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Staphylococcus Aureus Swabbing and Decolonization Before Neuromodulation Procedures: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: *Staphylococcus aureus (S aureus)* is the foremost bacterial cause of surgical-site infection (SSI) and is a common source of neuromodulation SSI. Endogenous colonization is an independent risk factor for SSI; however, this risk has been shown to diminish with screening and decolonization.

Materials and Methods: A systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines using the PubMed, Cochrane Library, and Embase data bases from inception to January 1, 2022, for the purposes of identifying all studies reporting on the use of *S aureus* swabbing and/or decolonization before neuromodulation procedures. A random-effects meta-analysis was performed using the metaphor package in R to calculate odds ratios (OR).

Results: Five observational cohort studies were included after applying the inclusion and exclusion criteria. The average study duration was 6.6 ± 3.8 years. Three studies included nasal screening as a prerequisite for subsequent decolonization. Type of neuromodulation included spinal cord stimulation in two studies, deep brain stimulation in two studies, intrathecal baclofen in one study, and sacral neuromodulation in one study. Overall, 860 and 1054 patients were included in a control or intervention (ie, screening and/or decolonization) group, respectively. A combination of nasal mupirocin ointment and a body wash, most commonly chlorhexidine gluconate soap, was used to decolonize throughout. Overall infection rates were observed at 59 of 860 (6.86%) and ten of 1054 (0.95%) in the control and intervention groups, respectively. Four studies reported a significant difference. The OR for intervention (screen and/or decolonization) vs no intervention was 0.19 (95% CI, 0.09–0.37; $p < 0.001$). Heterogeneity between studies was nonsignificant ($I^2 = 0.43\%$, $\tau^2 = 0.00$).

Conclusions: Preoperative *S aureus* swabbing and decolonization resulted in significantly decreased odds of infection in neuromodulation procedures. This measure may represent a worthwhile tool to reduce neuromodulation SSI, warranting further investigation.

Keywords: Deep brain stimulation, infection, intrathecal baclofen pump, neuromodulation, *Staphylococcus aureus*

Conflict of Interest: The authors reported no conflict of interest.

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INTRODUCTION

The foremost bacterial cause of surgical-site infections (SSI) is *Staphylococcus aureus* (*S aureus*), contributing to approximately 30% of all SSIs.[1] Furthermore, almost two-thirds of implantable device infections are due to *S aureus* or coagulase-negative staphylococci.[2] As such, endogenous colonization of *S aureus* has been associated with a two-to-nine times higher risk of SSI,[1,3,4] and it has been shown to be the most important risk factor for developing any SSI for patients receiving orthopedic implantation.[5] Given that more than 80% of health care–related *S aureus* infections are due to endogenous flora,[6–8] patients who develop *S aureus* SSI show a corresponding 80% to 85% match rate between the infected culture isolate and that colonizing the nares.[5] When considering approximately 30% of the general population carries *S aureus*[1,7] and this associated proclivity for causing SSI, screening and decolonization protocols emerge as an important area of interest for the reduction of SSI. Common approaches used for *S aureus* decolonization include isolated or combinations of mupirocin nasal ointment, oral antibiotics, and chlorhexidine washes in conjunction with generalized hygiene.

Randomized controlled trials (RCTs) have established the efficacy of *S aureus* nasal screening and subsequent decolonization for reducing rates of SSI.[9,10] A 2010 randomized, double-blind, placebo-controlled, multicenter study involving 917 patients by Bode et al[9] investigated whether preoperative identification of *S aureus* colonization through nasal swabbing followed by decolonization reduced the risk of *S aureus* infection. A 56% reduction in *S aureus* infection was observed for the cohort randomized to decolonization with mupirocin-chlorhexidine. A 2008 study by Hacek et al[11] implemented rapid nasal *S aureus* swabbing for 912 patients before orthopedic total joint procedures. Of those swabbed, 223 received positive screening results and were decolonized with mupirocin. A 75% reduction in *S aureus* SSI was found when compared with an historical control. The results of the study by Hacek et al are promising upon consideration that an *S aureus* screening and decolonization protocol was linked to decreases in SSI during orthopedic hip and joint implant operations. Further study on *S aureus* screening and decolonization is therefore warranted in the field of neuromodulation, which similarly uses implantable devices.

Furthermore, this reduction in SSI has been shown to deliver substantial reductions in health care costs within the orthopedic literature.[12,13] Given that patients with *S aureus* SSI have a higher risk of death and increased median hospital costs than do uninfected surgical site patients,[14,15] implementation of screening and decolonization protocols warrants further investigation.

Neuromodulation commonly uses implantable devices, which are especially susceptible to *S aureus*. This necessitates extra vigilance in this patient population because *S aureus* can form biofilms on implantable equipment and devices.[16,17] Thus, the failure to quickly detect these infections may result in complications such as pneumonia, septic shock, endocarditis, necrotizing fasciitis, bursitis, and death if explantation of this device is delayed or complicated.[18–21] Preventing these infections can improve patient outcomes, lower morbidity, lower mortality, and decrease costs.

Therefore, in this study, the authors examine the utility of *S aureus* swabbing before neuromodulation procedures by performing a systematic search and meta-analysis of the published literature for all studies with patients who underwent nasal swabbing for *S aureus*. To our knowledge, this is the first review of this nature examining the effectiveness of preoperative *S aureus* swabbing conducted before deep brain stimulation (DBS), spinal cord stimulation (SCS), and intrathecal (IT) pump implantation procedures.

MATERIALS AND METHODS

Data Base Query

This systematic review was performed using guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[22] A systematic literature search was conducted in January 2022 by two independent researchers using the PubMed and Embase data bases to identify literature reporting rates of *S aureus* infection after a perioperative swab and/or decolonization protocol. The search terms used to query the data bases were ("staphylococcus aureus" OR "staph" OR "MRSA" OR "MSSA") AND ("swabbing" OR "screen" OR "neuromodulation") AND ("DBS" OR "spinal stimulation" OR "intrathecal baclofen" OR "intrathecal pump" OR "implant" OR neuromodulate"). Wildcard modifiers ("*") were added to the Boolean search terms, where appropriate, to broaden the search. Covidence (Headquarters Melbourne, Australia) was used for systematic review management software. After extraction of the data from the data bases, duplicate citations were removed.

Screening

Two authors independently assessed titles and abstracts of studies in accordance with the predetermined inclusion criteria and exclusion criteria of this study. Any discrepancies during the screening process were resolved by consensus among all authors. Relevant articles were then assessed through a full-text review after initial title and abstract screening. References of articles selected for inclusion were also scrutinized according to the inclusion and exclusion criteria for their suitability in this review.

