Topical vancomycin surgical prophylaxis in pediatric open craniotomies: an institutional experience

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OBJECTIVE Topical antimicrobial compounds are safe and can reduce cost and complications associated with surgical site infections (SSIs). Topical vancomycin has been an effective tool for reducing SSIs following routine neurosurgical procedures in the spine and following adult craniotomies. However, widespread adoption within the pediatric neurosurgical community has not yet occurred, and there are no studies to report on the safety and efficacy of this intervention. The authors present the first institution-wide study of topical vancomycin following open craniotomy in the pediatric population.

METHODS In this retrospective study the authors reviewed all open craniotomies performed over a period from 05/2014 to 12/2016 for topical vancomycin use, SSIs, and clinical variables associated with SSI. Topical vancomycin was utilized as an infection prophylaxis and was applied as a liquid solution following replacement of a bone flap or after dural closure when no bone flap was reapplied.

RESULTS Overall, 466 consecutive open craniotomies were completed between 05/2014 and 12/2016, of which 43% utilized topical vancomycin. There was a 1.5% SSI rate in the nontopical cohort versus 0% in the topical vancomycin cohort ($p = 0.045$). The number needed to treat was 66. There were no significant differences in risk factors for SSI between cohorts. There were no complications associated with topical vancomycin use.

CONCLUSIONS Routine topical vancomycin administration during closure of open craniotomies can be a safe and effective tool for reducing SSIs in the pediatric neurosurgical population.

<https://thejns.org/doi/abs/10.3171/2018.5.PEDS17719>

KEYWORDS antibiotics; craniotomy infection; infection prophylaxis; surgical site infection; surgical prophylaxis; topical vancomycin; vancomycin powder; pediatric craniotomy

SURGICAL site infection (SSI) following open craniotomy represents a significant source of morbidity and cost in neurosurgical patients with rates as high as 5%³ and associated costs of more than \$14,126 per case.²⁰ Topical vancomycin application during wound closure achieves higher local concentrations at the surgical site while minimizing systemic toxicity.¹⁰ This is especially important given the increasing prevalence of nosocomial methicillin-resistant *Staphylococcus aureus*, which now represents as much as half of all SSIs.¹⁸ Utilization of topi-

cal vancomycin is a well-established strategy for decreasing SSIs in spine surgeries.^{5,13,16,24} Recent studies in adults have also demonstrated the efficacy of topical vancomycin when applied during closure in decreasing SSIs following open craniotomies, leading to a decreased SSI rate of 0%–1.3% and potential cost savings of \$660 per patient.^{1,22}

Despite the success of topical vancomycin in decreasing SSIs in adult spinal surgery and open craniotomy patients, this practice has not been adopted or well-studied in pediatric patients. We present the first institution-wide

ABBREVIATIONS SSI = surgical site infection.

SUBMITTED December 16, 2017. **ACCEPTED** May 30, 2018.

INCLUDE WHEN CITING Published online August 24, 2018; DOI: 10.3171/2018.5.PEDS17719.

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study of the impact of topical vancomycin utilization following open craniotomy in the pediatric population.

Methods

This was a retrospective study of the impact of topical vancomycin utilization for SSI prevention in pediatric patients receiving open craniotomies at Lucile Packard Children's Hospital (LPCH) Stanford. This study was approved by the Stanford Institutional Review Board. All open pediatric craniotomies performed at Stanford Children's Hospital between 05/2014 and 12/2016 were included in this study. Utilization of topical vancomycin was adopted at different time points by each provider over the study period but, once adopted, was then standard practice for every open craniotomy. Exclusion criteria included ventricular shunt operation without open craniotomies and operations for which at least 3 months of patient follow-up was not available in the medical record.

