Impact of Powdered Vancomycin on Preventing Surgical Site Infections in Neurosurgery: A Systematic Review and Meta-analysis

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BACKGROUND: Surgical site infections (SSIs) after spine and brain surgery present a major burden to patients and hospitals by increasing morbidity, mortality, and healthcare costs.
OBJECTIVE: To review available literature investigating the role of intrawound powdered vancomycin against SSIs after neurosurgical operations.
METHODS: All randomized and observational English language studies of intrawound powdered vancomycin use in spinal and cranial surgery were included and analyzed using random-effects modeling.
RESULTS: In spine surgery (25 studies with 16 369 patients), patients in the vancomycin group had a significantly lower risk for any SSI (odds ratio [OR]: 0.41; 95% confidence interval [CI]: 0.30-0.57; $P < .001$; $I^2 = 47\%$). However, when separate analyses were conducted for superficial and deep SSIs, a significant difference was found only for deep (OR: 0.31; 95% CI: 0.22-0.45; $P < .001$; $I^2 = 29\%$). Subgroup analyses for different vancomycin powder dosages (1 g vs 2 g vs composite dose) did not point to any dose-related effect of vancomycin. In cranial surgery (6 studies with 1777 patients), use of vancomycin was associated with a significantly lower risk for SSIs (OR: 0.33; 95% CI: 0.18-0.60; $P = .0003$; $I^2 = 45\%$). In meta-regression analysis, trial-level variability of diabetes had no influence on the association of vancomycin powder use with SSIs.
CONCLUSION: Use of vancomycin powder in spinal and cranial surgery might be protective against SSIs, especially against deep SSIs. No dose-related effect of vancomycin powder was identified. However, caution is needed in the clinical interpretation of these results, owing to the observational design of the included studies in this meta-analysis.

KEY WORDS: Vancomycin, Powder, Infection, Surgical site, Spine, Cranial

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The risk of surgical site infections (SSIs) after spinal operations ranges from 0.7% to 12%.[1-3] Despite comprehensive patient selection, meticulous operative technique, standard skin preparation, and timely administration of the appropriate systemic antibiotics, SSI rates remain high.[3,4] SSI leads to prolonged hospital stays, recurrent hospital admissions, increased healthcare costs, morbidity, and mortality.[5-7] Therefore, SSIs are both a common clinical problem and a health-economic burden.

Most SSIs are caused by native skin flora due residence on the patient near the wound exposure.[8] In spine and brain surgery, the most common contaminants include gram-positive cocci, primarily *Staphylococcus aureus* and *S. epidermidis*, which are also the leading causes of SSIs in the United States.[9,10] For several decades, use of cefazolin and other broad-spectrum antibiotics has been the standard of care for SSI prophylaxis.[11,12] However, several studies have shown that methicillin-resistant

ABBREVIATIONS: CI, confidence interval; **GRADE,** Grading of Recommendations Assessment, Development and Evaluation; **MD,** mean difference; **NSQIP,** National Surgical Quality Improvement Program; **NVG,** nonvancomycin group; **OR,** odds ratio; **RCT,** randomized controlled trial; **SSI,** surgical site infection; **VG,** vancomycin

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staphylococcus aureus SSI rates are rising, which in turn reduces the ability of cephalosporins to efficiently prevent SSIs.[13,14]

Experimental and clinical studies measuring the effect of intrawound powdered vancomycin during spinal surgery demonstrated promising outcomes.[7,14,15] This novel prophylactic measure has gained the attention of surgeons over the last few years in order to further decrease the incidence of SSIs.[16-18] Nevertheless, reported efficacy of intrawound powdered vancomycin in preventing SSIs is inconsistent across the literature.[19-22] Our objective was to qualitatively and quantitatively analyze the available literature on local intrawound vancomycin powder use in spine and brain surgeries in order to clarify its true potential in preventing SSIs in neurosurgery.

METHODS

This systematic review and meta-analysis adhered to the criteria outlined in the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[23] There was no study protocol registered for this meta-analysis.

Search Strategy and Selection Criteria

An electronic literature search was conducted in using PubMed, Scopus, and Cochrane Central for studies published till March 13, 2018. Keywords used for database searches included the following: vancomycin powder, spine, cranial, neurosurgery, and infection. The search was conducted by 2 independent investigators (PT and YY), and disagreements were resolved with input by a third investigator (VML). In addition, we manually reviewed the references of the included studies in order to identify any other potentially eligible articles.[24]

The following predefined inclusion criteria needed to be fulfilled for a study to be considered eligible for our meta-analysis: (i) randomized controlled trials (RCTs) or observational cohort studies comparing the incidence of SSIs with use of intrawound vancomycin powder and without use of vancomycin powder or any other product in spinal or cranial surgeries; (ii) studies reporting data on the outcomes of interest; (iii) studies published in the English language. In cases of duplicate studies, we included the most recent publication, unless the outcomes of interest were reported in the earliest version.[24] Our electronic search strategy is provided in the **Table**, **Supplemental Digital Content 1**.

Data Extraction and Critical Appraisal

Two reviewers were responsible for independently extracting the relevant data from the included studies. Any disagreements were resolved by consensus following discussion with a third reviewer (VML).[25,26] Data extraction was based on a pre-decided excel spreadsheet with the following variables: first author, year of publication, country and institution, study design and study period, sample size, follow-up duration, patient baseline demographics (gender, age, diabetes), type and location of the procedure, operative time, length of hospital stay, and dose of vancomycin applied. The primary outcome was incidence of SSI after a spinal or cranial operation. Secondary outcomes consisted of superficial and deep SSIs after spinal operation. As previously published, superficial SSIs were defined as "involvement of skin and subcutaneous tissue only purulent drainage; isolation of organism; deliberate opening of incision when patient has signs of local infection and the wound is culture positive or not cultured; or diagnosis of SSI by the surgeon or attending physician; and infection occurring within 30 days to 1 year." On the contrary, "deep SSIs were defined as abscess, purulent drainage, or a deep incision that spontaneously dehisces or is opened by a surgeon and is culture positive or not culture positive in a patient with fever or localized pain within 90 days to one year of the operative procedure."[32] The data extraction spreadsheet is available as **Supplemental Digital Content 2**.