Selection Criteria

Predetermined criteria were established for eventual inclusion in this study. The following inclusion/exclusion criteria were applied:

- Primary studies of postoperative infection rates after neuromodulation procedures that used *S aureus* nasal swabbing and/or decolonization (excluding poster presentations, expert opinions, and case reports)
- The study must have explicitly reported outcome data for postoperative infection rate in human patients
- Implementation of a nasal swab and/or decolonization procedure to address infection risk by *S aureus*, ultimately providing comparative outcome data between a treatment and control
- Full-text articles available in English. Any discrepancies were resolved through reaching a consensus among all authors.

Data Extraction and Qualitative Assessment

Independent and blinded reviewers extracted data from the eligible studies. Extraction variables included authorship, study duration, location, study design, patient number, treatment arms, decontamination protocol, swabbing schedule, infection rate, follow-up, and type of neuromodulation procedure. The primary outcome was postoperative infection rate between the two treatment arms. The secondary outcome was colonization rate. Eligible studies were assessed for risk of bias and inclusion in this study by

two investigators with the Joanna Briggs Institute (JBI) Critical Appraisal Tool for Cohort Studies.[23]

Statistical Analysis

The primary and secondary outcomes were presented using descriptive statistics in the forms of counts and percentages. In addition, meta-analysis was performed using the "metafor" package in R (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria) through Rstudio (build 443). Odds ratios (ORs) and pooled 95% CIs in a random-effects model were computed to assess for the effect of swabbing and decolonization on the primary outcome. Heterogeneity was quantified using the I^2 statistic, where $I^2 \geq 75.00\%$ indicated substantial heterogeneity, with $p < 0.05$ defined as the threshold for statistical significance. The τ^2 value was estimated using the restricted maximum likelihood method. Funnel plots were produced to assess for publication bias.

RESULTS

Systematic Search

In total, 172 articles were identified through the literature search (Fig. 1). After duplicates were removed, 105 articles remained. The 105 articles were then screened for project relevancy, and 91 were removed because they did not relate. The 14 full-text articles were then assessed: nine were excluded after evaluation, and five were selected for final inclusion.

Study Characteristics

All the included studies were prospective cohort studies using retrospective cohorts for control comparison (Table 1). Two studies were performed in the United States, with the other three being in the United Kingdom, Belgium, and France. Type of neuromodulation included DBS in two studies, SCS in two studies, IT baclofen in one study, and sacral neuromodulation in one study. Studies were conducted over an average of 6.6 ± 3.8 years (including follow-up), with the oldest study beginning in 2002 and the latest concluding in 2019. The total number of patients included averaged 393 ± 183 (minimum: 171, maximum: 688). The proportion of patients receiving intervention compared with the total number of patients studied ranged from 0.35:1 to 0.83:1. Two studies reported data on patient age, with a mean age of 49.6 ± 15.0 years. Minimum follow-up was a minimum of one week and a maximum of one year. Three of five studies (60%) used preoperative nasal swabbing, and all five used a decolonization protocol. Overall, 860 and 1054 patients were included in a control or intervention (ie, screening and decolonization) group, respectively. Overall infection rates were observed at 6.86% and 0.95% in the control and intervention groups, respectively (Table 2). Infection rates per study are displayed in Figure 2. Overall, 537 patients were swabbed preoperatively: of these, 91 were only swabbed for methicillin-resistant *Staphylococcus aureus* positive (MRSA+) colonization. When tested for, MRSA+ colonization was 9.1%.

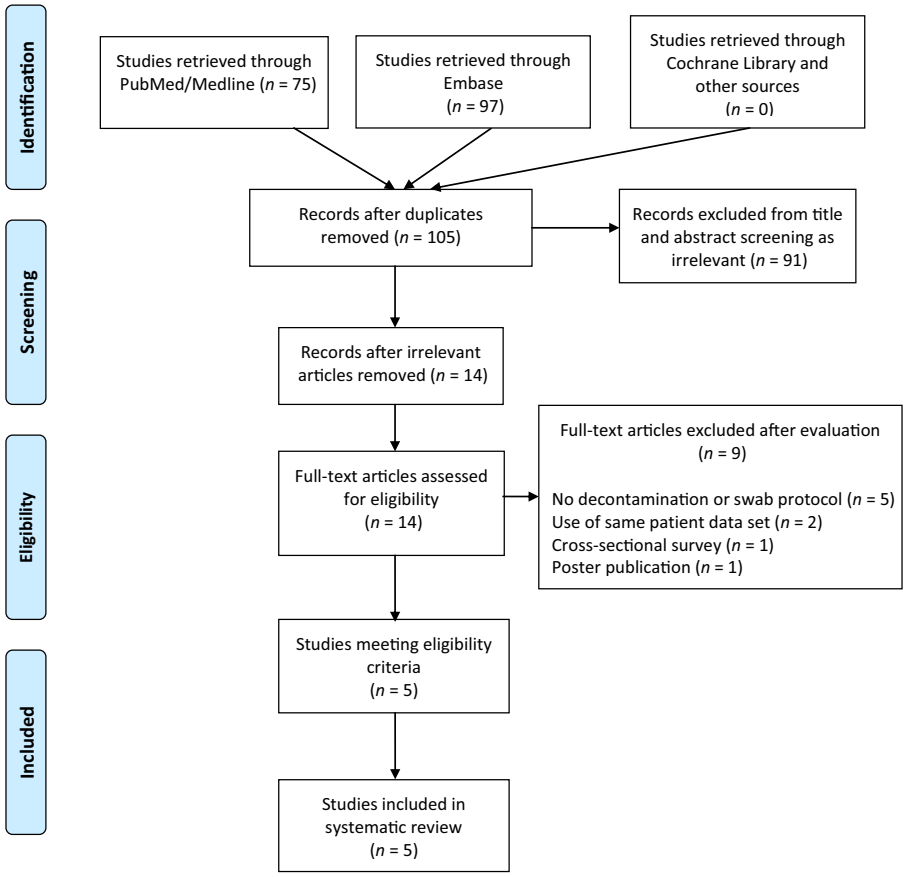

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram. [Color figure can be viewed at www.neuromodulationjournal.org]

Table 1. Characteristics of Comparative Cohort Studies Implementing Preoperative *Staphylococcus Aureus* Screening and/or Decolonization.