For each operation included in this study, the following information was extracted from the electronic medical record: operation date, diagnosis, procedure, length of operation, use of intra- and perioperative steroids, use of intra- and perioperative antibiotics, whether the surgery was emergent, and whether the operative wound was clean or contaminated. The following patient demographics were extracted: age, body mass index, and sex. Additionally, we collected data on the following potential SSI risk factors: cardiovascular disease, previous craniotomy, cancer, immunosuppression, diabetes, and hypertension. Finally, the postoperative period was scrutinized for SSIs occurring within 3 months of the operative date. The occurrence of a postoperative SSI was determined using the CDC guidelines and included any operative wound-related infection that involves the skin, subcutaneous tissue, deep soft tissues beneath the incision, and/or deeper parts of the body opened or manipulated during the operative procedure, and at least one of the following: purulent drainage, organisms identified from aseptically obtained specimens, or, if aseptic culture-based testing is not performed, the presence of at least one of the following signs or symptoms: pain or tenderness, localized swelling, erythema, or heat.¹⁹ For cases in which a patient underwent multiple procedures included in this cohort, the SSI was linked to the most recent craniotomy. We chose to analyze each surgery performed as an independent event as this study was intended as a retrospective analysis of topical vancomycin utilization per surgery for all surgeries performed at LPCH. The postoperative period was examined for SSI regardless of whether additional surgeries were performed.

All patients included in this study were treated with standard-of-care antibiotic prophylaxis during surgery, encompassing pre- and postoperative antibiotic prophylaxis with 50 mg/kg of intravenous ceftriaxone or cefazolin given within 30 minutes of the skin incision. Postoperative antibiotic treatment included ceftriaxone given every 12 hours for a total of 24 hours postoperatively. Patients with known penicillin allergies were treated with 15 mg/kg of vancomycin intravenously.

Operations done in the intervention group included the use of a solution of 1 g of vancomycin in 10–20 ml of

sterile normal saline used to irrigate the surgical wound at the completion of the procedure. This dose and method of vancomycin administration was chosen based on prior studies indicating its safety in pediatric patients.² Irrigation was chosen as a means of vancomycin delivery in order to maximize surface area covered. Vancomycin solution was applied following replacement of bone flap, or in cases of craniectomy following either primary dural closure or closure using a synthetic dural substitute graft. It should be also noted that it was the standard practice for all patients in this study to receive copious amounts of saline irrigation with bacitracin during closure. This occurred extradurally and prior to application of topical vancomycin in patients receiving vancomycin. Following vancomycin application, wounds were closed in a standard multilayer fashion using sutures and/or staples as indicated.

Statistical analysis was performed using 2-sample proportion z-tests and unpaired t-tests to compare variables between control and treatment groups. We performed an ad hoc cost analysis by comparing the costs of SSIs and vancomycin between groups. The unit cost of a pediatric SSI was determined through literature search to be \$27,288.²³ The unit cost of 1 g of vancomycin was \$49.40. Group costs were determined by summing the observed number of SSIs multiplied by the unit cost of a pediatric SSI combined with the number of uses of vancomycin within the group multiplied by the unit cost of 1 g of vancomycin.

Results

Overall, 466 consecutive pediatric craniotomies were included in this analysis, 265 of which comprised the control group and 201 of which included prophylactic use of vancomycin for surgical site irrigation. Distribution of surgical etiologies is shown in Fig. 1. In terms of location, 49.6% of cases were supratentorial, 32.6% were infratentorial, and 17.8% were extraaxial cranial lesions.

We compared demographic data between the two groups and tested for significant differences in known SSI risk factors. There were significantly more patients in the vancomycin group receiving craniofacial procedures, but no other significant differences in demographic characteristics between the two groups were identified (Table 1). We additionally compared operative characteristics associated with the risk for SSI, including whether the procedure was performed emergently, whether the operative site was contaminated, and what the length of surgery was, and no significant differences were observed.

The primary outcome of this study was the incidence of postoperative SSIs between the control group and the vancomycin group. We observed 4 incidences of SSI in this study (Table 2). Of these, none occurred in procedures that included prophylactic use of vancomycin irrigation. This equates to an SSI incidence of 1.5% in the control group and 0% in the vancomycin group, and the absolute risk reduction between the groups was 1.5% ($p = 0.045$, 95% CI 0.04%–2.9%). Based on this calculation, the number needed to treat is 66 operations (95% CI 33–2198). Two of the 4 infections were seen in craniofacial proce-

FIG. 1. All craniotomies included in the study classified by surgical diagnosis. Figure is available in color online only.

dures, and there was one patient with a culture-indeterminate clinical infection for which no organism could be isolated from the culture, likely due to antibiotic initiation prior to wound culture sampling. There were no side effects or complications associated with topical vancomycin use, and there were no vancomycin-resistant organisms identified. A multivariable logistic regression was also performed controlling for all variables shown in Table 1, with $p < 0.20$. This yielded a nonsignificant odds ratio for all variables.