Two reviewers independently conducted quality scoring for each observational study included in our meta-analysis according to the recommendations of the Meta-analysis Of Observational Studies in Epidemiology group.[27] For randomized studies, quality was appraised using the Cochrane Collaboration's tool for assessing risk.[28] Finally, confidence in estimate of all outcomes was analyzed as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[29]

Statistical Synthesis and Analysis

We summarized categorical outcomes using odds ratios (ORs) with the corresponding 95% confidence intervals (CIs), while the mean difference (MD) was estimated for synthesis of continuous variables. Random effects model was applied wherever the heterogeneity was considered high, which was assessed with the Higgins I-square (I^2). I^2 greater than 50% indicated significant heterogeneity.[30] In cases where continuous data were presented using medians and range, we employed the proposed method by Hozo and colleagues[31] in order to estimate the respective means and standard deviations. Effect sizes and pooled estimates are graphically displayed using forest plots.[24,26] Funnel plots were generated to detect publication bias. Subgroup analyses were conducted for studies that administered 1 g or 2 g or a composite dose of powdered vancomycin. Meta-regression analysis was performed adjusting for the presence of diabetes mellitus as a study-level covariate. The exponentiated coefficient is provided, since the dependent variable in the meta-regression model is the logarithm of the OR. A P value $< .05$ was considered significant. Statistical analysis was conducted using STATA 14.1 (StataCorp, College Station, Texas) and Review Manager 5 (Cochrane Collaboration, Oxford, United Kingdom).

RESULTS

Search Results

Our literature search yielded a total of 3004 unique articles. Following screening of titles and abstracts, 58 articles were underwent full-text evaluation, of which 31 studies met the predefined eligibility criteria and were included in the qualitative and quantitative synthesis (Figure 1).

Characteristics of the Studies and Patients

Thirty of the included studies were observational cohort analyses[7,14,16-18,21,22,32-54] and 1 was an RCT.[13] In total, 18,146 patients were included in this meta-analysis. No heterogeneous concerns in study quality were observed in the included studies; however, none of the studies had the outcome independently assessed **Tables**, **Supplemental Digital Content 3** and **4.** Detailed patient and study characteristics are summarized in Table 1. Patients in the included studies most commonly underwent posterior or anterior fusion with decompression at