Study	Country	Duration	Total patients	Patients in intervention	Age, years, mean (SD)	Minimum follow-up	Neuromodulation	Nasal swab	Decolonization
Hill et al,[24] 2020	USA	2011–2019	463	383	–	1 wk	Sacral neuromodulation	Y	Y
Arocho-Quinones et al,[25] 2019	USA	2013–2017	688	356	50 (7)	12 mo	SCS, DBS, IT pump	N	Y
Yusuf et al,[26] 2017	Belgium	2014–2016	410	161	–	–	SCS	N	Y
Lefebvre et al,[27] 2016	France	2008–2015	182	63	–	1 mo	DBS	Y	Y
Pepper et al,[28] 2016	UK	2002–2014	171	91	48 (20)	9 mo	DBS	Y	Y

N, no; Y, yes.

Identified Pathogens

All five of the included studies reported an instance of positive *S aureus* cultures, either through preoperative nasal swabbing or postoperative infection samples. There was one study that delimited positive nasal cultures by methicillin-resistant *S aureus* (MRSA) or methicillin-susceptible *S aureus* (MSSA) positivity;[24] 71.7% were MRSA+, and 28.3% were MSSA+. One study performed 100 total preoperative nasal swabs and found zero MRSA colonizations.[28] *S aureus* was identified as the most common cause of infection in the control group for three studies, with rates of 66.6%,[25] 61.5%,[27] and 50%.[28] In the intervention groups, one study reported three total infections, with one due to *Staphylococcus epidermidis* (*S epidermis*) and one due to *Pseudomonas aeruginosa*—the other culture grew no organisms.[25] *Enterobacter aerogenes* (*E aerogenes*) was the cause of the single infection in one study.[27] Two studies did not report infectious causes in the intervention group, and one study observed zero infections.[28]

Nasal Swabbing and Decolonization Effectiveness

Three studies used preoperative nasal swabbing to screen for *S aureus* colonization. Rate of colonization for any form of *S aureus* was imputed at an overall *S aureus* colonization rate of 19.3% across all studies. Two studies[24,28] identified *S aureus* colonization on the basis of methicillin sensitivity, observing MRSA+ at an imputed overall colonization rate of 9.1%. Infection rate in the control groups ranged from 3.31% to 10.9%, and from 0% to 1.6% in the intervention groups. All five studies reported decreased rates of infection with either swabbing and decolonization as intervention or decolonization as intervention. The absolute number of infections seen in the intervention groups ranged from zero to three. Of these, in only two of five studies can the *S aureus* contribution to infection be determined[25,28]—there were no infections due to *S aureus* in either study after decolonization. Of the four studies that reported statistical analysis between groups, all reported a statistically significant decrease in infection, with the intervention group at an α of 0.05.

Decolonization Protocol

Every study used a unique protocol (Table 3). Nasal mupirocin 2% was incorporated in all five studies, most commonly three times a day for five days (2/5 studies), followed by three times a day for one day (1/5 studies) and twice a day for one day in conjunction with once in the morning of surgery (1/5 studies), and finally, for seven days (1/5 studies). One study[24] used nasal mupirocin for seven days as the sole decolonization agent in the days before surgery if patients were colonized at all, adding intravenous vancomycin on induction if MRSA+.

Surgical-Site Infection Criteria

The definition of and detection of SSI varied between all studies, when reported. Hill et al[24] defined it as any device explant with signs and symptoms of infection. Arocho-Quinones et al[25] defined it using the Centers for Disease Control and Prevention (CDC) guidelines for deep SSI,[29] which, briefly, use clinical suspicion of infection or purulent exudate from suspected site of infection or microbiological evidence or skin erosion with any of the above. Yusuf et al[26] defined it as the presence of positive culture from the site or signs and symptoms of SSI as determined by a neurosurgeon or medical microbiologist. Pepper et al[28] used only infections in direct relation to the hardware. Lefebvre et al[27] did not report their working definition of SSI.

Qualitative Assessment

All five studies were therapeutic observational studies with prospective intervention groups matched with retrospective control. According to the Oxford Centre for Evidence Based Medicine, this constitutes level IV evidence throughout.[30] The JBI Critical Appraisal Tool for Cohort Studies[23] was used to assess risk of bias. This is an 11-item questionnaire wherein an answer of "no" to any question increases the risk of bias for the study. Two of the same questions were not applicable across all studies. Ultimately, every study yielded a "no" rate of three of nine (33.3%), all in response to the same questions. The study groups were not strictly from the same population given the combined prospective/retrospective nature of the studies. In addition, identification of confounding factors and methods to address these were not addressed. At this risk of bias, it was deemed all studies were suitable for inclusion in this review.

Random-Effects Meta-Analysis

Overall, implementation of *S aureus* decolonization with or without the addition of preoperative nasal swabbing was associated with a decreased risk of postoperative SSI when compared with no specific infection prevention measures. The OR for intervention (screen and/or decolonization) vs no intervention was 0.19 (95% CI, 0.09–0.37; $p < 0.001$) Effect sizes for each study included in the random-effects model are displayed in Figure 3. Heterogeneity between studies was nonsignificant ($I^2 = 0.45\%$, $\tau^2 = 0.00$, $\chi^2 = 1.64$, df = 4, $p = 0.80$). Meta-regression analysis evaluating the effect of moderator variables in the form of nasal swabbing and additional infection prevention measures in some studies, such as the "infection prevention bundle" in Arocho-Quinones et al, yielded nonsignificant differences on odds of infection. Assessment of publication bias was performed with funnel plot analysis

Table 2. Experimental Parameters of Studies Using *S Aureus* Screening and/or Decolonization With Outcome Data.

Study	Control	Intervention			Rate of			Additional notes
		Screen (location, time)**	Decolonization protocol		Colonization *n* (%)	Infection		
			Antimicrobial	Schedule		Control *n* (%)	Intervention *n* (%)	*p* Value	
Hill et al,[24] 2020	No decolonization	Y (nasal, N/A)	Nasal mupirocin 2% IV vancomycin, if MRSA +	7 days Induction	60 (15.6)	4 (5.0)	3 (0.78)	0.005*	43 MRSA+ colonizations 17 MSSA colonizations
Arocho-Quinones et al,[25] 2019	No decolonization	N	Body wash, chlorhexidine gluconate 2% nasal mupirocin 2%	Evening before and morning of surgery Two times a day and morning of surgery	–	11 (3.31)	3 (0.01)	–	*S aureus* and *S epidermidis* most common organisms Risk factors for infection in intervention group: obesity and previous implant-related SSI
Yusuf et al,[26] 2017	No decolonization	N	Body wash, povidone-iodine	Once preoperatively	–	25 (10.0)	3 (0.02)	0.003*	Operating room personnel limited to 5 at a time in intervention group
			Nasal mupirocin 2%	Three times a day for 1 day					*S aureus* most common organism
Lefebvre et al,[27] 2016	Povidone-iodine shower night before and morning of surgery	Y (nasal, preop consult)	Body wash, chlorhexidine gluconate 4%	Once daily for 5 days	26 (36.5)	13 (10.9)	1 (1.6)	0.04*	*S aureus* most common organism in control
			Nasal mupirocin 2%	Three times a day for 5 days					*E aerogenes* infection in intervention
Pepper et al,[28] 2016	No decolonization	Y (skin and nasal, preop assessment clinic	Body wash, chlorhexidine gluconate 4%	Once daily for 6 days	0	6 (7.5)	0	0.003*	Only decolonized if history of MRSA+, or missed screening (4 decolonizations)
			Hair wash, chlorhexidine gluconate 4%	Every other day for 5 days					Vancomycin irrigation of the pocket was implemented in MRSA + patients
			Nasal mupirocin 2%	Three times a day for 5 days					*S aureus* most common cause of infection