We also performed an ad hoc cost analysis of the use of vancomycin in pediatric craniotomies. We compared SSI and vancomycin costs between the groups, using the work of Sparling et al.²³ to estimate the average cost of a pediatric craniotomy infection as \$27,288 and approximating the cost of 1 g of vancomycin powder as \$49.40. Based on these assumptions, the SSI-associated costs in the control group were \$109,152, or \$411.80 per operation. As no SSIs were observed in the treatment group, the total cost was the number of operations multiplied by the cost of 1 g of vancomycin, equating to a total of \$9,929.40, or \$49.40 per operation (Table 3). This translates into a \$362.49 potential cost savings per patient and an estimated overall cost savings of \$72,861.36 to the hospital with utilization of topical vancomycin in this study.

Discussion

In this study, we present the first large institutional series of consecutive pediatric open craniotomy patients treated with topical vancomycin with the goal of preventing postoperative SSI. SSI following open craniotomy incurs significant morbidity, mortality, and cost in neurosurgery patients. Adult SSI rates following craniotomy range from 2.2% to 4.7%.⁸ However, these rates are higher in the pediatric population, estimated to be around 4.7%–6.3%, and are even higher in children under 2 years of age.^{4,6}

SSIs also represent the second-most common reason for pediatric readmission following neurosurgery, second only to shunt-related complications.⁶ Thus, decreasing SSIs following craniotomies in the pediatric population represents a significant quality improvement target for the field. In our institutional study, we investigated the efficacy of topical vancomycin solution as it was adopted over time for SSI prophylaxis. We demonstrated that utilization of topical vancomycin solution in children is safe, cost-

TABLE 1. Demographics and operative characteristics between vancomycin-treated and control patients

Characteristic	Vanco (n = 201)	Control (n = 265)	p Value
Age, yrs	6.8 ± 5.5	7.1 ± 5.8	0.45
Intraop steroids	59 (29.4%)	93 (35.1%)	0.19
Periop steroids	83 (41.3%)	99 (37.4%)	0.39
BMI, mean	18.1 ± 4.3	18.3 ± 5.1	0.58
Sex (male = 1)	109 (54%)	160 (60%)	0.18
Previous craniotomy	44 (21.9%)	54 (20.4%)	0.69
Cancer	34 (17.1%)	46 (17.4%)	0.92
Diabetes	3 (1.5%)	6 (2.3%)	0.55
Hypertension	0 (0.0%)	2 (0.8%)	0.22
Immunosuppression	16 (8.0%)	28 (10.6%)	0.34
Emergent	26 (13.2%)	39 (15.1%)	0.56
Contaminated	4 (2.0%)	9 (3.4%)	0.35
Length of op, mean	235.1 ± 132.7	246.6 ± 141.6	0.37
Craniofacial type procedure	48 (23.9%)	38 (14.3%)	0.010
SSI	0 (0.0%)	4 (1.5%)	0.045

BMI = body mass index; Vanco = vancomycin.

Values are presented as the mean ± SD or number of patients (%) in each group. Boldface type indicates statistical significance ($p < 0.05$).

TABLE 2. Characteristics of observed SSIs

Pt No.	Diagnosis	Age (yrs)	Sex	BMI (g/cm ²)	Operative Details	Vanco Use	Organism Cultured	Finding
1	Coronal synostosis	1.3	M	18.6	Rt craniotomy frontal orbital reconstruction	No	Yeast—believed to be culture contaminant*	Wound debridement & hardware removal + 6-wk course of cefazolin
2	Congenital abnormality of skull shape	16.4	F	23.6	Skull cranioplasty w/ bone matrix & absorbable mesh	No	<i>Enterobacter cloacae</i>	Wound debridement & graft reconstruction + 4-wk course of cefepime
3	Craniosynostosis	4.41	M	15.51	Bifrontal craniotomy; bifrontal orbital advancement w/ bone grafts	No	<i>Microsporum gypseum</i> , <i>Propionibacterium acnes</i>	Wound debridement & subgaleal washout + 2-wk course of ciprofloxacin & griseofulvin
4	Suprasellar cyst	4.12	M	20.18	Rt cranial frontal cyst fenestration; placement of Ommaya reservoir	No	<i>Aspergillus niger</i>	Wound debridement & subgaleal washout + 2-wk course of fluconazole

Pt = patient.

