Review Article
The value of topical vancomycin powder prophylaxis in spinal surgical site infection with a focus on bacterial spectrum: a systematic review

Yu He[1*], Qifeng Liu[1,2*], Yan Wang[3*], Yu Zhao[1]

[1]Department of Orthopaedics, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [2]Department of Orthopaedics, Shanxi Changping Coal Limited Liability Company Wang Tai Hospital, Jincheng, Shanxi, China; [3]Department of Medical Laboratory Diagnosis Center, Jinan Central Hospital, Jinan, Shandong, China. *Equal contributors.

Abstract: Introduction: Surgical site infections (SSIs), associated with high morbidity and mortality, are potentially devastating complications in spine surgery. Topical vancomycin powder (TVP) prophylaxis is a promising option to reduce the number of SSIs. The aim of this study is to determine whether the existing data support the routine use of TVP in spine surgery, with a focus on the spectrum of bacteria. Materials and Methods: A systematic literature search was conducted through Ovid Medline and PubMed as of May 2017. Eligible data were extracted to evaluate the outcomes of SSIs and bacterial spectrum. Statistical analysis was performed to determine differences. Results: Twenty-three studies were included in the review. A significant difference was found between the patients treated with additional TVP and those treated with sole intravenous administration of antibiotics ($P < 0.001$). MRSA infections were found in 6 patients with TVP (50.0%) and in 45 without TVP (56.3%, $P = 0.685$). The incidence of Gram-negative infections was 43.1% in patients with TVP prophylaxis, significantly higher than with standard prophylaxis (22.2%, $P = 0.003$). Conclusions: TVP is a viable recommended option because it decreases the overall incidence of SSIs in spine surgery, although no conclusions can be drawn as to whether TVP affects the incidence of Gram-negative infections and reduces the MRSA infection rate, owing to the limited amount of high-quality literature. Therefore, further research with unified standards and long-term follow-up are required to evaluate this issue.

Keywords: Vancomycin, powder, topical application, spine, surgery, surgical site infection, prophylaxis, spectrum of bacteria, MRSA, adverse events

Introduction

Postoperative surgical site infections (SSIs) are among the most common acute complications and occur in up to 30% of patients undergoing spine surgery [1-3]. Several studies have demonstrated significant morbidity with SSIs after spinal procedures [4-6]. Multiple reoperations, instrumentation removal, long-term antibiotic therapy, prolonged hospital stays, incremental hospital complications, and poor patient outcomes have been reported exhaustively [7-9]. The substantial problem created by morbidity and mortality associated with SSIs creates an economic burden for the American health-care system costing from 1 to 10 billion dollars annually [10].

The use of perioperative prophylactic antibiotics in spine surgery is a well-accepted practice for the prevention of SSIs. First-generation cephalosporins and clindamycin have been preferentially used because of their high activity against Gram-positive organisms, particularly *Staphylococcus aureus*, which is the most common cause of SSIs [9]. However, local ischemia, hematoma, and seroma of surgical sites impair the intravenous delivery of antibiotics, leading to inadequate local concentrations [11]. Moreover, increasing resistance to common antibiotic medications has led to ineffective prophylaxis against methicillin-resistant *Staphylococcus aureus* (MRSA), which has undergone a significant increase in frequency and is notoriously difficult to treat [12-14].