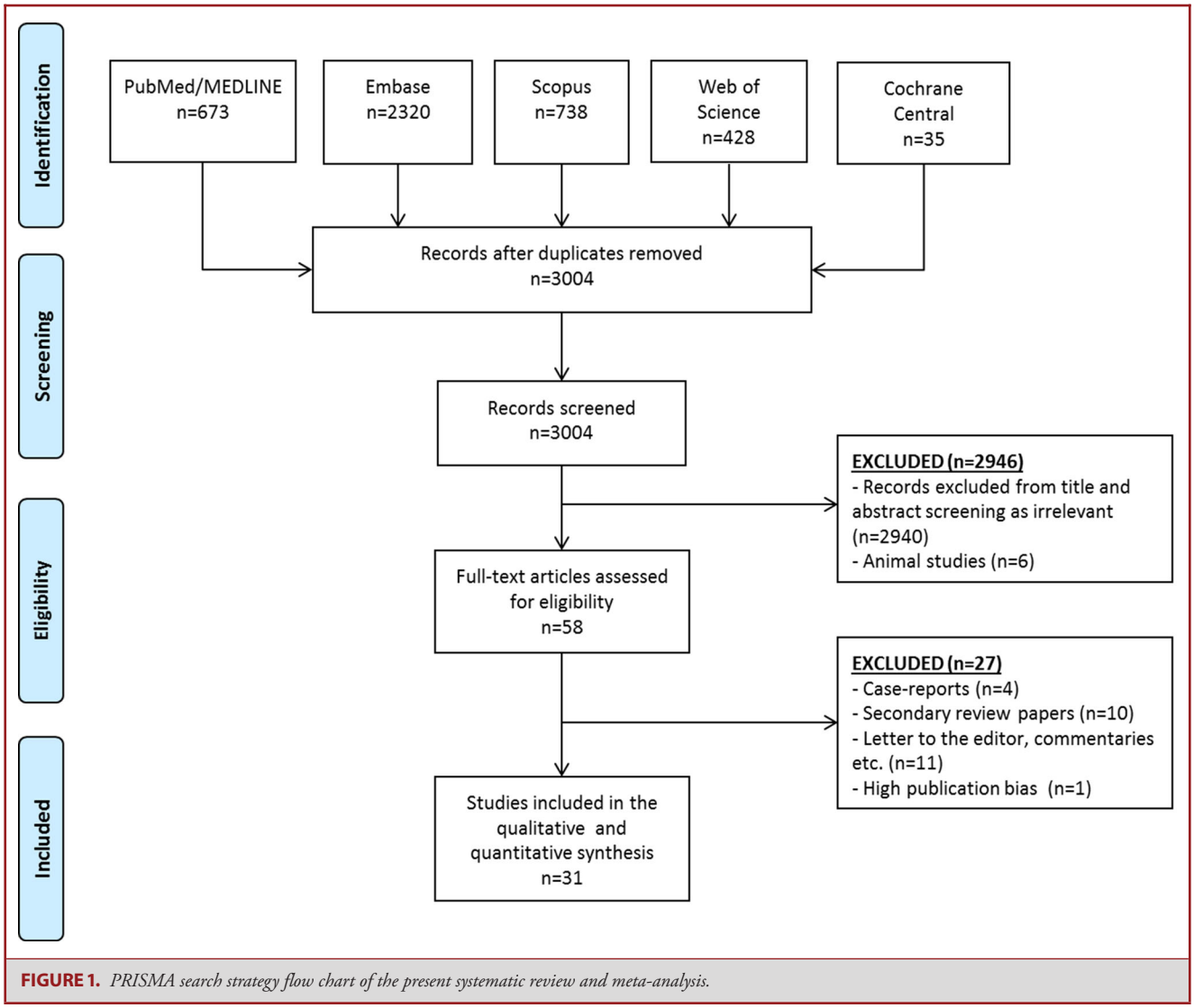

FIGURE 1. *PRISMA search strategy flow chart of the present systematic review and meta-analysis.*

the cervical, thoracic, or lumbar levels. The initial funnel plot demonstrated high risk of publication bias in one study,[55] which was eventually excluded from this meta-analysis (**Figure**, **Supplemental Digital Content 5**); however, this study also created significant heterogeneity in our results possibly because it was the only study on intrathecal pump insertions among the included studies.

Spinal SSIs

SSIs after a spinal surgery occurred in a total of 133 (1.9%) and 410 (4.3%) patients in the vancomycin group (VG) and nonvancomycin group (NVG) respectively, based on 25 studies (Table 1). Patients in the VG group had a significantly lower risk for SSIs overall (OR: 0.41; 95% CI: 0.30-0.57; $P < .001$; $I^2 = 47\%$; Figure 2). Subgroup analyses for vancomycin doses of 1 g, 2 g, and composite vancomycin dose (0.5-2 g) following spinal surgery showed that vancomycin use was associated with significantly less SSIs in the 1 g (OR: 0.37; 95% CI: 0.22-0.62; $P < .001$; $I^2 = 54\%$), 2 g (OR: 0.42; 95% CI: 0.20-0.91; $P = .03$; $I^2 = 57\%$), and composite dose subgroups (OR: 0.40; 95% CI: 0.25-0.65; $P < .001$; $I^2 = 0\%$; Figure 2).

When separate analyses were conducted for superficial and deep SSIs, a significant difference was found only for deep (OR: 0.31; 95% CI: 0.22-0.45; $P < .001$; $I^2 = 29\%$; Figure 3A), while superficial SSIs were similar between the 2 study groups (OR: 0.66; 95% CI: 0.43-1.01; $P = .05$; $I^2 = 0\%$; Figure 3B). The length of operation was similar between the VG and NVG groups following spinal surgery; however, with significant heterogeneity (MD: –1.07 min; 95% CI: –29.87 to 27.72; $P = .94$; $I^2 = 97\%$; **Figure**, **Supplemental Digital Content 6**).

TABLE 1. Summary of Study Design and Patient Demographics Among Spine Studies

SPINE									Overall			Vancomycin group (VG)			No vancomycin group (NVG)		
Study	Country	Design; Institu-tions	Study period	Sur veillance time (mo)	Type of operation (spinal level)	Diabetic ratio (%in VG/%in NVG)	SSI type	VP dose (g)	Cohort (n)	Male (n, %)	Mean age (yr)	Cohort (n, %)	Male (n, %)	Mean age (yr)	Cohort (n, %)	Male (n, %)	Mean age (yr)
Caroom et al[32]	USA	R, OS; 1	2003-2011	>6	Fusion (C)	0.86	NS	1	112	NR	58,6	40, 36%	NR	59.8	72, 64%	NR	56.4
Chotai et al[33]	USA	P, OS; 1	2010-2014	12	Fusion (C, L)	1.16	Deep, superficial	1	2802	1405, 50%	57,8	1215, 43%	NR	NR	1587, 57%	NR	NR
Emohare et al[34]	USA	R, OS; 1	2010-2012	20, mean	Fusion,decompression, discectomy (T,L)	0.35	Deep, superficial	1	303	135, 45%	56,8	96, 32%	42, 44%	53,7	207, 68%	93, 45%	58,2
Gaviola et al[35]	USA	R, OS; 1	2010-2014	NR	Fusion (C,T,L)	1.10	NS	2	326	184, 56%	NR	116, 36%	65, 56%	NR	210, 64%	119, 57%	NR
Ghobrial et al[55]	USA	R, OS; 1	2011-2013	NR	IT baclofen	NR	NS	0.5-1	300	-	NR	26, 8.6%	16, 70%	46.5	274, 91.4%	NR	NR
Godil et al[36]	USA	R, OS; 1	NR	>1	Fusion (C,T,L)	0.61	Deep, superficial	1	110	70, 64%	NR	56, 51%	35, 63%	45	54, 49%	35, 65%	43
Haller et al[37]	USA	R, OS; 1	2002-2015	>6	Rib distraction (T)	NR	NS	NR	1287	735, 57%	6,11	252, 20%	139, 55%	7,12	1035, 80%	596, 58%	7,12
Heller et al[38]	USA	R, OS; 1	2008-2011	>3	Fusion (C,T,L)	1.19	NS	0.5-2	683	323, 47%	52,2	342, 50%	155, 45%	55,3	341, 50%	168, 49%	49,1
Hey et al[17]	Singapore	R, OS; 1	2012-2013	12	Fusion, decom-pression (C,T,L)	0.78	Deep, superficial	1	434	197, 51%	47,1	117, 27%	51, 44%	45	272, 63%	146, 53%	48
Hida et al[53]	Japan	R, OS; 1	2014-2016	>12	NR	0.29	Deep	0.5-1	174	79, 45.4%	NR	81	36, 44%	48.4	93	43, 46%	50.3
Hill et al[39]	USA	R, OS; 1	2010-2012	>1	Fusion, decom-pression, kyphoplasty (C,T,L)	0.43	Deep, superficial	1-2	300	147, 49%	56,1	150, 50%	80, 53%	54,1	150, 50%	67, 45%	58,3
Kim et al[40]	Korea	R, OS; 1	2012	NR	Fusion, (C,T,L)	0.44	Deep, superficial	1	74	39, 52%	NR	34, 46%	21, 62%	57,8	40, 54%	17, 43%	60
Lee et al[41]	Korea	R, OS; 1	2012	9.5, mean	NR, (L)	1.05	NS	1	571	328, 57%	NR	275, 48%	155, 57%	50,2	296, 52%	173, 59%	52,1
Liu et al[42]	USA	R, OS; 1	2011-2014	-	Fusion, osteotomy (C,T,L)	0.71	Deep	0.5-2	334	144, 43%	63,9	180, 54%	78, 43%	65,4	154, 46%	66, 43%	62.2

