The Spine Journal 19 (2019) 1076–1084

Review Article

Selection pressures of vancomycin powder use in spine surgery: a meta-analysis

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Received 9 October 2018; revised 14 January 2019; accepted 14 January 2019

Abstract

BACKGROUND CONTEXT: Surgical site infection (SSI) is a serious and costly complication of spine surgery. Many surgeons apply vancomycin powder to the surgical wound to prevent SSIs. While multiple studies have reported reduced rates of SSI, others have suggested that widespread use of intrawound vancomycin may increase the incidence of vancomycin-resistant, gram-negative, or polymicrobial spinal infections.

PURPOSE: To systematically review the current literature on vancomycin powder in spine surgery and its impact on SSI culture profiles.

STUDY DESIGN: Meta-analysis.

SAMPLE: We included observational studies, retrospective chart reviews, and randomized controlled trials of patients who underwent spine surgeries with and without vancomycin powder application to surgical wounds and reported SSI rates.

OUTCOME MEASURES: The primary outcome was postoperative SSIs. Subgroup analyses compared rates of postoperative SSIs.

METHODS: We performed a comprehensive search of numerous electronic databases and conference proceedings pertaining to this topic. Our meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Inclusion criteria consisted of spine surgeries with or without use of vancomycin powder, case-control design, sample sizes of at least 10 in each arm, SSIs identified with bacterial cultures, and follow-up of at least 1 month. Data extracted from eligible studies included, but was not limited to, SSI rates, cultured organisms, and vancomycin powder dose. Chi-square analyses were used to assess pooled risk-estimates of intrawound vancomycin powder on reducing SSIs and selecting for gram-negative and/or polymicrobial organisms compared to controls. Pooled odds ratios, relative risks, and relative risk increase for observed outcomes were calculated. A meta-analysis was then performed with a forest plot to determine risk estimates' heterogeneity with I^2 index, Q-statistic, and p value under a fixed-effects model. Funnel plot was used to assess publication bias. None of the authors received funding or other support for this review.

RESULTS: After reviewing nearly 400 titles and abstracts, 28 articles met inclusion criteria. They included two randomized controlled trials, one observational study, and 25 retrospective analyses. There were 412 cases of SSI (3.8%) in the control group (N=10,846) compared to 197 SSIs (2.3%) in the vancomycin powder group (N=8,456). The pooled odds ratio was 0.60 (95% confidence intervalCI 0.51–0.71, p<.05). The rate of gram-positive SSI was significantly higher in the control group compared to the vancomycin group (70% vs. 45.1%, p<.05). The rate of gram-negative and polymicrobial SSI was significantly higher in the vancomycin group (35.8% vs. 18.5%, p<.05). The risk of developing a gram-negative or polymicrobial SSI was nearly twice (93.5% higher) in

FDA Device/Drug Note: Not applicable.

Author disclosures:***AG:*** Nothing to disclose; ***AR:*** Nothing to disclose; ***TC:*** Royalties: Spineart (B). Consulting: Spineart (B). Speaking/Teaching Arrangements: Spineart (B). Trips/Travel (B). ***NB:*** Royalties: Alphatec (B), Biomet (C), Stryker (C), Seaspine (C), Seaspine (F). Consulting: Difusion (B), Spineart (D), Seaspine (B). ***YPL:*** Consulting: Depuy (C).

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https://doi.org/10.1016/j.spinee.2019.01.002

the vancomycin group. Study heterogeneity and synthesizing mostly retrospective data were primary limitations.

CONCLUSIONS: Widespread use of prophylactic intrawound vancomycin may increase the incidence of gram-negative and polymicrobial SSIs. Vancomycin powder should likely be restricted to procedures and patients most at risk for infection.

Keywords: Spine surgery; Surgical site infection; SSI; Selection; Vancomycin powder

Introduction

Surgical site infections (SSI) are the second most common health care-associated infections in the United States. Klevens et al. estimated that 290,485 SSIs occurred in the United States in 2002 and that 8,205 of these infections resulted in death [1]. SSIs have a profound impact on patients and often necessitate reoperation for irrigation and debridement of the wound. Some studies estimate that non-methicillin-resistant *S. aureus* (MRSA) SSIs extend patients' length of hospital stay by 11.2 days (at an increased cost of $20,785 per patient) and MRSA SSIs extend patients' length of hospital stay by 23.0 days at an increased cost of $42,300 per patient [2].