Table 1. The characteristics of included studies

Authors	Years	Country	Study design	LOE	COI Statement	Funding	TVPIA prophylaxis			IA prophylaxis			Follow-up
							Sample size	Gender (F/M)	Age (years old)	Sample size	Gender (F/M)	Age (years old)	
Dennis et al. [16]	2016	Singapore	Retrospective	3	Yes	No	117	73/44	45	272	219/53	48	1 year
Gaviola et al. [17]	2016	United States	Retrospective	3	No	No	116	51/65	62	210	91/119	55	NR
Lee et al. [22]	2016	Korea	Retrospective	3	Yes	NR	275	147/128	40.7% > 60 yr	296	152/144	42.9% > 60 yr	> 8 months
Schroeder et al. [18]	2016	United States	Retrospective	3	Yes	No	1224	647/577	56.3	2253	1200/1053	57.1	12 months
Liu et al. [23]	2015	United States	Retrospective	3	Yes	No	180	102/78	61.8	154	88/66	60.4	3 months postoperatively
Devin et al. [24]	2015	United States	Retrospective	3	Yes	No	966	489/477	60.5	1090	553/537	59.5	30-day postoperatively
Heller et al. [25]	2015	United States	Retrospective	3	Yes	Yes (Academic funds)	342	187/155	55.3	341	173/168	49.1	> 90-day postoperatively
Martin et al. [26]	2015	United States	Retrospective	3	Yes	No	115	57/58	62.3	174	83/91	57.6	NR
Hill et al. [27]	2014	United States	Retrospective	3	Yes	No	150	70/80	54.14	150	83/67	58.33	Mean 9.4 months
Theologis et al. [28]	2014	United States	Retrospective	3	Yes	No	151	103/48	62.4	64	35/29	60	Mean 26 months
Martin et al. [29]	2014	United States	Retrospective	3	Yes	No	156	107/49	63.4	150	101/49	62.7	NR
Caroom et al. [30]	2013	United States	Retrospective	3	Yes	Yes (Industrial funds)	40	NR	59.8	72	NR	56.4	Mean 18 months
Kim et al. [31]	2013	Korea	Retrospective	3	No	NR	34	13/21	57.88	40	23/17	60.05	NR
Tubaki et al. [20]	2013	India	Prospective RCT	2	Yes	Yes (Academic funds)	433	198/235	44.1	474	200/274	46.7	Mean 12.4 months
Pahys et al. [32]	2013	United States	Retrospective	3	Yes	No	195	70/125	57.1	483	213/270	53.6	> 3 months
Strom et al. [33]	2013	United States	Retrospective	3	Yes	No	79	34/45	60	92	37/55	60	Mean 3.4 years
Strom et al. [34]	2013	United States	Retrospective	3	Yes	No	156	67/89	64	97	45/52	64	Mean 3.2 years
Sweet et al. [35]	2011	United States	Retrospective	3	Yes	No	911	465/446	56	821	394/427	53	Mean 2.5 years
O'Neill et al. [36]	2011	United States	Retrospective	3	Yes	No	56	21/35	43	54	19/35	45	Mean 28.5 weeks
Murphy et al. [21]	2016	Ireland	Prospective	4	Yes	NR	52	20/32	53.2	-	-	-	2 years
Okafor et al. [37]	2016	United States	Retrospective	4	Yes	NR	35	11/24	61.4	-	-	-	NR
Ghobrial et al. [38]	2014	United States	Retrospective	4	Yes	No	981	487/494	59.4	-	-	-	NR
Molinari et al. [39]	2011	United States	Retrospective	4	Yes	No	1512	NR	NR	-	-	-	NR

COI, Conflict of Interest; IA, Intravenous administration of antibiotics; LOE, Level of evidence; NR, Not reported; TVPIA, Combined application of topical vancomycin powder and intravenous administration of antibiotics.

The application of topical vancomycin powder (TVP) seems to be a promising option [15, 16]. This method has been investigated in cardiothoracic, orthopedic, and vascular surgery with achievement of protective benefit [16]. In spine surgery, several studies demonstrated that combined application of TVP and IA (TVPIA) prophylaxis reduced postoperative SSIs in comparison with IA prophylaxis alone [17-19]. However, two questions remain unanswered: (1) Does additional TVP reduce the incidence of MRSA infections? (2) Does additional TVP change the incidence of Gram-negative infections? The aim of this literature review is to determine whether the existing data support the utilization of intra-wound vancomycin powder in routine spine surgery, with a focus on the spectrum of bacteria.

Materials and methods

The guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses were followed in conducting this systematic review [20].

Data sources

Electronic searches were conducted on Ovid Medline and PubMed using a combination of the following search terms: "vancomycin powder", "topical application", "spine surgery", "surgical site infection", and their synonyms. Both prospective and retrospective studies that described TVP administration for adult patients before May 2017 were included. There were no restrictions related to surgical indication, type of spine surgery, dose of vancomycin powder, definition of infection, and demographic data of patients. Non-English articles, abstracts from conferences, and unpublished articles were excluded. Studies with unclear reporting of methods or results were also excluded.

Two reviewers with methodological and content expertise independently screened all titles and abstracts for eligibility. After abstract screening, studies meeting the eligibility criteria underwent a full-text review. References from the articles were reviewed to identify additional studies of interest. All discrepancies were resolved by consensus through a process that required reviewers to discuss the rationale for their decisions. Reviewers were blinded to author names, journal names, and year of publication.

