degree, effective in eliminating preoperative *S. aureus* colonization near the incision site. However, topical vancomycin does not appear to further reduce the persistence of *S. aureus* skin colonization.

Rates of new colonization of postoperative *S. aureus* may be a risk predictor of infection. Of interest is the subgroup of patients lacking preoperative *S. aureus* colonization of the skin near the surgical site but showing positive *S. aureus* colonization following surgery (Table 4 column 7, "No Preop Skin Colonization: Postop Skin Colonized"). As expected, topical vancomycin treatment does not significantly increase postoperative *S. aureus* colonization rates of the anterior nares or the skin near the surgical site. It remains unclear whether topical application of vancomycin reduces the risk of *S. aureus* colonization following cranial surgery.

Interestingly, we found that Asian race was associated with a significantly higher rate of preoperative *S. aureus* colonization of the anterior nares. Nasal carriage of *S. aureus* was previously investigated across multiple races/ethnicities, although no association was found with Asian race; however, the study involved a survey of healthy New Zealand residents.⁶ It is possible that *S. aureus* carriage patterns among the Asian community in New York may vary. Considering the high prevalence of wound infection by *S. aureus* in New York City, the city's Asian population may be at an increased risk, although further data are needed to substantiate this plausibility.^{34,38}

Higher BMI and longer LOS both increase the risk of postoperative SSI.^{8,25} However, no association of these risk factors with pre- or postoperative *S. aureus* colonization was found. Based on current data, no evidence exists for selectively using prophylactic, topical vancomycin based on *S. aureus* colonization patterns.

Conclusions

Our study supports the use of topical vancomycin in cranial and uninstrumented spine neurosurgery. There is minimal systemic absorption, no significant difference in AEs or hearing changes, and no increase in methicillin- or vancomycin-resistant microorganisms. Additionally, topical vancomycin does not appear to significantly change *S. aureus* colonization patterns. We conclude that topical vancomycin treatment is safe in the setting of neurological surgery. For a full description of the study and projected timeline of enrollment, please see the previously published protocol by Jonokuchi et al.²⁴

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Disclosures

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Author Contributions

Conception and design: Radwanski, Lowy, Knopman, Connolly. Acquisition of data: Radwanski, Martinez, Rothbaum, Lowy, Knopman, Connolly. Analysis and interpretation of data: Radwanski, Christophe, Connolly. Drafting the article: Radwanski, Christophe, Pucci, Connolly. Critically revising the article: Radwanski, Christophe, Pucci, Bagiella, Connolly. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Radwanski. Statistical analysis: Radwanski, Christophe, Pucci, Bagiella. Administrative/technical/material support: Radwanski, Christophe, Pucci, Martinez, Rothbaum, Connolly. Study supervision: Martinez, Bagiella, Lowy, Knopman, Connolly.

Supplemental Information

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