TABLE 1. Continued

SPINE									Overall			Vancomycin group (VG)			No vancomycin group (NVG)		
Study	Country	Design; Institu-tions	Study period	Sur veillance time (mo)	Type of operation (spinal level)	Diabetic ratio (%in VG/%in NVG)	SSI type	VP dose (g)	Cohort (n)	Male (n, %)	Mean age (yr)	Cohort (n, %)	Male (n, %)	Mean age (yr)	Cohort (n, %)	Male (n, %)	Mean age (yr)
Martin et l[16]	USA	R, OS; 1	2011-2013	1	Fusion, (T,L)	1.28	Deep	2	306	98, 32%	63,1	156, 51%	49, 31%	63,4	150, 49%	49, 33%	62,7
Martin et al[51]	USA	R, OS; 1	2011-2013	1	Fusion, (C)	1.13	Deep	2	289	149, 52%	59,5	115, 40%	58, 50%	62,3	174, 60%	91, 52%	57,6
O'Neill et al[7]	USA	R, OS; 1	NR	7, mean	Fusion, (C,T,L)	0.65	Deep, superficial	1	216	70, 32%	44	54, 25%	35, 65%	43	56, 26%	35, 63%	45
Ross et al[47]	Mexico	R, OS; 1	NR	>12	Fusion, (L)	NR	Deep	1	210	101, 48%	56	70, 33%	NR	NR	140, 67%	NR	NR
Schroeder et al[21]	USA	R, OS; 1	2012-2013	12	Fusion, decom-pression (C,T,L)	NR	Deep	1-1.5	3477	1630, 47%	56,8	1224, 25%	577, 47%	56,3	2253, 65%	1053, 47%	57,1
Strom et al[43]	USA	R, OS; 1	2007-2011	>12	NR, (L)	1.06	NS	1	253	141, 58%	64	156, 62%	89, 57%	60	97, 38%	52, 54%	60
Strom et al[44]	USA	R, OS; 1	2007-2011	>12	Fusion, (C)	0.68	NS	1	171	100, 58%	60	79, 46%	45, 57%	64	92, 54%	55, 60%	64
Suh et al[22]	Korea	R, OS; 1	2006-2012	0.5, mean	Fusion, (L)	NR	NS	2	86	19, 22%	65,1	43, 50%	15, 35%	63,2	43, 50%	4, 9%	67,1
Sweet et al[14]	USA	R, OS; 1	NR	>12	Fusion, (T,L)	NR	Deep	2	1732	892, 52%	56	911, 53%	465, 51%	NR	821, 47%	427, 52%	NR
Theologis et al[42]	USA	R, OS; 1	2008-2012	3	Fusion, osteotomy, V.C. resection (T,L)	NR	Deep	2	215	77, 36%	61,7	151, 70%	48, 32%	62,4	64, 30%	29, 45%	60
Tubaki et al[13]	India	P, RCT; 1	2011-2012	>3	NR, (C,T,L)	1.06	Deep, superficial	1	907	509, 56%	45,5	433, 48%	235, 54%	44,3	474, 52%	274, 58%	46,6
Van Hal et al[18]	USA	R, OS; 1	2010-2013	1	Fusion, dexom-pression, (T,L)	NR	NS	1	1148	NR	NR	496, 43%	NR	NR	652, 57%	NR	NR
			TOTAL						**16475**			**6842**			**9527**		

C: cervical; L: lumbar; NS: not specified; NR: not reported; NVG: nonvancomycin group; OS: observational, R: retrospective; T: thoracic; VG: vancomycin group.