Data extraction and evaluation

Data from included studies were extracted by two reviewers independently and verified by the third reviewer. The data extracted from each article included study design, levels of evidence, conflict of interest statement, source of funding, sample size, gender, mean age, follow-up, surgical type, use of instrumentation, location and dose of vancomycin powder, infection outcomes, pathogens, adverse events, definition of infection, and antibiotic regimens.

Contrastive research that compared TVPIA prophylaxis in spine surgery against standard practice with regard to the outcome of infections and the bacterial spectrum was eligible for inclusion. Non-comparative studies were additionally included to determine the definition of infection, incidence of SSI, adverse events, and antibiotic regimens. General SSI rate, MRSA infections, and Gram-negative/-positive bacterial spectrum were the key points for evaluation.

Assessment of study quality

Study quality was graded using the systematic quality assessment described by the Oxford Centre for Evidence Based Medicine guidelines. Two authors of the present study independently graded the quality of each study. Disagreements among any of the above data were resolved through discussion among all authors.

Statistical analysis

Statistical analysis was performed by determination of descriptive statistics, and differences between the groups were calculated using categorical variables and the chi-squared test. A P value of less than 0.05 was considered statistically significant.

Results

Study characteristics

Twenty-three articles (2 prospective studies [21, 22] and 21 retrospective studies [17-19, 23-40]) met the inclusion criteria (**Table 1**). Nineteen studies were compared research.

Table 2. Definition of infection and antibiotic regimens

Authors	Infection criteria			Antibiotic Regimens		
	General	Superficial	Deep	Preoperative	Intraoperative	Postoperative
Dennis et al. [16]	CDC criteria			1 g cefazolin IV	NR	Continued for 48 hours
Gaviola et al. [17]	CDC criteria			2 g cefazolin IV	Redosed every 3 hours	NR
Lee et al. [22]	Infection occurring within 12 weeks following the operation, requiring an additional operation (i.e., an irrigation and debridement) and having positive wound cultures.	Occurring above the lumbosacral fascia	Beneath the lumbosacral fascia	2 g cefotetan IV	Redosed every 4 hours	2 g cefotetan IV every 12 hours for 5 days
Schroeder et al. [18]	NR	NR	NR	1 or 2 g cefazolin IV	NR	24 h regimen
Liu et al. [23]	NR	NR	NR	Cefazolin or clindamycin	NR	Subsequent doses every 8 hours for a day
Devin et al. [24]	Visual wound inspection and contrast-enhanced MRI	NR	NR	2 g cefazolin IV	NR	1 g cefotetan IV every 8 hours for 1 days
Heller et al. [25]	Infections occurring within 90 days following the operation, requiring an additional operation (i.e. an irrigation and debridement) and having positive wound cultures.	Occurring above the lumbosacral fascia	Beneath the lumbosacral fascia	20 mg/kg body weight of Ancef IV	Redosed every 4 hours	1 g Ancef IV every 8 hours for 24 hours
Martin et al. [26]	Defined as being diagnosed during the initial hospitalization or during a hospital readmission or postoperative clinic appointment within 30 days of the surgery.	NR	NR	Cefazolin IV	NR	Cefazolin IV every 8 hours for 1 day
Hill et al. [27]	NR	Involving superficial skin or subcutaneous tissue	Involving subfascial tissue, requiring irrigation, surgical debridement plus oral antibiotics, or intravenous antibiotic administration, depending on the infectious disease recommendation.	1-2 g Cefazolin IV	NR	24-hour period
Theologis et al. [28]	Requiring revision surgery within 90 days.	NR	NR	Intravenous antibiotics	NR	NR
Martin et al. [29]	Defined as being diagnosed during the initial hospitalization or during a hospital readmission or postoperative clinic appointment within 30 days of the surgery.	NR	NR	Cefazolin IV	NR	Cefazolin IV every 8 hours for 1 day
Caroom et al. [30]	NR	NR	NR	Cefazolin, clindamycin, or vancomycin IV	NR	Until 24 hours after the drain was removed on postoperative day 2
Kim et al. [31]	NR	Confirmed by the results of swab culture of surgical wound discharge	Confirmed by culture results of the drainage line tip.	1 g cefazolin IV	NR	1 g cefazolin IV every 8 hours for 1 day
Tubaki et al. [20]	NR	NR	NR	750 mg cefuroxime IV	NR	750 mg cefuroxime IV every 8 hours for 1 day for noninstrumented; 750 mg cefuroxime IV every 8 hours until drain removal for instrumented
Pahys et al. [32]	Postoperative acute wound infections (involving the suprafascial and/or subfascial space) were defined as infections requiring a formal irrigation and debridement in the operating room.	NR	NR	Cephalosporins IV	NR	24-hour period