IV, intravenous; N, no; N/A, not applicable; Y, yes.
*Denotes statistical significance at $p < 0.05$.
**Detection method was performed via microbial cultures.

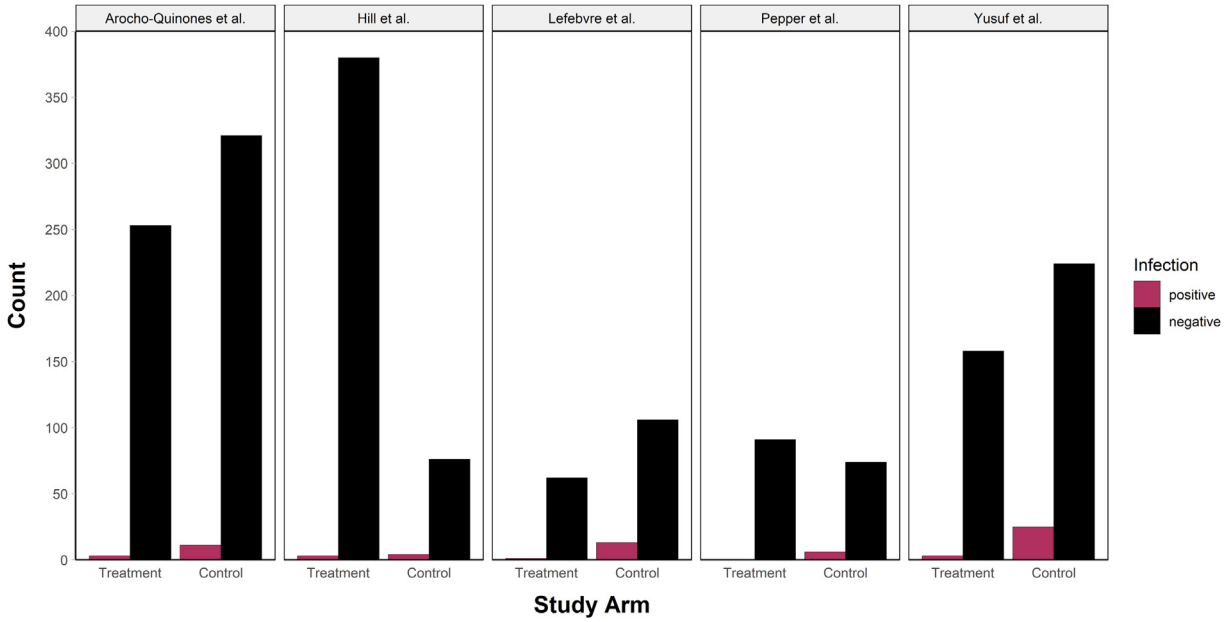

Figure 2. Bar plot displaying the primary outcome result—total number of infections—in each of the five included studies over their duration. The treatment study arm consisted of either *S aureus* screening with subsequent decolonization or decolonization of all included subjects. [Color figure can be viewed at www.neuromodulationjournal.org]

(Supplementary Data Supplementary Material 1), which indicated no focal paucity of studies, indicating a low likelihood of publication bias.

DISCUSSION

This study yielded five studies for final inclusion.[24–28] The intervention group in the studies included a mix of nasal screening/decolonization and decolonization for all patients. The control group mostly consisted of no screening and/or decolonization. Overall, postneuromodulation infection rates in the control groups were observed at 6.86% (59/860), which fell to 0.95% (10/1054) in the intervention groups—an 86% reduction. These results are echoed in the overall infectious disease literature, with one randomized, double-blind placebo-controlled, multicenter trial demonstrating a significant reduction in SSI when performing rapid screening and subsequent decolonization for nasal carriers of *S aureus*.[9] A nearly 60% reduction in SSI was seen in the decolonization group compared with the placebo group. This reduction in SSI, achieved through preoperative screening and decolonization, has been further established by a prospective cohort study with two-year follow-up in the orthopedic literature.[10] Despite the inclusion of just five studies in this meta-analysis, a strong pooled effect size in favor of decolonization was obtained (OR = 0.19). This can perhaps be explained by the previous establishment of the effectiveness of decolonization in reducing SSI, as evidenced by a 0.21 relative risk of deep SSI in surgical patients who received preoperative mupirocin-chlorhexidine treatment.[9] This constant statistical evidence in favor of treatment points toward a reliable biological effect in reducing SSI.

In a randomized, double-blind, placebo-controlled trial, Perl et al show that SSI is only significantly reduced with prophylactic intranasal decolonization in *S aureus* carriers.[1] In this systematic review, there were four studies that reported on significance for infection rate between groups. Three studies reported a significant reduction in the intervention group; however, they followed the screen-then-decolonize approach, whose efficacy is bolstered by the findings of Perl et al.[1] There was one study by Yusuf et al[26] that reported a significant decrease in SSI between the control and the indiscriminate decolonization group. However, there were uncontrolled variables between groups; most notably, decolonization was simply one aspect of the intervention, added within a larger effort to stymy SSI termed a "care-bundle." This included performing the neuromodulation at the earliest scheduled operating-room time, limiting operating-room personnel, educating home-care nurses on methods to limit SSI, and educating patients on proper wound care. Therefore, the veracity of the previous conclusions made through randomized, placebo-controlled trials in the study by Yusuf et al cannot be taken as strong evidence against the conclusion by Perl et al. Nevertheless, randomized, controlled inquiry evaluating the efficacy of swabbing and decolonization for neuromodulation-related SSI remains an unexplored avenue. Taken as such, the Neurostimulation Appropriateness Consensus Committee (NACC) only recommends decolonization if *S aureus* screening returns positive results, which is recommended to be performed in all patients who undergo neuromodulation.[31] Specifically, they recommend decolonization with nasal mupirocin ointment and chlorhexidine baths.