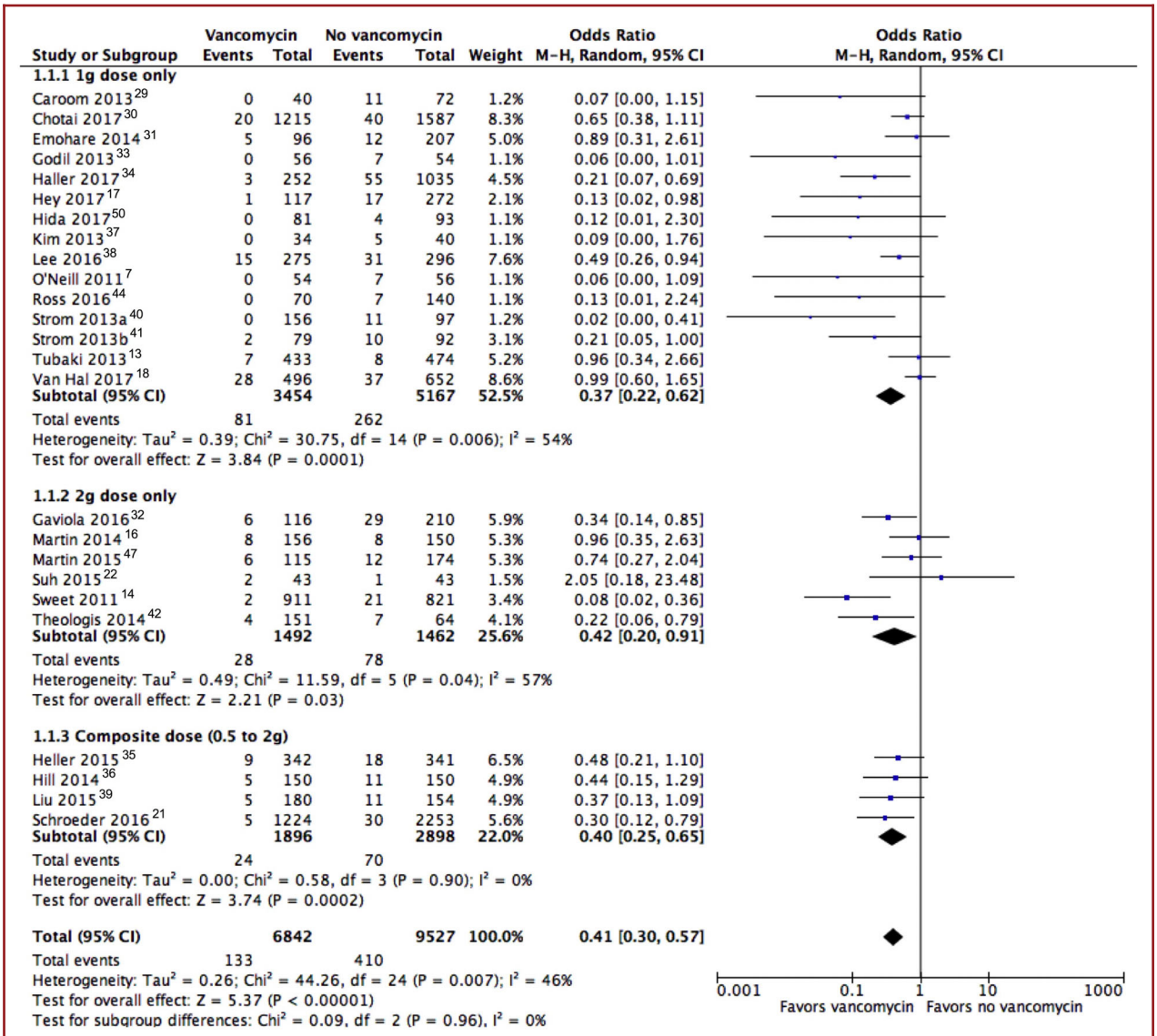

FIGURE 2. *Forest plot comparing SSIs after spinal surgery, subdivided based on vancomycin dosage. SD, standard deviation; CI, confidence interval; M-H, Mantel-Haenszel.*

Meta-regression analysis did not point to any modifying effect of diabetes on SSIs overall (exponentiated coefficient: 1.71; 95% CI: 0.48-6.03; **Figure**, **Supplemental Digital Content 7**).

Cranial SSIs

SSIs after a cranial surgery occurred in a total of 12 (1.4%) and 45 (5%) patients in the VG and NVG respectively, based on 6 studies (Table 2). Patients in the VG had a statistically significant lower risk for a SSI (OR: 0.33; 95% CI: 0.18-0.60; $P = .0003$; $I^2 = 45\%$; Figure 4).

GRADE Assessment of Outcomes

Based on GRADE approach, confidence in estimates was found to be moderate for overall SSI and deep SSI in spine, and low for superficial SSI spine and overall SSI cranial (Table 3).

DISCUSSION

This meta-analysis studied the effect of vancomycin powder on the incidence of SSIs after spinal and cranial surgeries. The main finding of this study is that vancomycin powder use after a spinal and cranial operation provides significant protection against SSIs