Vancomycin powder prophylaxis in spinal SSIs

Strom et al. [33]	NR	NR	NR	Cefazolin or vancomycin IV	NR	Continued while the drains were in place
Strom et al. [34]	NR	NR	NR	Cefazolin IV	NR	continued while the drains were in place
Sweet et al. [35]	Clinical examination and constitutional symptoms	Involved the superficial skin or subcutaneous tissues	Involving the subfascial layers and the spinal instrumentation	2 g cefazolin IV	NR	Continued for 24 hours
O'Neill et al. [36]	NR	Identified by wound inspection	Identified with axial imaging if necessary	1 g cefazolin IV	NR	1 g cefazolin IV every 8 hours for 1 day
Murphy et al. [21]	NR	NR	NR	1.5 g cefuroxime IV	NR	1.5 g cefuroxime IV for 24 h
Okafor et al. [37]	NR	NR	NR	Intravenous cephalosporin/900 mg of intravenous clindamycin	NR	At least 24 h
Ghobrial et al. [38]	At the discretion of the attending surgeon	NR	NR	1 g cefazolin IV	NR	Cephalosporin given two more doses every 8 hours
Molinari et al. [39]	NR	NR	Surgical database, patient medical records, and clinical evidence were searched to identify evidence.	1 g cefazolin IV	NR	NR

CDC, Centers for disease control and prevention; IV, Intravenous; NR, Not reported.

One Level II, 18 Level III, and 4 Level IV studies were included. Three studies reported funding from industrial or academic establishment.

The total sample size was 15,563. The number of patients in observational studies ranged from 35 to 3,477, and the minimum follow-up reported was 30 days. The sole randomized controlled trial (RCT) had a sample size of 907 and a mean follow-up of 12.4 months [21]. Another prospective study had a sample size of 52 and a mean follow-up of 2 years [22].

All studies covered spine surgery with varying surgical indications, such as degenerative, deformity, neoplastic, traumatic, and other pathologies. Operative sites were diverse, ranging from occipitocervical to iliolumbar fusion through anterior, posterior, and lateral approaches. Twelve studies reported that all patients underwent instrumented spine surgery, while the other 10 reported partial instrumentation.

Definition of infection

The reports included were complicated by the inconsistent definitions of SSI. The most common definitions adhered to the Centers for Disease Control and Prevention National Healthcare Safety Network definition of SSI [41] or similar definition. Superficial SSI was defined as infection occurring within 30 days postoperatively; involvement of skin and subcutaneous tissue only; purulent drainage; isolation of organism; deliberate opening of the incision when the 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. Deep SSI was defined as a patient with fever or localized pain within 90 days of the operation; involvement of an abscess, purulent drainage or a deep incision that spontaneously dehisces or is opened by a surgeon; and culture positive or not cultured.

Other SSI definitions included "visual wound inspection and contrast-enhanced magnetic resonance imaging [25]", "infections requiring a formal irrigation and debridement in operating room [33]", "clinical examination and constitutional symptoms [36]", and "at the discretion of the attending surgeon [39]". The details of SSI definitions are given in **Table 2**.

Antibiotic regimens

Many kinds of antibiotics were administered, such as cefotetan, cefazolin, cefuroxime, clindamycin, and vancomycin, at different doses (**Table 2**). Preoperative antibiotic regimens were relatively consistent in that patients received an intravenous dose within 60 minutes prior to surgical incision. Intraoperative antibiotics were readministered every 3 or 4 hours. There was some ambiguity in the reporting of postoperative regimens, for example, "24 h regimen [19, 24-28, 30-33, 36]", "continued for 48 hours [17]", "every 12 hours for 5 days [23]", and "continued while the drains were in place [31, 34, 35]".