The NACC recommendations are partly derived from the protocols implemented in the two previously described RCTs.[9,10] In a study by Bode et al,[9] a 2% mupirocin ointment was used in combination with chlorhexidine gluconate soap, set at a schedule of ointment twice a day and the soap as a once-daily full-body wash, for five days. The RCT[10] by Rao et al used the same decolonization protocol. Interestingly, although all five studies included in this

Table 3. Additional Infection Prevention Measures Employed in Each Study in Addition to Targeted *Staphylococcus Aureus* Antimicrobial Decolonization

Study	Additional infection prevention measures
Hill et al,[24] 2020	N/A
Arocho-Quinones et al,[25] 2019	IPB : 1) preoperative patient counseling regarding safe infection prevention practices 2) post-operative wound care education 3) post-operative 24-hour antibiotics for overnight patients, or else one dose of antibiotics on discharge.
Yusuf et al,[26] 2017	Performing the neuromodulation procedure in the earliest OR time slot; ensuring a minimal amount of OR personnel; providing home care nurses with SCS wound care instruction; providing wound care instruction to patients orally.
Lefebvre et al,[27] 2016	N/A
Pepper et al,[28] 2016	Vancomycin/saline wash was used to irrigate the IPG wound pocket (only in the intervention arm).

IPB, infection prevention bundle; IPG, implantable pulse generator; N/A, not applicable.

review incorporated 2% nasal mupirocin ointment in their protocol, there was a variety of schedules. Although three of the five studies used all the same decontaminants,[25,27,28] none of these studies, nor the other two, followed the schedule of the RCT exactly. Three of the five studies opted for a protocol with either greater frequency or duration of application, with two implementing greater frequency of nasal mupirocin at three times a day for five days[27,28] and one with greater duration at seven days.[24] The other two studies used nasal mupirocin for just one day before and the morning of surgery.[25,26] Despite this variability, all the studies were effective in reducing SSI. Laboratory study has shown effective decolonization within a shorter duration of three days.[32] However, long-term decolonization with mupirocin can lead to treatment failure and subsequent relapse owing to the emergence of antibacterial resistance.[32] Correspondingly, the incorrect use of mupirocin or chlorhexidine in individuals who are not *S aureus* -colonized could potentially foster an environment for specific or generalized antibacterial resistance. In a study by Truong-Buldoc et al, mupirocin application against *S aureus* infection induced multidrug resistance response in the sensitivity of *S aureus* to ciproflaxin and chlorhexidine.[33] A global systematic review observed a significant increase over the past decade and 13.8% prevalence of mupirocin-resistant methicillin-resistant *S aureus*.[34] For the sake of retaining effectiveness of antibiotic agents and infection control, it is emphasized that antibiotic agents only be used in cases with obvious patient benefit.[35]

In addition to nasal decolonization, four of the five studies included full-body decontamination with either chlorhexidine gluconate baths or preoperative povidone-iodine. These are used to eradicate *S aureus* from other sites of colonized anatomy, such as the perianal and groin regions.[31] Two of the five studies[25,26] used decolonization as part of an overall "care-bundle" approach to limiting neuromodulation SSI. The efficacy of these approaches notwithstanding,[36–38] they limit the conclusions that can be made regarding the effect size of the *S aureus* decolonization itself on the reduced SSIs observed. The care bundles often act as forcing functions that optimize health care professionals' behavior toward reducing SSI.[28] An international survey of 506 physicians performing neuromodulation demonstrated low compliance rates for infection-control recommendations made by the CDC, with only four of 15 recommendations having a compliance rate of greater than or equal to 80%.[39] Presumably, these recommendations would be more completely adhered to in a study implementing a comprehensive care-bundle approach, which would certainly play a role in reducing SSI.

A single study differed from the other four by exploiting local vancomycin irrigation into the implantable pulse generator surgical pocket.[28] The authors advocate for these methods owing to increased "intrawound concentrations than would be possible via IV administration alone," which is especially advantageous in the fibrous pocket because of its reduced blood supply. In line with the NACC recommendations, this irrigation was only used in MRSA+ or high-risk patients.[31] Despite the low complication profile of intrawound vancomycin, there are no official practice guidelines or

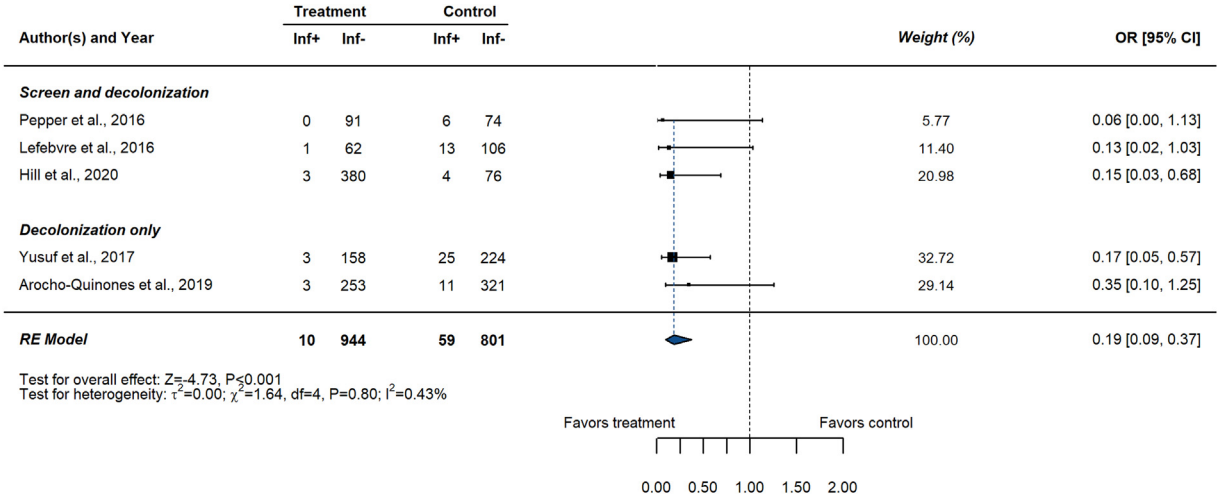

Figure 3. Forest plot comparing log odds of infection between patient receiving intervention (screening and/or decolonization) or no intervention in a random-effects model. Patients receiving intervention were less likely to experience postoperative infection (OR = 0.19 [95% CI, 0.09–0.37]; $p < 0.001$). [Color figure can be viewed at www.neuromodulationjournal.org]

recommendations for surgical wound irrigation.[40] In addition, vancomycin powder has shown promise in preventing SSI through systematic review and meta-analysis of the spine literature.[41–45] However, like irrigation, there is limited evidence to support the use of vancomycin powder in reducing neuromodulation-related SSI.[46,47] Given the success of Pepper et al in yielding a 0% intervention SSI rate,[28] and the low complication profile, further research into local vancomycin in neuromodulation procedures for positive carriers is certainly warranted.