The most common organisms cultured in SSIs after spine surgery is gram-positive bacteria such as *Staphylococcus aureus (S. aureus), Staphylococcus epidermidis,* and *Enterococcus* [3–6]. Of 7,000 spine SSIs reported to the National Healthcare Safety Network (NHSN) from 2006 to 2008, *S. aureus* caused 30% of all SSIs, 51% of SSIs following neurological procedures, and 49% of SSIs following orthopedic procedures [7]. Therefore, the current recommendation for perioperative prophylaxis in spinal surgery is a first or second generation cephalosporin (or clindamycin for patients with beta-lactam hypersensitivity) [8].

In addition to intravenous antibiotics and thorough skin preparation, several retrospective studies suggest that intrawound vancomycin powder reduces rates of infection following spinal surgery [9–16]. Although conflicting reports exist, a recent meta-analysis of 10 studies found that patients undergoing spine surgery without vancomycin powder were *three* times more likely to develop an SSI [10]. The number needed to treat was 36 patients to prevent one SSI [17]. While multiple studies have reported a protective benefit, others have suggested that widespread use of intrawound vancomycin may increase the incidence of vancomycin-resistant, gram-negative, or polymicrobial spinal infections [18–20]. The purpose of this meta-analysis is to investigate the use of vancomycin powder in spine surgery and a potential selection pressure for gram-negative and/or polymicrobial species in SSIs. To our knowledge, no previous meta-analysis has been published on vancomycin powder use in spine surgery and its association with gram-negative and polymicrobial SSIs. Our specific objectives were to compare rates of SSI, gram-positive infection, and gram-negative and/or polymicrobial infection in patients treated with and without vancomycin powder during spine surgery.

Methods

Search strategy

The present meta-analysis was conducted following Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. A protocol was developed for this review but was not registered. A thorough literature search was performed using PubMed, Cochrane Database of Systematic Reviews, Web of Science, ClinicalTrials.gov, EMBASE databases, and conference abstracts from American Academy of Orthopedic Surgeons and the Scoliosis Research Society annual meetings up to April 2018. A flowchart of our search strategy is found in Fig. 1. Two coauthors (AG & AR) independently searched, evaluated, and collected search results. They were not blinded to the journals, organizations, or author information. The following query or Medical Subject Headings (MeSH) terms included but were not limited to "vancomycin," "powder," "spine," "intrawound," "infection," "antibiotic prophylaxis," and "topical." A comprehensive search was performed within the databases as well as the citation sections of review papers and meta-analyses pertaining to this topic. Outside experts were not consulted for the identification of additional studies. The titles and abstracts were assessed independently for relevant articles. Any study that potentially met the inclusion criteria was retrieved and reviewed. Disagreement between the coauthors was resolved through discussion and consensus. None of the authors received funding or support for this review.

We included retrospective cohort studies, observational studies, and randomized controlled trials of humans that involved vancomycin powder application to spine surgical wounds for postoperative prophylaxis. The inclusion criteria were as follows: (1) spine surgeries with or without intraoperative use of vancomycin powder, (2) comparison groups without vancomycin powder application, (3) sample sizes of at least 10 in each arm of a corresponding study, (4) SSIs identified with bacterial cultures, (5) reported SSI rates, and (6) follow-up for at least 1 month. Only articles in English and those using human subjects were considered. Exclusion criteria for the data collection were as follows: (1) sample sizes in each arm of a study less than 10, (2) reviews, meta-analyses, abstracts or case reports, (3) no positive cultures for all SSIs in the control or experimental cohorts, and (4) follow-up shorter than 1 month as an SSI can be defined as infections that occur within 1 year if an