Topical vancomycin

The descriptions of dosing and location of TVP were variable (**Table 3**). The most common dose was 1 g (ranging from 0.25 to 6.0 g). In their detailed description of intraoperative application, most authors stated that TVP was directly applied on the muscle, fascia, and subcutaneous tissues; others reported that placement was solely on the subfascial space. The powder was applied so that "the bone graft or dura mater was not exposed" for most surgeons. By contrast, Gaviola et al. described that when powder was applied "no specific effort is made to keep it off exposed neural elements or vessels [18]". In four studies the bony element was exposed to vancomycin powder [18, 24, 31, 36]. Sweet et al. even described that approximately 1 g of vancomycin powder was mixed with the bone grafting material and that an additional 1 g of vancomycin power was applied directly into the wound [36]. Gaviola et al. [18], Liu et al. [24], and Caroom et al. [31] reported that powder was exposed to implants, whereas Strom et al. described a contrasting method of application [34, 35].

Surgical site infections

In 19 contrastive studies, 96 infections were identified among the 5,696 patients who received TVP (1.69%), compared with 318 among the 7,287 patients who did not (4.36%). A significant difference was found between the patients treated with TVPIA and with IA prophylaxis (chi-squared = 74.300; P < 0.001; **Table 3**).

Table 3. Clinical details of included studies

Authors	Surgery type	Instrumented	Topical Vancomycin Powder		TVPIA prophylaxis		IA prophylaxis		Adverse Events	Conclusions
			Location	Dose	Infection Rate (%)	Pathogens	Infection Rate (%)	Pathogens		
Dennis et al. [16]	Spine surgery	Partly	NR	1 g	0.9	*Pseudomonas aeruginosa*	6.3	MRSA, *Coagulase-negative Staphylococcus, Bacillus cereus, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae*	No	Recommend
Gaviola et al. [17]	Multilevel Spinal Fusion	All	Soft tissues, implants, and bony elements. No specific effort is made to keep it off exposed neural elements or vessels.	2 g	5.2	MSSA, *Coagulase-negative Staphylococcus sp, Enterococcus sp, Clostridium sp, MRSA, Escherichia coli, Proteus sp, Bacteroides fragilis*	11	MSSA, *Coagulase-negative Staphylococcus sp, Peptostreptococcus sp, Enterococcus sp, Propionibacterium sp, Corynebacterium sp, Escherichia coli, Proteus sp, Morganella sp, Pseudomonas sp*	No	Recommend
Lee et al. [22]	Posterior lumbar surgeries	Partly	NR	NR	5.5	Staphylococcal, MRSA, Nonstaphylococcal	10.5	Staphylococcal; MRSA; Non-staphylococcal	No	Recommend
Schroeder et al. [18]	Degenerative spine surgery	Partly	Covering all the layers of the wound	1-1.5 g	0.4	*P. acnes, E. coli, MRSA*	1.3	MSSA, MRSA, *Staphylococcus coagulase negative, Propionibacterium acnes, Escherichia coli,* gram negative infections	NR	Recommend
Liu et al. [23]	Posterior instrumented spine surgeries	All	Evenly sprayed on the muscle, fascia, implants, and grafted bone in the surgical site before wound closure	1 g (0.5-2)	2.8	*Staphylococcus aureus, Coagulase-negative staphylococcus, Enterobacter cloacae, Citrobacter koseri*	7.1	*Staphylococcus aureus, Proteus mirabilis, MRSA, Enterococcus, MRSA, Coagulase-negative staphylococcus, Staphylococcus lugdunensis*	No	Recommend for nontumor spine patients
Devin et al. [24]	Posterior spine degenerative surgery	Partly	Placed directly on the muscle, fascia, and subcutaneous tissues taking care not to expose bone graft or dura mater.	1 g per 10 cm wound length	2.2	NR	5.1	NR	NR	Recommend
Heller et al. [25]	Posterior instrumented spinal arthrodesis	All	Applied directly to the wound	0.5-2 g	2.6	NR	8.8	NR	No	Recommend
Martin et al. [26]	Posterior cervical fusion surgery	All	Directly on the deep wound and subfascial muscle tissues, taking care not to expose bone graft or dura.	2 g	5.2	MSSA, *Enterobacter cloacae, Morganella morganii, Pseudomonas aeruginosa, Coagulase-negative staphylococci, Diphtheroids, Coagulase-negative staphylococci, Propionibacterium*	6.9	*Coagulase-negative staphylococci, MSSA, Proteus mirabilis, Propionibacterium, Serratia marcescens, Escherichia coli, S.marcescens, Peptostreptococcus*	NR	Not recommended
Hill et al. [27]	Posterior spinal surgery	Partly	NR	1-2 g	3.3	NR	7.4	MRSA, *Enterococcus*	No	Relative recommended
Theologis et al. [28]	Complex adult deformity reconstruction	NR	Placed solely in the subfascial space; none was placed subcutaneously.	2 g	2.6	MRSA; *Corynebacterium jeikeium; Citrobacter freundii; Escherichia coli*	10.9	MRSA; MSSA; *Corynebacterium afermentans var Lipophilicum; Staphylococcus epidermidis; Pseudomonas mirabilis; Proteus mirabilis, Enterobacter cloacae, Escherichia coli*	No	Recommend