Infection rates for neuromodulation implants in the literature range from 0% to 10% for SCS systems,[26,48] 3% to 15% for IT pump systems,[47,49,50] and 1% to 9% for DBS systems.[31,51] Overall infection rate in this study, including both controls and intervention groups, fell within the respective ranges, occurring in the following order from highest to lowest frequency: SCS (5.39%), IT pump (5.18%), DBS (2.49%), and sacral stimulation (1.51%). Indeed, SCS often has higher reported rates of infection than other types of implants, including joint replacement prostheses and pacemakers.[2] *S aureus* has been shown to be the most common causative agent for SCS-related SSI, present in up to 48% of cases.[52,53]

Limitations

This systematic review is not without limitations. None of the included studies is a prospective RCT; this allows for substantial heterogeneity of experimental variables among the five studies. This includes neuromodulation type, additional decontamination efforts surrounding *S aureus* decolonization, decolonization protocols, surgeon experience, and follow-up duration. Given these sources of heterogeneity and the limited study number of this review, it is difficult to discern the true effect of *S aureus* swabbing and decolonization as they relate to neuromodulation. Indeed, there was a wide variety of follow-up durations in the included studies, which would directly affect the number of postoperative infections captured and may underestimate this value if adequate follow-up duration is not implemented. These clear sources of heterogeneity notwithstanding, the meta-analysis model did not detect an overall significant source of heterogeneity. Although prospective studies should maintain consistency, this result highlights the potential external validity of the results of this study. According to the NACC, SSIs related to an implantable device are defined as infection within the region of the implanted device within one year postoperatively.[31] Future studies investigating the use of these SSI-reducing efforts within neuromodulation should strive for this mark. Variability in surgeon experience may also significantly alter conclusions made, given that operative time is a risk factor for SSI and this operative time may decrease with greater experience in performing the neuromodulation procedure, as stated by one of the authors.[28] This presents another possible limitation of a single-surgeon prospective observational cohort study with retrospective controls. The surgeon has necessarily accrued more experience, which, in the case of one study, contributed to significantly reduced operative times.[28]

Moving forward, it would be of great value to the field of neuromodulation if greater efforts were taken to standardize study design in these infection-prevention studies. If the ideal of an RCT cannot be achieved, ensuring a balanced allocation of subjects between study arms would be ideal in observational cohort studies because large variability, as was the case in Hill et al,[24] limits the predictive validity of these data in inferential statistics. In addition, robust reporting of study design is essential to test for moderators in effect sizes. Although most studies were explicit in the decolonization protocol and reporting of swabbing location, time of swabbing and mean follow-up duration were not consistently reported. An adequate follow-up duration is critical because some of the shorter follow-up times seen in the included studies may very well have underreported the rate of SSI, given the CDC definition of deep SSI extends the cutoff to 90 days.[29] In addition, standardization in confirming the presence of SSI is warranted because clinical and laboratory markers may be due to a systemic inflammatory response triggered by the implantation of a foreign neuromodulation device.[54] Although this study analyzed the effects of screening and additional infection prevention measures on top of screening and/or decolonization as moderators, the observed nonsignificant difference in effect size between these groups in the meta-analyses is a tenuous conclusion, given the relative dearth in sample sizes comprising each group. Therefore, a greater number of these studies over time will contribute to a more adequately powered analysis, able to confidently detect these differences, if present, and strengthen the recommendations derived therein. Furthermore, although it can be argued that any such study ought to include preoperative swabbing in their methods given the previously established efficacy of swabbing and subsequent decolonization,[1] not nonselective decolonization, this distinction has yet to be proven in neuromodulation procedures specifically. Therefore, if clinical trials with both screened and nonscreened arms cannot be implemented, observational cohort studies using only nonselective decolonization maintain statistical value, given the present need for data in both groups to answer the question: to screen, then decolonize, or simply decolonize?

CONCLUSIONS

This systematic review and meta-analysis found five studies using *S aureus* screening and/or decolonization before neuromodulation procedures. All five studies reported reduced rates of infection in the intervention groups, with four of them reporting statistically significant differences. Overall infection rate in the control groups was 6.86% compared with 0.95% for intervention, a decrease of 86.2%. IT pump and SCS neuromodulation had the highest rates of both control and intervention infection rates, whereas DBS procedures had the lowest. In the meta-analysis, patients receiving intervention were less likely to experience postoperative infection. Of the studies reporting on infectious etiology, *S aureus* was identified as the most common infectious organism in the control group whereas no instances of *S aureus* infection were found in any intervention groups. Decolonization protocols contained a combination of nasal mupirocin ointment and full-body decolonization with either povidone-iodine or, most commonly, chlorhexidine gluconate soap. Taken together, the use of *S aureus* swabbing before neuromodulation procedures represents a promising method to decrease the incidence of SSI, further validating the usefulness of prospective RCTs to investigate the true utility of this measure.

Authorship Statements

Neal Patel, Justin Gold, and Nolan J. Brown were responsible for the conceptualization, data curation, formal analysis, methods, original draft, review, and editing of the manuscript. Mickey Abraham, Ryan S. Beyer, Shane Shahrestani, Julian Gendreau, and

Antonios Mammis were responsible for the supervision, validation, review, and editing of the manuscript. All authors approved the final manuscript.

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1016/j.neurom.2022.07.013.