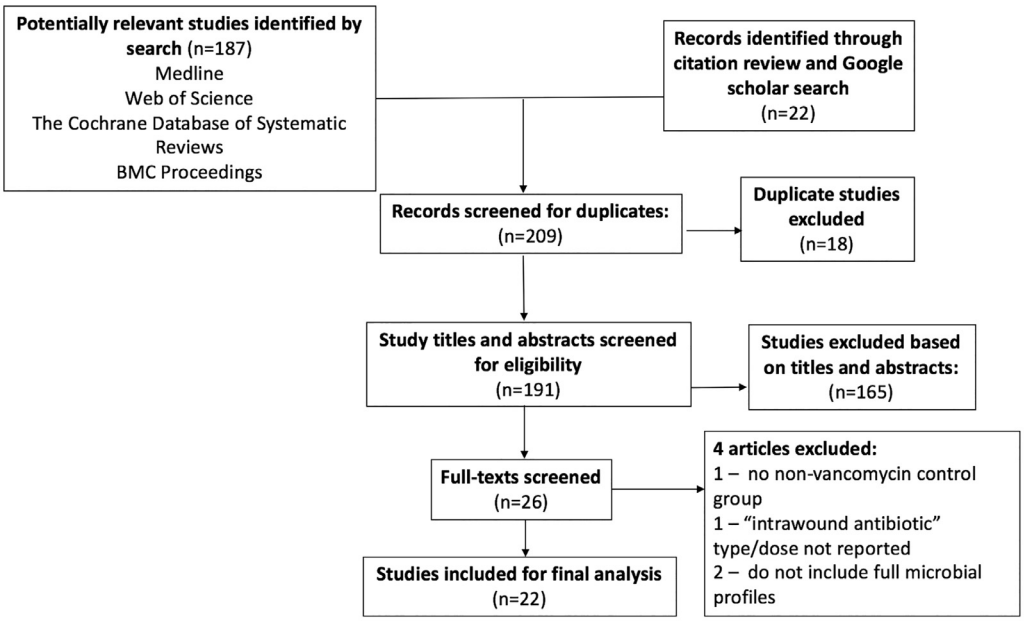

Fig. 1. Flowchart of article search strategy.

implant is placed or within 30 days after surgery with no implant.

Data extraction and outcome measures

The following variables were collected in a standardized Excel form: author list, publication years, sample sizes, sample characteristics, vancomycin powder doses, perioperative IV antibiotics, follow-up duration, SSI demographics, cultured organisms, and nature of SSIs (superficial vs. deep). Exposure of interest was the application of vancomycin powder to the surgical wound in spine surgeries. The primary outcomes were the number of gram-positive, gram-negative, and polymicrobial SSIs (superficial or deep incisional) reported in the vancomycin and control groups. The secondary outcome of interest was differences in gram-negative and/or polymicrobial SSIs between the two groups. The accuracy of the data extraction was confirmed independently by the coauthors (AG and AR).

Data syntheses

Descriptive statistics of the control versus experimental groups were combined and obtained using Microsoft Excel 2017 (Microsoft Inc, Seattle, USA). Given the nonparametric nature of the data, chi-quare χ^2 statistics were performed between the two arms of pooled data to identify any significant differences in observed and expected frequencies of gram-negative and/or polymicrobial SSIs with the use of intraoperative vancomycin powder. We chose a priori to perform analyses to identify differences in SSI rates between controls and vancomycin powder groups, as well as a subgroup analysis to determine selection of gram-negative and/or polymicrobial SSIs between the two groups. Pearson's chi-square, relative risk (RR), odds ratios, 95% confidence intervals (CI), and two-tailed p values were compiled. $p<.05$ was the standard of significance.

Heterogeneity and publication bias

We assessed these outcome variables' heterogeneity using the Q statistic, I^2 index, and p value under a fixed-effects model on a forest plot. We used the Cochrane Database's Review Manager software to generate forest and funnel plots. A p value for the Q-statistic less than 0.1 suggests that significant heterogeneity exists in the data. Additionally, the I^2 (range: 0%−100%) value establishes a quantitative degree of variation among the included studies. The risk of publication (reporting) bias was evaluated at a study level using a funnel plot. No additional prespecified or ad hoc analyses were performed. The coauthors, AG and AR, performed a study-level independent risk of bias assessment using the modified Downs and Black Quality Assessment checklist [21] (Table 5).

Results

Our initial literature search yielded nearly 400 articles pertaining to vancomycin powder use in spine surgery (Fig. 1). After excluding irrelevant, incomplete, and duplicate studies, only 28 articles met the inclusion criteria for our study. They included two randomized controlled trials (7.2%), one observational study (3.6%), and 25 retrospective papers (89.4%) (Table 1).