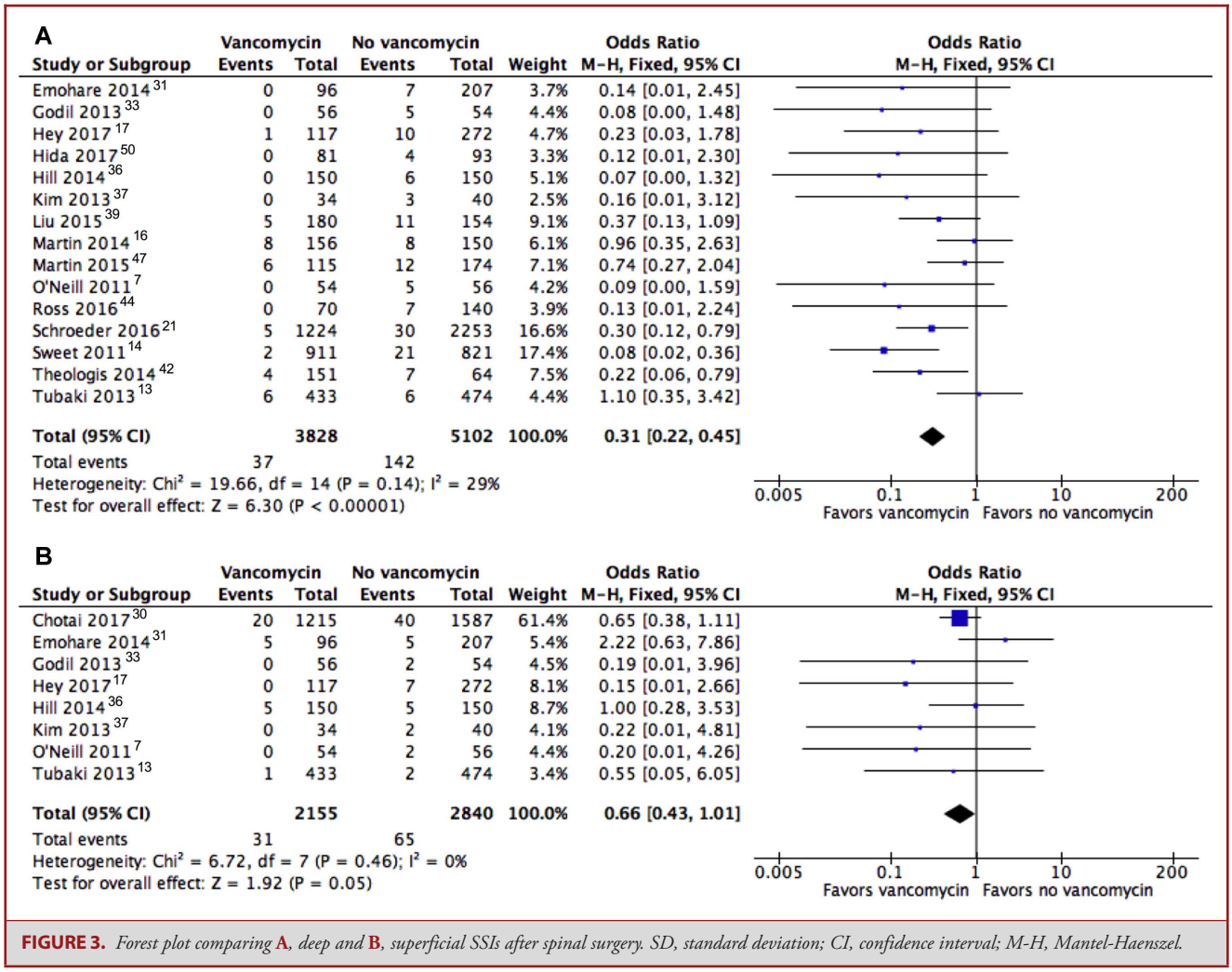

FIGURE 3. *Forest plot comparing* **A**, *deep and* **B**, *superficial SSIs after spinal surgery. SD, standard deviation; CI, confidence interval; M-H, Mantel-Haenszel.*

(OR: 0.41; CI: 0.30-0.57) and (OR: 0.33; CI: 0.18-0.60), respectively. Our results also indicate that vancomycin powder use in spinal operations is protective against deep (OR: 0.31; $P < .001$) but not superficial (OR: 0.66; $P = .05$) SSIs. Finally, this study showed that the preventive effect of vancomycin was sustained across all dosage ranges (1 g: OR = 0.37, $P < .001$; 2 g: OR = 0.42, $P = .03$; composite dose between 0.5 g and 2 g: OR = 0.40, $P < .001$).

Our results regarding overall SSIs and deep incisional SSIs after spinal surgery are in agreement with previous meta-analyses on this topic; however, this meta-analysis included an almost 4-fold patient sample compared to them.[19,56] Deep SSIs were similarly defined across the included studies, involving the subfascial tissues and/or the spinal implant.[33,39] Their treatment involves surgical debridement, intravenous antibiotics, and potentially implant removal.[36,40] The advantage conferred by powdered vancomycin in this context should be appreciated, as deep SSIs are a major cause of extended hospital stays, multiple hospital admissions, and increased morbidity and mortality.[6,7] Even though our pooled results in terms of overall SSI reached statistical significance, a separate analysis on superficial SSIs did not point to a significant protective effect of vancomycin. Superficial SSIs are milder in clinical course than deep SSIs, and are commonly treated with local wound care and broad-spectrum oral antibiotic medication, until swab culture and antibiogram results are generated.[39,40] Importantly, relative contraindications to the use of powdered vancomycin were cerebrospinal fluid leak leak and incidental durotomy in cranial and spinal surgeries, respectively.

A National Surgical Quality Improvement Program (NSQIP) analysis reported that SSIs occurred in 2% of patients.[57] Several types of wound infections can appear after a brain surgery including meningitis, epidural abscess, subdural empyema, brain abscess, and bone flap osteomyelitis.[58] This is the first meta-analysis to investigate the effect of vancomycin powder in cranial surgeries. Our results point to a statistically significant reduction