REFERENCES

1. Perl TM, Cullen JJ, Wenzel RP, et al. Intranasal mupirocin to prevent postoperative Staphylococcus aureus infections. *N Engl J Med*. 2002;346:1871–1877. https://doi.org/10.1056/NEJMoa003069.
2. Darouiche RO. Treatment of infections associated with surgical implants. *N Engl J Med*. 2004;350:1422–1429. https://doi.org/10.1056/NEJMra035415.
3. Kluytmans J, van Belkum A, Verbrugh H. Nasal carriage of Staphylococcus aureus: epidemiology, underlying mechanisms, and associated risks. *Clin Microbiol Rev*. 1997;10:505–520. https://doi.org/10.1128/cmr.10.3.505.
4. Wenzel RP, Perl TM. The significance of nasal carriage of Staphylococcus aureus and the incidence of postoperative wound infection. *J Hosp Infect*. 1995;31:13–24. https://doi.org/10.1016/0195-6701(95)90079-9.
5. Kalmeijer MD, van Nieuwland-Bollen E, Bogaers-Hofman D, de Baere GA. Nasal carriage of Staphylococcus aureus is a major risk factor for surgical-site infections in orthopedic surgery. *Infect Control Hosp Epidemiol*. 2000;21:319–323. https://doi.org/10.1086/501763.
6. von Eiff C, Becker K, Machka K, Stammer H, Peters G. Nasal carriage as a source of Staphylococcus aureus bacteremia. Study Group. *N Engl J Med*. 2001;344:11–16. https://doi.org/10.1056/nejm200101043440102.
7. Weinstein HJ. The relation between the nasal-staphylococcal-carrier state and the incidence of postoperative complications. *N Engl J Med*. 1959;260:1303–1308. https://doi.org/10.1056/nejm195906252602601.
8. Wertheim HF, Vos MC, Ott A, et al. Risk and outcome of nosocomial Staphylococcus aureus bacteraemia in nasal carriers versus non-carriers. *Lancet*. 2004;364:703–705. https://doi.org/10.1016/s0140-6736(04)16897-9.
9. Bode LG, Kluytmans JA, Wertheim HF, et al. Preventing surgical-site infections in nasal carriers of Staphylococcus aureus. *N Engl J Med*. 2010;362:9–17. https://doi.org/10.1056/NEJMoa0808939.
10. Rao N, Cannella B, Crossett LS, Yates AJ Jr, McGough R 3rd. A preoperative decolonization protocol for staphylococcus aureus prevents orthopaedic infections. *Clin Orthop Relat Res*. 2008;466:1343–1348. https://doi.org/10.1007/s11999-008-0225-4.
11. Hacek DM, Robb WJ, Paule SM, Kudrna JC, Stamos VP, Peterson LR. Staphylococcus aureus nasal decolonization in joint replacement surgery reduces infection. *Clin Orthop Relat Res*. 2008;466:1349–1355. https://doi.org/10.1007/s11999-008-0210-y.
12. Chen AF, Wessel CB, Rao N. Staphylococcus aureus screening and decolonization in orthopaedic surgery and reduction of surgical site infections. *Clin Orthop Relat Res*. 2013;471:2383–2399. https://doi.org/10.1007/s11999-013-2875-0.
13. van Rijen MM, Bode LG, Baak DA, Kluytmans JA, Vos MC. Reduced costs for Staphylococcus aureus carriers treated prophylactically with mupirocin and chlorhexidine in cardiothoracic and orthopaedic surgery. *PLoS One*. 2012;7:e43065. https://doi.org/10.1371/journal.pone.0043065.
14. Engemann JJ, Carmeli Y, Cosgrove SE, et al. Adverse clinical and economic outcomes attributable to methicillin resistance among patients with Staphylococcus aureus surgical site infection. *Clin Infect Dis*. 2003;36:592–598. https://doi.org/10.1086/367653.
15. Anderson DJ, Kaye KS, Chen LF, et al. Clinical and financial outcomes due to methicillin resistant Staphylococcus aureus surgical site infection: a multi-center matched outcomes study. *PLoS One*. 2009;4:e8305. https://doi.org/10.1371/journal.pone.0008305.
16. Luan S, Williams I, Nikolic K, Constandinou TG. Neuromodulation: present and emerging methods. *Front Neuroeng*. 2014;7:27. https://doi.org/10.3389/fneng.2014.00027.
17. Akhtar A, Kadir H, Chandran P. Surgical site infection risk following pre-operative MRSA detection in elective orthopaedic surgery. *J Orthop*. 2014;11:117–120. https://doi.org/10.1016/j.jor.2014.07.001.
18. Gofeld M. New horizons in neuromodulation. *Curr Pain Headache Rep*. 2014;18:397. https://doi.org/10.1007/s11916-013-0397-9.
19. Levy RM. Centers of excellence for neuromodulation: a critical proposal. *Neuromodulation*. 2014;17:1–9. https://doi.org/10.1111/ner.12155.
20. Canadian Agency for Drugs and Technologies in Health (CADTH). Pre-operative screening for methicillin-resistant Staphylococcus aureus (MRSA) infection: a review of the clinical-effectiveness and guidelines. *CADTH Technol Overv*. 2010;1:e0114.
21. Green BN, Johnson CD, Egan JT, Rosenthal M, Griffith EA, Evans MW. Methicillin-resistant Staphylococcus aureus: an overview for manual therapists. *J Chiropr Med*. 2012;11:64–76. https://doi.org/10.1016/j.jcm.2011.12.001.
22. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *BMJ*. 2009;339:b2535. https://doi.org/10.1136/bmj.b2535.
23. Munn Z, Moola S, Riitano D, Lisy K. The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. *Int J Health Policy Manag*. 2014;3:123–128. https://doi.org/10.15171/ijhpm.2014.71.
24. Hill H, Dukovac T, Long A, Conner J, Goudelocke C. A novel sacral neuromodulation infection protocol is associated with reduction in device infection. *J Urol*. 2020;203(suppl 4):e438–e439. https://doi.org/10.1097/JU.0000000000000869.03.
25. Arocho-Quinones EV, Huang CC, Ward BD, Pahapill PA. Care bundle approach to minimizing infection rates after neurosurgical implants for neuromodulation: a single-surgeon experience. *World Neurosurg*. 2019;128:e87–e97. https://doi.org/10.1016/j.wneu.2019.04.003.
26. Yusuf E, Bamps S, Thüer B, et al. A multidisciplinary infection control bundle to reduce the number of spinal cord stimulator infections. *Neuromodulation*. 2017;20:563–566. https://doi.org/10.1111/ner.12555.
27. Lefebvre J, Buffet-Bataillon S, Henaux PL, Riffaud L, Morandi X, Haegelen C. Staphylococcus aureus screening and decolonization reduces the risk of surgical site infections in patients undergoing deep brain stimulation surgery. *J Hosp Infect*. 2017;95:144–147. https://doi.org/10.1016/j.jhin.2016.11.019.
28. Pepper J, Meliak L, Akram H, et al. Changing of the guard: reducing infection when replacing neural pacemakers. *J Neurosurg*. 2017;126:1165–1172. https://doi.org/10.3171/2016.4.Jns152934.
29. Surgical site infection event (SSI). The National Healthcare Safety Network. Accessed March 1, 2022. https://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf.
30. OCEBM levels of evidence. The Centre for Evidence-Based Medicine. Accessed March 1, 2022. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence.
31. Deer TR, Provenzano DA, Hanes M, et al. The Neurostimulation Appropriateness Consensus Committee (NACC) recommendations for infection prevention and management. *Neuromodulation*. 2017;20:31–50. https://doi.org/10.1111/ner.12565.
32. Walker ES, Vasquez JE, Dula R, Bullock H, Sarubbi FA. Mupirocin-resistant, methicillin-resistant Staphylococcus aureus: does mupirocin remain effective? *Infect Control Hosp Epidemiol*. 2003;24:342–346. https://doi.org/10.1086/502218.
33. Truong-Bolduc QC, Wang Y, Reedy JL, Vyas JM, Hooper DC. Staphylococcus aureus efflux pumps and tolerance to ciprofloxacin and chlorhexidine following induction by mupirocin. *Antimicrob Agents Chemother*. 2022;66:e0184521. https://doi.org/10.1128/aac.01845-21.
34. Dadashi M, Hajikhani B, Darban-Sarokhalil D, van Belkum A, Goudarzi M. Mupirocin resistance in Staphylococcus aureus: a systematic review and meta-analysis. *J Glob Antimicrob Resist*. 2020;20:238–247. https://doi.org/10.1016/j.jgar.2019.07.032.
35. Van den Poel B, Saegeman V, Schuermans A. Increasing usage of chlorhexidine in health care settings: blessing or curse? A narrative review of the risk of chlorhexidine resistance and the implications for infection prevention and control. *Eur J Clin Microbiol Infect Dis*. 2022;41:349–362. https://doi.org/10.1007/s10096-022-04403-w.
36. Manolis AS, Melita H. Prevention of cardiac implantable electronic device infections: single operator technique with use of povidone-iodine, double gloving, meticulous aseptic/antiseptic measures and antibiotic prophylaxis. *Pacing Clin Electrophysiol*. 2017;40:26–34. https://doi.org/10.1111/pace.12996.
37. Polyzos KA, Konstantelias AA, Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. *Europace*. 2015;17:767–777. https://doi.org/10.1093/europace/euv053.
38. Schweizer ML, Chiang HY, Septimus E, et al. Association of a bundled intervention with surgical site infections among patients undergoing cardiac, hip, or knee surgery. *JAMA*. 2015;313:2162–2171. https://doi.org/10.1001/jama.2015.5387.
39. Provenzano DA, Deer T, Luginbuhl Phelps A, et al. An international survey to understand infection control practices for spinal cord stimulation. *Neuromodulation*. 2016;19:71–84. https://doi.org/10.1111/ner.12356.
40. Barnes S, Spencer M, Graham D, Johnson HB. Surgical wound irrigation: a call for evidence-based standardization of practice. *Am J Infect Control*. 2014;42:525–529. https://doi.org/10.1016/j.ajic.2014.01.012.