The median postoperative follow-up among studies that reported it (82%) was 4.5 months (range 1−34 months). Standard perioperative IV antibiotics were administered in all studies but reported only in 86% (N=24) (Table 2). Ancef was used in 79% (N=19) of the studies and other cephalosporins were used in 21% (N=5). The median dose of vancomycin

Table 1
Articles that met inclusion criteria of evaluating vancomycin powder use in preventing postoperative SSIs

First author (year)	Study design	Level of evidence	Size	Follow-up time	Definition of outcome
Caroom (2013)	Retrospective cohort	III	112	≥6 months	SSI rate
Chotai (2017)	Prospective web-based registry	II	2,802	≥12 months	SSI requiring return to OR within postoperative 90 days
Gaviola (2016)	Retrospective cohort	III	326	≥3 months	SSI by CDC definition
Ghobrial (2014)	Retrospective cohort	III	2,568	Not described	SSI requiring return-to-surgery
Godil (2013)	Retrospective cohort	III	110	Median 25 weeks	SSI determined by visual wound inspection and MRI
Heller (2013)	Retrospective cohort	III	683	≥3 months	SSI within 90 days requiring additional operation + positive wound cultures
Hey (2017)	Retrospective cohort	III	389	≥12 months	SSI rate
Hill (2014)	Retrospective cohort	III	300	≥1 month	SSI requiring operative irrigation and debridement (deep) or local wound care and antibiotics (superficial)
Kim (2013)	Retrospective cohort	III	74	Not described	SSI rate
Lee (2016)	Retrospective cohort	III	571	Mean 8 months	SSI within 12 weeks requiring additional operation (irrigation, debridement) and positive wound culture
Liu (2015)	Retrospective cohort	III	324	≥3 months	SSI requiring reoperation, irrigation, debridement
Martin (2014)	Retrospective cohort	III	306	≥1 month	SSI by CDC definition
Martin (2014)	Retrospective cohort	III	289	≥1 month	SSI by CDC definition
O'Neill (2011)	Retrospective cohort	III	110	Median 25 weeks	Incidence of SSI by axial imaging (deep) or wound inspection (superficial)
Schroeder (2016)	Retrospective cohort	III	3,477	≥12 months	SSI requiring reoperation, irrigation, debridement
Strom (2013)	Retrospective cohort	III	171	≥12 months	SSI rate and pseudarthrosis
Strom (2013)	Retrospective cohort	III	253	≥12 months	SSI rate and pseudarthrosis
Sweet (2011)	Retrospective cohort	III	1,732	Average 2.5 years, range 1−7 years	SSI rate
Theologis (2014)	Retrospective cohort	III	215	Mean 34 months (control) and 18 months (vancomycin)	SSI requiring revision surgery within 90 days
Tomov (2015)	Retrospective cohort	III	2,425	Not described	SSI requiring reoperation, irrigation, debridement
Tubaki (2013)	Prospective RCT	II	907	Mean 12.2 months (control) and 12.5 months (vancomycin)	SSI rate
Van Hal (2017)	Retrospective cohort	III	1,148	Not described	SSI defined by blood or surgical site cultures or clinical evidence

RCT, randomized controlled trial; OR, odds ratio; SSI, surgical site infections; CDC, centers for disease control and prevention.

Table 2
Summary of pertinent clinical data from all included studies

First author (year)	Perioperative IV antibiotics	Intrawound vancomycin dose (g)	SSI rate – control group	SSI rate – vancomycin group	Most common causes of SSI in Vancomycin group
Caroom (2013)	Cefazolin	1	15.28%	0.00%	N/A
Hey (2017)	Cefazolin	1	6.25%	0.85%	Pseudomonas
Chotai (2017)	Cefazolin	1	2.52%	1.65%	*S. aureus*, Gram negative rods
Gaviola (2016)	Cefazolin	2	10.95%	5.17%	MSSA, *E. coli*, Proteus
Ghobrial (2014)	Cefazolin	1.13 mean	3.59%	6.73%	MSSA, Coagulase negative staphylococci, MRSA, *E. coli*, Klebsiella, Proteus
Godil (2013)	Cefazolin	1	12.96%	0.00%	N/A
Heller (2013)	Cefazolin	0.5-2.0	5.28%	2.63%	*S. aureus, S. epidermidis*
Hill (2014)	Cefazolin	1	7.33%	3.33%	Not described
Kim (2013)	Cefazolin	11	12.50%	0.00%	N/A
Lee (2016)	Cefotetan	1	10.47%	5.45%	MSSA, non-staphylococcal
Liu (2015)	Cefazolin	0.5-2	7.14%	2.78%	Coagulase negative staphylococci, *S. aureus*, Enterobacter, Citrobacter
Martin (2014)	Cefazolin	2	5.33%	5.13%	Coagulase negative staphylococci, *S. marcescens*
Martin (2014)	Cefazolin	2	6.90%	5.22%	MSSA, Enterobacter, Coagulase negative Staphylococci, propionibacterium, diphtheroids
O'Neill (2011)	Cefazolin	1	12.96%	0.00%	N/A
Schroeder (2016)	Cefazolin	1-1.5	1.33%	0.41%	Propionibacterium, *E. coli*, MRSA, MSSA
Strom (2013)	Cefazolin	1	10.87%	2.53%	MRSA, Gram negative rods
Strom (2013)	Cefazolin	1	11.34%	0.00%	N/A
Sweet (2011)	Cephalexin	2	2.56%	0.22%	Clostridium septicum, *E. coli*
Theologis (2014)	Not described	2	10.94%	2.65%	MRSA, Corynebacteria, Citrobacter, *E. coli*
Tomov (2015)	Not described	1	2.40%	1.28%	MRSA, mixed flora
Tubaki (2013)	Cefuroxime	1	1.69%	1.62%	*S. aureus*, Klebsiella, Gram negative rods
Van Hal (2017)	Not described	1	5.67%	3.23%	MSSA, MRSA