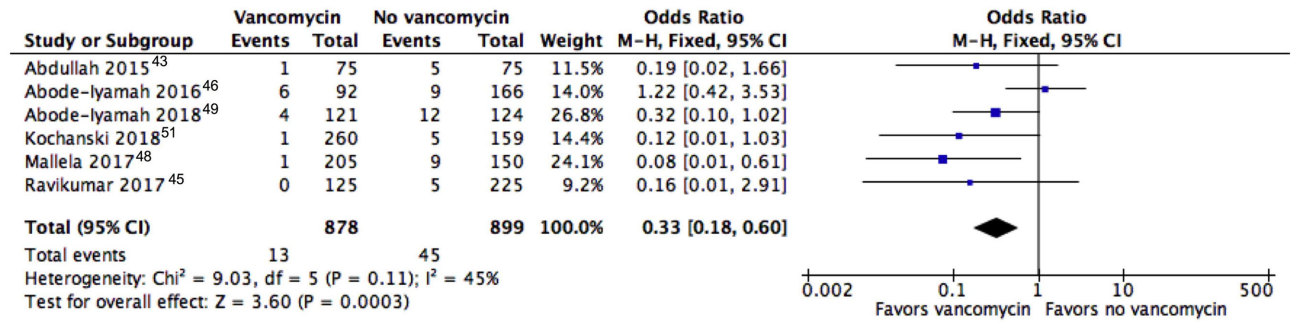

FIGURE 4. *Forest plot comparing SSIs after cranial surgery. SD, standard deviation; CI, confidence interval; M-H, Mantel-Haenszel.*

from 5% to 1.4% in SSIs after cranial surgeries, which is a novel finding not having been previously investigated or described by other meta-analyses. Nevertheless, the reported 4.8% rate in the NVG is relatively high compared to current literature, which can limit the generalizability of this study in terms of cranial SSI outcomes.[57,59]

Other than the decrease in SSIs after spinal operations, several studies have shown the favorable effect of vancomycin in healthcare costs. SSIs are the most common hospital-acquired infections, even surpassing catheter-associated urinary tract infections and central-line infections.[56] The estimated cost to treat a single SSI ranges between $20 000 USD and $100 000.[6,33,36] Specifically, results from the cost-benefit analysis by Godil et al[36] showed that vancomycin powder use led to $433 765 USD savings per 100 posterior spinal fusions. A similar trend was demonstrated by another study which led to $244 402 USD savings per 100 complex spinal surgeries.[45] One of the 3 included studies in cranial surgeries that performed a cost-benefit analysis also showed that use of vancomycin was associated with a reduction in healthcare costs, although to a lesser extent when compared to spinal surgeries.[48]

Several risk factors have been found to be significantly associated with the development of SSI after spinal and cranial surgery. The NSQIP database analysis of 12 021 craniotomies for brain neoplasms demonstrated that age, male gender, prior wound infection, and length of operation were associated with increased risk for SSIs.[57] Lee et al[41] showed on multivariate analysis that diabetes mellitus, length of hospital stay, and the number of spinal instrumented levels were significant predictors of deep SSIs after posterior lumbar surgery. Higher body mass index > 30, smoking, preoperative steroid therapy, posterior spinal fusion, poor nutritional status (preoperative albumin < 3.5 mg/dL), postoperative radiation, and duration of surgery > 3 h are well-established risk factors for SSI after spinal surgery.[60-63] Unfortunately, patient-level data for the above variables were unavailable in the included studies and consequently sensitivity analyses could not be conducted. However, we were able to extract data on the prevalence of diabetes and duration of operation among patients in the 2 study groups. We then proceeded to a meta-regression analysis to adjust for differences in the prevalence of diabetes among the VG and NVG, measured at a study level. Our results did not indicate any influence of study-level variability of the ratio of diabetic: nondiabetic patients on the association between vancomycin powder and risk of SSIs (exponentiated coefficient: 1.71; 95% CI: 0.48-6.03). The mean difference of the length of operation was insignificant between the 2 groups (MD: –1.07 min; $P = .94$), thus further isolating the protective effect of vancomycin powder against SSIs from the risk of prolonged operative exposure; however, these results are limited by the significant amount of heterogeneity.

It is also worth mentioning that several studies have investigated the effect of local vancomycin on human cells. Eder at al[64] showed that 3 mg/cm^2 of local vancomycin applied on a human osteoblast culture were enough to significantly inhibit cellular migration and growth, whereas 6 mg/cm^2 induced cellular death. Furthermore, another experimental in vitro study demonstrated that local vancomycin inhibits proliferation of human dural fibroblasts and even cause cellular necrosis in a dose-dependent manner.[65] Therefore, it is likely that powdered vancomycin can delay the normal healing process, especially when a durotomy (intentional or unintentional) is involved in the surgery.[13,65] Further in vivo studies are needed in order to define a safe bactericidal dose of intrawound vancomycin that will not affect normal dural healing. Furthermore, randomized studies specifically designed not only for the general population, but also for high risk for SSI populations, are needed in order to provide insights on the optimal use of powder vancomycin in neurosurgery. It is promising to note that there is 1 biinstitutional RCT (NCT02284126; clinicaltrials.gov) currently recruiting patients to either a 2 g topical vancomycin arm vs a nonvancomycin standard of care arm in both spinal and cranial operations. The study is anticipated to be completed by October 2019.

There exists a number of potential confounders that compose the clinical heterogeneity facing the current literature with respect to this topic. Intersurgeon differences may influence