* This patient's SSI included local erythema and swelling as well as subgaleal collection and purulent discharge noted on wound drainage. Antibiotics were given before samples were sent for culture.

effective, and associated with a significantly decreased SSI rate of 1.5% to 0%.

In a recent large meta-analysis, risk factors associated with SSI following open craniotomies were identified and included other infection, number of previous operations, CSF leak, CSF drainage, duration of operation, venous sinus entry, ASA (American Society of Anesthesiologists) score > 2, sex (male), and nontraumatic surgical indications.⁸ In the pediatric population, risk factors associated with SSIs following craniotomy procedures include CSF leak, previous craniotomy, longer operating room and procedure time, longer interval between antibiotic administration and incision, and longer interval to antibiotic redosing.^{12,17} Though we studied some but not all of these variables, there were no significant differences between the control and vancomycin-treated cohorts in the SSI risk factors we examined.

The spine surgery literature has the most supporting evidence for use of topical vancomycin as a surgical infection prophylaxis. A recent meta-analysis of over 5000 spine surgery patients found that use of intrawound vancomycin powder led to a 33% reduction in SSI risk with no associated complications.¹⁵ There have been two large studies to date of topical vancomycin following adult open craniotomies. Abdullah et al., in a cohort of 150 consecutive patients, demonstrated a statistically significant reduction in infections (6.7% to 1.3%, $p < 0.05$). A larger follow-up study by Ravikumar et al. of 350 consecutive patients also found a statistically significant reduction in SSIs despite a lower preintervention SSI rate (2.2% to 0%, $p < 0.05$).²² Our study, with 466 patients, represents the largest reported series of craniotomies in children receiving topical vancomycin. We demonstrated a statistically significant reduction in the SSI rate ($p = 0.045$) despite an even lower preintervention SSI incidence of 1.5%. This supports the notion that even with low rates of SSI, the addition of topical vancomycin can still have a beneficial effect on SSI following open craniotomies.

Though the cost data are sparse in the pediatric neurosurgery literature for craniotomies specifically, the mean

overall cost of pediatric SSI for all types of surgery is estimated to be around \$27,288.²³ Some studies have reported a range of \$26,977–\$961,722 cost for wound complications following pediatric spinal deformity surgeries.^{11,14} In their adult open craniotomy series, Ravikumar et al. estimated the range of cost savings associated with utilization of topical vancomycin in adult open craniotomy patients at \$23,492–\$66,140 per 100 patients.²² Based on a pediatric SSI range of 4.7%–6.3%, we estimate the range of possible cost savings of utilization in pediatric craniotomy patients to be \$128,253–\$171,914 per 100 patients. SSIs and their resultant hospital readmissions are now tracked quality and outcome metrics that are intricately linked to reimbursement from both government and private payers. In this way, this intervention may also provide indirect financial gains from increased reimbursement with lower SSI rates.

Vancomycin toxicity is always a concern with administration in children and can manifest as several different adverse effects, including anaphylaxis, renal failure, and ototoxicity. However, this is typically seen with intravenous administration and toxicity is typically seen at therapeutic serum vancomycin levels > 15–25 µg/ml.²¹ Several studies of intrawound topical vancomycin following spine surgery in adults have demonstrated undetectable serum vancomycin levels, though intrawound vancomycin levels remained supratherapeutic for several days postoperatively.²⁴ Similar studies of pediatric spinal deformity patients have found undetectable to minimally low levels of serum vancomycin.⁹ Even with doses up to 1 g of vancomycin, serum vancomycin levels remained well below therapeutic and toxic levels (mean 2.5 µg/ml).² In a similar fashion, in their adult series of open craniotomy patients, Abdullah et al. demonstrated that, in a subset with local and systemic vancomycin concentrations, serum vancomycin levels were undetectable while local levels were supratherapeutic.¹ In our study, there were no adverse events or side effects associated with vancomycin, demonstrating the safety of topical vancomycin in a large series of pediatric craniotomy patients.