powder used in the experimental group was 1 gram (range 0.5–2 g). Gram-positive organisms were the most numerous in the study, with methicillin-sensitive *S. aureus* (MSSA), coagulase-negative *Staphylococcus,* and MRSA comprising the most common organisms across all patients (Table 3).

There were 412 cases of SSIs (3.8%) in the control group (N=10,846) compared to 197 SSIs (2.3%) in the experimental group (N=8,456) (Table 4). Supplementing operative wounds with vancomycin powder produced an absolute risk reduction of 1.5% and a RR reduction of 39.5%. Overall odds ratio was 0.60 (95% CI 0.51–0.71, p<.05), RR was 0.62 (95% CI 0.53–0.74, p<.05) and the number needed to treat was 67 patients. These findings indicate that the risk of SSIs is 1.6 times more likely in the control group and that vancomycin powder may have prevented 1 infection in every 67 patients.

Chi-square analyses revealed a significant difference in SSI rates between the control and experimental groups (χ^2: 19.7, p<.05). As expected, the rate of gram-positive SSIs was significantly higher in the control group (N=306, 70%, χ^2: 39, p<.05) compared to the experimental group (N=107, 45.1%).

Of note, there was a significant selection for polymicrobial and gram-negative flora in the experimental group (N=81, 35.8%, χ^2: 24.3, p<.05) compared to the control group, (N=85, 18.5%) (Table 4). The absolute risk increase was 17.3% and the RR increase was 93.5%. The pooled vancomycin powder group had a RR of 1.93 (95% CI 1.49–2.51, p<.05) and the number needed to harm was 6 patients. Therefore, the risk of developing a gram-negative or polymicrobial infection was 93.5% higher in the experimental group compared to the control group. Excluding culture negative profiles from both groups did not affect the analyses conducted in the study.

Significant heterogeneity was present across all studies (Q statistic=74.60, p<.01, I^2=72%) (Fig. 2). The funnel plot found evidence of publication bias favoring the use of vancomycin powder in reducing overall SSI rates compared to controls (Fig. 3). Individual study quality and risk of bias are reported in Table 5. Higher scores on the modified

Table 3
Summary of SSIs by culture profiles

Group	Gram positive	Gram negative	Polymicrobial	Not reported/no growth
Control (N=437)	306 (70%)	40 (9%)	41 (9%)	50 (11%)
Experimental (N=237)	107 (45%)	62 (26%)	23 (10%)	45 (19%)
Total	413	102	64	96