41. Bakhsheshian J, Dahdaleh NS, Lam SK, Savage JW, Smith ZA. The use of vancomycin powder in modern spine surgery: systematic review and meta-analysis of the clinical evidence. *World Neurosurg*. 2015;83:816–823. https://doi.org/10.1016/j.wneu.2014.12.033.
42. Chiang HY, Herwaldt LA, Blevins AE, Cho E, Schweizer ML. Effectiveness of local vancomycin powder to decrease surgical site infections: a meta-analysis. *Spine J*. 2014;14:397–407. https://doi.org/10.1016/j.spinee.2013.10.012.
43. Khan NR, Thompson CJ, DeCuypere M, et al. A meta-analysis of spinal surgical site infection and vancomycin powder. *J Neurosurg Spine*. 2014;21:974–983. https://doi.org/10.3171/2014.8.Spine1445.
44. Tubaki VR, Rajasekaran S, Shetty AP. Effects of using intravenous antibiotic only versus local intrawound vancomycin antibiotic powder application in addition to intravenous antibiotics on postoperative infection in spine surgery in 907 patients. *Spine (Phila Pa 1976)*. 2013;38:2149–2155. https://doi.org/10.1097/brs.0000000000000015.
45. Xiong L, Pan Q, Jin G, Xu Y, Hirche C. Topical intrawound application of vancomycin powder in addition to intravenous administration of antibiotics: a meta-analysis on the deep infection after spinal surgeries. *Orthop Traumatol Surg Res*. 2014;100:785–789. https://doi.org/10.1016/j.otsr.2014.05.022.
46. Amrani J. Intraoperative powdered vancomycin use with paddle lead placement. *Neuromodulation*. 2015;18:177–180 [discussion: 181]. https://doi.org/10.1111/ner.12216.
47. Ghobrial GM, Thakkar V, Singhal S, et al. Efficacy of intraoperative vancomycin powder use in intrathecal baclofen pump implantation procedures: single institutional series in a high risk population. *J Clin Neurosci*. 2014;21:1786–1789. https://doi.org/10.1016/j.jocn.2014.04.007.
48. Pahapill PA. Incidence of revision surgery in a large cohort of patients with thoracic surgical three-column paddle leads: a retrospective case review. *Neuromodulation*. 2015;18:367–375. https://doi.org/10.1111/ner.12239.
49. Malheiro L, Gomes A, Barbosa P, Santos L, Sarmento A. Infectious complications of intrathecal drug administration systems for spasticity and chronic pain: 145 patients from a tertiary care center. *Neuromodulation*. 2015;18:421–427. https://doi.org/10.1111/ner.12265.
50. Taira T, Ueta T, Katayama Y, et al. Rate of complications among the recipients of intrathecal baclofen pump in Japan: a multicenter study. *Neuromodulation*. 2013;16:266–272 [discussion: 272]. https://doi.org/10.1111/ner.12010.
51. Frizon LA, Hogue O, Wathen C, et al. Subsequent pulse generator replacement surgery does not increase the infection rate in patients with deep brain stimulator systems: a review of 1537 unique implants at a single center. *Neuromodulation*. 2017;20:444–449. https://doi.org/10.1111/ner.12605.
52. Follett KA, Boortz-Marx RL, Drake JM, et al. Prevention and management of intrathecal drug delivery and spinal cord stimulation system infections. *Anesthesiology*. 2004;100:1582–1594. https://doi.org/10.1097/00000542-200406000-00034.
53. Fletcher N, Sofianos D, Berkes MB, Obremskey WT. Prevention of perioperative infection. *J Bone Joint Surg Am*. 2007;89:1605–1618. https://doi.org/10.2106/jbjs.F.00901.
54. Davies MG, Hagen PO. Systemic inflammatory response syndrome. *Br J Surg*. 1997;84:920–935. https://doi.org/10.1002/bjs.1800840707.

COMMENT

Collecting literature and analyzing results is a tedious work, and the author's efforts should be acknowledged. Although there may be some defects, this work must be carried out continuously and continuously tracked and improved. I hope the authors can continue to adhere to his research direction and achieve more results. Good luck!

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