TABLE 3. Cost analysis

Treatment	Unit Cost	Control Group	Vanco Group	Total Cost
Craniotomy infection	\$27,288	4	0	\$109,152
Vanco (1 g)	\$49.40	0	201	\$9,929.40

The other major criticism of topical vancomycin as a surgical prophylaxis is that global utilization may select for gram-negative or drug-resistant pathogens. However, a large study of over 1200 patients receiving intrawound vancomycin following spine surgery found that the occurrence of *Staphylococcus aureus* was significantly lower in patients receiving vancomycin, and none of these pathogens developed resistance to vancomycin. There were higher rates of gram-negative organisms and indeterminate or culture-negative SSIs in patients receiving intrawound vancomycin.⁷ Of note, the causal organisms in the SSIs we identified in this study represent relatively rare organisms. This may be due to the postoperative gram-positive IV prophylaxis given to all patients in this study. Additionally, this may be the result of empirical SSI treatment with gram-positive antibiotics prior to samples being collected for culture. Nonetheless, it is possible that topical vancomycin would not have prevented SSIs due to these organisms.

Limitations

Despite the strong associations found in this study, there are limitations to its wider applicability. First, this is a single-institution, retrospective experience that may not be representative of populations across the United States. The decision to utilize topical vancomycin was made by each individual provider over time and not with the intent to establish any case-control study. The basis for this decision was promising reports from the adult and spine literature that topical vancomycin was effective in reducing SSI. Given the organic nature with which this intervention was adopted by our institution, we felt it was important to report the findings as an institutional experience. It can be assumed that adoption of topical vancomycin may proceed in a similar fashion at other institutions, and so our report, though observational, may be representative.

Additionally, this study utilized a surgery-centered analysis, in which each surgery was analyzed as a single event regardless of whether a patient underwent multiple surgeries. This approach was taken since utilization of topical vancomycin was dependent on each individual surgery and not each individual patient. However, we do not believe that this choice of analysis methodology affects our conclusions as none of the SSIs we detected occurred following multiple surgeries. Another limitation of the retrospective design is that there is always a chance of unreported infections or complications from patients being seen at outside institutions. However, access to medical record documentation for at least 3 months is adequate to capture any infections, adverse events, or complications relevant to this study. There was also a greater number of contaminated cases in our control cohort (9 vs 4). This

was not a statistically significant difference and none of the infected cases were contaminated cases, so this was felt to not be a factor in influencing SSI rate in our study.

Of note, there was a significantly greater number of craniofacial procedures performed in the vancomycin-treated cohort. However, given that craniofacial procedures have a higher risk of infection, we do not believe that finding effects our results as we would expect to see more SSIs in the vancomycin-treated arm. Finally, while we included as many relevant SSI risk factors as possible in our study, there remain some that were more difficult to obtain. As we aim to present guarded initial evidence of topical vancomycin for open craniotomy in the pediatric population, a more comprehensive study of all risk factors related to postoperative infection is warranted before more conclusive recommendations can be made. Future prospective, multiinstitutional, and possibly randomized studies would provide stronger evidence for the association found in this study.

Conclusions

This institution-wide study of all open craniotomies at a children's hospital is the first to demonstrate an association between use of topical vancomycin and a significant reduction in SSI rate in the pediatric population. There were no adverse events, side effects, or vancomycin resistance related to topical vancomycin administration. Therefore, given the decrease in SSI rate, safety profile, and cost savings found in our study, topical vancomycin may be considered following open craniotomies in the pediatric population.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Grant, Ho, Li. Acquisition of data: Ho, Cannon, Mohole. Analysis and interpretation of data: Grant, Ho, Cannon, Mohole, Pendhakar, Sussman, Li. Drafting the article: Grant, Ho, Cannon, Mohole. Critically revising the article: Grant, Ho, Pendhakar, Sussman, Edwards, Cheshier. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Grant. Statistical analysis: Ho. Administrative/technical/material support: Grant, Pendhakar, Sussman, Edwards, Cheshier. Study supervision: Grant, Li, Edwards.

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