Table 4
Summary of SSIs by organisms

		Control, N: 437	Experimental, N: 237	*p<.05
Gram positive		N=306	N=107	†p<.05
	Staphylococcus aureus	28 (9.1%)	4 (3.7%)	
	Coagulase negative staph (CONS)	55 (17.9%)	24 (22.4%)	
	MSSA	125 (40.8%)	48 (44.9%)	
	MRSA	75 (24.5%)	19 (17.8%)	
	Enterococcus	14 (4.5%)	3 (2.8%)	
	Corynebacterium	2 (0.6%)	0	
	Bacillus cereus	1 (0.3%)	0	
	Propionibacterium acnes	4 (1.3%)	3 (2.8%)	
	Peptostreptococcus	2 (0.6%)	0	
	Clostridium species	0	2 (1.9%)	
	Streptococcus species	0	1 (0.9%)	
	Diphtheroids	0	1 (0.9%)	
Gram negative		N=40	N=62	‡p<.05
	Gram negative rods	10 (25.0%)	8 (12.8%)	
	Escherichia coli	8 (20.0%)	16 (25.8%)	
	Proteus mirabilis	4 (10.0%)	10 (16.1%)	
	Pseudomonas aeruginosa	8 (20.0%)	5 (8.1%)	
	Acinetobacter	1 (2.5%)	0	
	Klebsiella pneumoniae	3 (7.5%)	11 (17.7%)	
	Morganella morganii	3 (7.5%)	0	
	Serratia marcescens	3 (7.5%)	3 (4.8%)	
	Enterobacter species	0	4 (6.4%)	
	Bacteroides fragilis	0	2 (3.2%)	
	Citrobacter species	0	3 (4.8%)	
Polymicrobial		41	23	
Not reported		50	45	

MSSA, methicillin-sensitive *S. aureus*; MRSA, methicillin resistant *S. aureus*.
*Significant difference in SSIs, control > experimental group.
†Significant difference in gram positive SSIs, control > experimental group.
‡Significant difference in gram negative/polymicrobial SSIs, experimental > control group.

Downs and Black scale reflect better study quality with lower bias. Scores ranged from 14.5 to 20, showing low to moderate quality secondary to confounding bias and lack of internal validity in each study.

Discussion

Vancomycin powder application to surgical wounds is widely used to minimize SSI rates following spine surgery, which range from 0.7% to 12.0% [22–26]. Although there has been conflicting evidence regarding the effectiveness of vancomycin powder in reducing infections, recent studies have demonstrated its ability to lower SSIs while also raising concern for potential selection of more virulent organisms with widespread use [19,27]. As such, we reviewed all appropriate studies from the literature in this systematic review. Our analysis revealed that the routine use of vancomycin powder in spine surgical wounds may select for gram-negative and polymicrobial SSIs compared to cephalosporin perioperative prophylaxis alone (p<.05). Patients with vancomycin powder application had nearly twice (RR=1.93) the risk of developing a polymicrobial or gram-negative SSI compared to controls.

Evidence of gram-negative and polymicrobial selection

Ghobrial et al. presented a single-institution experience of more than 900 consecutive cases in which vancomycin powder was routinely applied during surgical closure. Among the 66 (6.7%) patients who developed postoperative SSI, the most common organism among positive wound cultures was *S. aureus* [18]. There were more than 30 gram-negative SSIs (60%) in the vancomycin powder group versus 12 cases (21%) in a historical control group. In addition, they reported a trend toward higher ‘incidence of polymicrobial infections (19%) in the vancomycin cohort versus the historical control (15%, p value=.96). This study highlights the potential for more virulent superinfections with gram-negative and polymicrobial flora secondary to organism resistance in the context of widespread vancomycin powder usage.

A prospective cohort study by Chotai et al. in 2017 reported single-center data comparing intrawound vancomycin administration (N=1215) and standard perioperative antibiotics alone (N=1,587). Vancomycin powder use lowered SSI rates from 2.5% to 1.6%, (p value=.02). Similar to findings in our study, there was a significantly lower rate of *S. aureus* SSIs in the treatment group (32% vs. 65%,