TABLE 2. Summary of Study Design and Patient Demographics Among Cranial Studies

Cranial									Overall			Vancomycin group (VG)			No vancomycin group (NVG)		
Study	Country	Design; Institutions	Study period	Surveillance time (mo)	Type of operation	Diabetic ratio	SSI type	VP Dose (g)	Cohort (n)	Male (n, %)	Mean age (yr)	Cohort (n, %)	Male (n, %)	Mean age (yr)	Cohort (n, %)	Male (n, %)	Mean age (yr)
Abdullah et al[46]	USA	R, OS; 1	2011-2013	3	Craniotomy, craniectomy	1.8	NS	1	150	78, 52%	65,8	75, 50%	38, 51%	49,4	75, 50%	37, 49%	52,1
Abode-lyamah et al[52]	USA	R, OS; 1	2005-2015	12	DBS	-	NS	0.2-0.25	245	162, 66.1%	62.9	121	NR	NR	124	NR	NR
Abode-lyamah et al[49]	USA	R, OS; 1	2008-2014	3	Craniotomy, craniectomy	1.8	NS	0.5-2	258	159, 62%	48,8	92, 36%	59, 64%	49,3	166, 64%	100, 60%	48,5
Kochanski et al[54]	USA	R, OS; 1	2015-2017	6	DBS	0.47	NS	1	419	245, 58%	NR	260, 62%	145, 56%	60,7	159, 38%	100, 63%	65,1
Mallela et al[51]	USA	R, OS; 1	2013-2015	4	DBS	0.73	NS	1	355	190, 53.5%	NR	205, 58.8%	109, 53%	52.4	150, 42.2%	81 54%	54.5
Ravikumar et al[48]	USA	R, OS; 1	2011-2015	3	Craniotomy, craniectomy	1.57	NS	1	350	196, 56%	54,1	125, 36%	63, 50%	51,7	225, 64%	133, 59%	55,5
			Total						**1777**			**878**			**899**		

NS: not specified; NR: not reported; NVG: nonvancomycin group; OS: observational, R: retrospective; T: thoracic; VG: vancomycin group.

TABLE 3. Grading of Recommendations Assessment, Development and Evaluation (GRADE) Assessment of Quality of Evidence

Outcome	No. of studies	No. of patients	RoB	Inconsistency	Indirectness	Imprecision	Estimate of effect (95% CI)	Confidence in effect estimates (GRADE)
Overall SSI - spine	25	16,369	Serious	Not serious	Not serious	Not serious	0.41 (0.30-0.57)	Moderate
Deep SSI - spine	15	8930	Serious	Not serious	Not serious	Not serious	0.31 (0.22-0.45)	Moderate
Superficial SSI - spine	8	4995	Serious	Not serious	Not serious	Serious	0.66 (0.43-1.01)	Low
Overall SSI - cranial	6	1777	Serious	Not serious	Not serious	Not Serious	0.33 (0.18-0.60)	Moderate

RoB: risk of bias; SSI: surgical site infection.

inherent practice tendencies which may predispose patients to greater infection risk. Additionally, specific type of neurosurgical intervention and associated adjuncts may affect exposure risk, eg, additional implants or inserts requiring thorough sterilization in instrumented spine surgery. Selection bias in reporting studies would be best overcome by increasing cohort size and stratification by operation technique. Research is poised to investigate the effect on infection risk of operation duration and presentation of comorbidities such as diabetes, which was analyzed for in this study, and chronic steroid-managed conditions. Future studies should attempt to implement transparent control measures of the aforementioned factors in order to further augment the confidence of vancomycin's role in neurosurgery.

Limitations

Our meta-analysis has limitations as well. First, our meta-analysis is limited by the observational design in 30 out of 31 included studies. In those studies, vancomycin powder could be associated with other clinical characteristics that may have affected the incidence of SSIs, for example, the indication for surgery and preoperative health status. To try and minimize interference of these, a random-effects model was utilized in outcomes with high I^2 values. Although we were only able to propose that diabetes did not likely influence our pooled results by performing a meta-regression analysis, without having patient-level data, other possible confounders were unavailable to be investigated for effect on these results. Second, our meta-analysis relied on study-level and not patient-level data. Third, we did not have sufficient information to account for potential differences in outcomes related to individual surgeons or centers, and the potential selection bias in patient and operation choice and approach. Fourth, follow-up intervals were variable between the included studies, which make robust conclusions difficult to describe at this current point in time. Finally, this study did not show a dose–response relation which poses limitations in the causal inference of our results.

CONCLUSION

This study demonstrated that there is likely an important role for vancomycin powder in spine and brain surgery in the prevention of SSIs. The conferred infection protection is most demonstrable following spinal surgery, particularly against deep SSIs, and is not influenced by the medical history of diabetes. Dose regimens of vancomycin from 0.5 g to 2 g did not seem to affect the pooled OR estimate. Also, vancomycin use in cranial surgery significantly decreased the risk for SSIs. More prospective, larger, randomized, longer follow-up studies are required to corroborate the findings of this meta-analysis.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplemental Digital Content 1. Table. Electronic search strategy.
Supplemental Digital Content 2. Data extraction spreadsheet.
Supplemental Digital Content 3. Table. MOOSE assessment for all included studies. The MOOSE criteria are 1. Clear definition of study population? 2. Clear definition of outcomes and outcome assessment? 3. Independent assessment of outcome parameters? 4. Sufficient duration of follow-up? 5. No selective loss during follow-up? 6.Important confounders and prognostic factors identified?
Supplemental Digital Content 4. Table. Quality assessment of included randomized controlled trial. The criteria used were 1. Random sequence generation 2. Allocation concealment 3. Blinding of participants and personnel 4. Blinding of outcome assessment 5. Incomplete outcome data 6. Selective reporting 7 Other bias. These can be answered Yes (Y), No (N) or Unclear (U).
Supplemental Digital Content 5. Figure. Funnel plots for all included studies examining SSI incidence in **A,** spinal and **B,** cranial surgery. The study at OR = 10 in Figure 1A was excluded from the meta-analysis due to its location and potential publication bias.
Supplemental Digital Content 6. Figure. Forest plot comparing operative time between groups that received vancomycin and those that did not.
Supplemental Digital Content 7. Figure. Bubble plot of diabetic ratio (DR) of each study against the OR of each study measuring the likelihood powdered vancomycin will prevent SSI when compared to no vancomycin. DR was defined as ratio of cohort with: without diabetes. Exponentiated coefficient: 1.71; 95% CI: 0.48-6.03. OR, odds ratio; SSI, surgical site infection.