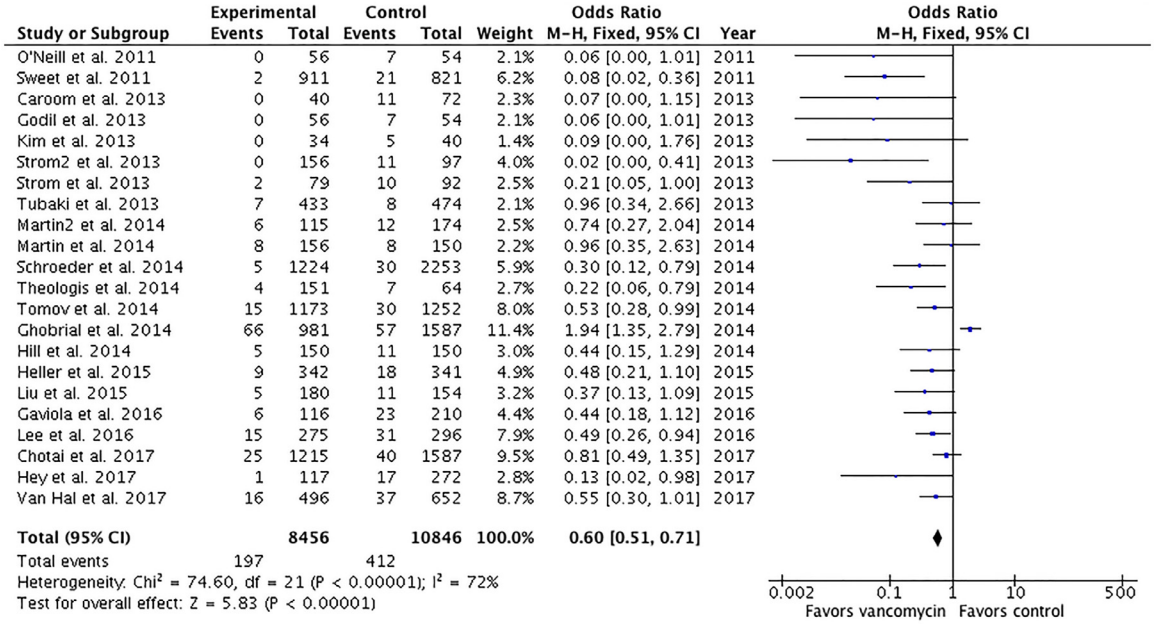

Fig. 2. Forest plot of fixed effects model of the comparison between vancomycin powder application versus controls in their association with SSIs. CI, confidence interval; M-H, Mantel-Haenszel.

p value = .003) [27]. Although no vancomycin-resistant *S. aureus* SSIs were observed, there was a higher incidence of gram-negative SSIs (28%, N=7 vs. 13%, N=5) in the treatment group. Culture profiles were markedly different (p value=.003) in the vancomycin cohort, which included a greater proportion of *Escherichia coli, pseudomonas, Citrobacter, Klebsiella*, and *Serratia* organisms. Furthermore, more patients with gram-negative SSIs (27%) required chronic suppressive antibiotic therapy versus those with gram-positive SSIs (12%). This finding underscores the potential adverse implications of gram-negative SSIs in the setting of routine vancomycin powder prophylaxis.

Several studies have identified patient and operative risk factors for SSI, including advanced age, increased body mass index, diabetes, smoking, alcohol abuse, longer operation times, and anterior and/or posterior spinal fusion [3,28]. An analysis of data reported to the NHSN from 2006 to 2008 found that the mean SSI rate was 0.7% for spinal fusions and 0.7%–2.3% for laminectomies depending on the NHSN risk class [29]. Despite the low rates of SSIs associated with most spinal surgeries, there is room for improvement given the high healthcare expenditures and morbidity associated with revision surgeries [30]. One such estimate of cost-savings

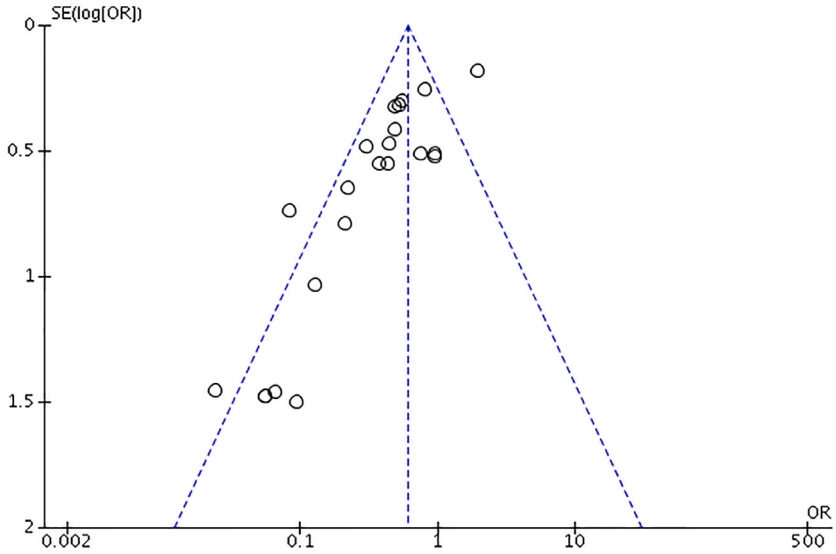

Fig. 3. Funnel plot of the association between estimated effect size of each study and standard error. OR, odds ratio; SE, standard error.

Table 5
Modified Downs and Black scale for assessment of study quality *(max values)*

Author (year)	Reporting (11)	External validity (3)	Internal validity: bias (7)	Internal validity: confounding(6)	Power (1)	Total quality score (28)
Caroom (2013)	8.5	2.5	3	2	1	17
Chotai (2017)	8	2	5	2	0	17
Gaviola (2016)	8	2	5	1	0	16
Ghobrial (2014)	9	2	5	1	0	17
Godil (2013)	8.5	2	5	2	0	17.5
Heller (2013)	9.5	3	5	2	1	20.5
Hey (2017)	9.5	2	5	2	0	18.5
Hill (2014)	10	2.5	4	1	0	17.5
Kim (2013)	9	2	4.5	1	0	16.5
Lee (2016)	9	2	4.5	1	0	16.5
Liu (2015)	10	2	4	1	0	17
Martin (2014)	7	2	5	1	1	16
Martin (2014)	9	2	5	1	0	17
O'Neill (2011)	9	2	4	2	1	18
Schroeder (2016)	7	2.5	4	1	0	14.5
Strom (2013)	10	2	5	2	0	19
Strom (2013)	9	2	4.5	1	0	16.5
Sweet (2011)	9.5	3	5	2	1	20.5
Theologis (2014)	9	2	4	1	0	16
Tomov (2015)	8.5	2	3.5	2	0	16
Tubaki (2013)	8.5	3	6	3	0	20.5
Van Hal (2017)	7	1	3	1	0	12

associated with vancomycin powder prophylaxis is $438,165 (per 100 patients) [12].

However, with increasing use of vancomycin powder there is a concern for generalized microbial selection pressure not only in the experimental cohort but also in controls. Hey et al. compared the SSI profiles of their vancomycin powder (N=117) and control groups (N=272). Out of 19 SSIs —18 in the control group and 1 in experimental group— there was a predominance of gram-negative organisms (*Klebsiella, P. aeruginosa*) in the control group [31]. The authors attributed this unexpected finding to microbial evolution with routine vancomycin powder use in spine surgery. Perhaps with more prospective trials [32] on routine vancomycin powder use, we can formulate antibiotic stewardship algorithms and restrict its use to patients who need it the most. Ultimately, more gram-negative and polymicrobial SSIs may necessitate additional antibiotic usage, more complex treatment regimens, and longer lengths of stay.

Limitations, bias, and future research

The limitations of our study are inherent to the structure of meta-analyses or systematic reviews. Assumptions regarding the consistency of data collection, evaluation, and presentation are integral to such investigations. Study heterogeneity can significantly impact the analysis as papers with larger cohorts will influence the overall statistical outcomes to a greater degree than smaller studies. Most of the studies included in this meta-analysis are retrospective, which are often influenced by selection bias, lack of randomization, inconsistent quality in data reporting and/or collection, and inadequate control of confounding factors [33–35]. The 22 studies in our meta-analysis had low to moderate quality, which was related primarily to lack of internal validity and failure to account for potential confounding effects. Only two (9%) studies acknowledged and adjusted for potential confounders affecting SSI rates between the control and experimental groups. Only six (27%) studies recruited the subjects or collected data simultaneously between the two groups, whereas the majority (73%) opted to use historical controls that do not account for temporal variations in antibiotic stewardship, hospital bacterial ecology, intraoperative and perioperative infection prevention protocols and refinements in operative technique. There was also significant heterogeneity and publication bias as seen in the forest and funnel plots, respectively.

Furthermore, our study may also exhibit the "file-drawer" effect of not including all relevant studies in the scientific literature. Lastly, culture negative SSIs were reported frequently in the literature. Potential etiologies of culture negative profiles are myriad in nature, ranging from occult infections to local inflammatory cascades causing fat necrosis [27]. The role of vancomycin powder in triggering these events remains unclear. Future studies would benefit from a randomized, blinded design that is adequately powered for robust statistical analyses, account and adjust for confounding factors, use consistent definitions of SSIs, standardize doses used in spinal wounds and document all local or systemic adverse effects of vancomycin powder.

Conclusions

Our findings have important clinical implications on perioperative antibiotic prophylaxis in modern day spine surgery.

Pending results of more random intrawound vancomycin should likely be restricted to procedures and patients most at risk for infection. If routine vancomycin powder use is perpetuated, additive antibiotics may be required to cover gram-negative and polymicrobial SSIs.

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