Vancomycin powder prophylaxis in spinal SSIs

Study	Surgery	IA	Application	Dose	Rate	Organisms	Rate	Organisms		Recommendation
Martin et al. [29]	Thoracolumbar and lumbar spine fusion for deformity cases	All	Placed directly on the muscle, fascia, and subcutaneous tissues taking care not to expose bone graft or dura.	2 g	5.1	*Coag-neg Staph, E. cloacae, MSSA, S. marcescens, MRSA, K. pneumoniae, C. freundii*	5.3	MSSA, *Coag-neg Staph,* MRSA, *E. aerogenes, P. mirabilis, Enterococcus, P. aeruginosa*	NR	Not recommended
Caroom et al. [30]	Posterior cervical fusion	All	Applied to the wound subfascially along the bone graft and instrumentation	1 g	0	-	15	MRSA, MRCNS	No	Recommend
Kim et al. [31]	Instrumented spinal fusion	All	Directly applied on the muscle, fascia, and subcutaneous tissues after ensuring that the bone graft or dura mater was not exposed.	1 g	0	-	12.5	MRCNS, *Acinetobacter baumannii,* MSSA	No	Recommend
Tubaki et al. [20]	Spine surgery	Partly	Placed directly on the muscle, fascia, and Subcutaneous tissues taking care not to expose bone graft or dura.	1 g	1.61	*Staph aureus and Klebsiella*	1.68	*Escherichia coli, Staph aureus*	No	Not recommended
Pahys et al. [32]	Posterior cervical spine operations	Partly	NR	500 mg	0	-	1.86	MRSA	No	Recommend
Strom et al. [33]	Posterior cervical fusion	All	Muscle, fascia, and subcutaneous tissue	1 g	2.5	MRSA, Gram-negative rod	10.9	MSSA, MRSA, *coagulase-negative staphylococci,* Gram-negative rods	No	Recommend
Strom et al. [34]	Lumbar laminectomy and posterior fusion	Partly	Sprinkled onto the muscle, fascia, and sub-cutaneous tissue just prior to closure; it was not applied to theninstrumentation or bone graft	1 g	0	-	11	MSSA, MRSA, *coagulase-negative staphylococci,* Gram-negative rods	No	Recommend
Sweet et al. [35]	Instrumented thoracolumbar fusions	All	Approximately 1 g of vancomycin powder was mixed in with the bone grafting materialThe remaining 1 g of vancomycin powder was sprinkled evenly in the deep and superficial portions of the wound.	1 + 1 g	0.2	*Clostridium septicum;Escherichia coli*	2.6	*Staphylococcus aureus, coagulase negative staphylococcus organism*	No	Recommend
O'Neill et al. [36]	Posterior spine fusions for traumatic injuries	All	Placed directly on the muscle, fascia, and subcutaneous tissues taking care not to expose bone graft or dura	1 g	0	-	13	MRSA, Polymicrobial	No	Recommend
Murphy et al. [21]	Elective and trauma surgeries of thoracic or lumbar region	All	Subfascial layer	1 or 2 g	NR	-	-	-	No	Recommend
Okafor et al. [37]	Spine tumor surgery	All	The deep fascia and subcutaneous tissue	1 g (250 mg for anterior cervical surgeries)	4.9	*Staphylococcus aureus, Enterobacter cloacae*	-	-	NR	Recommend
Ghobrial et al. [38]	Spinal procedures	Partly	Subfascial and epifascial layers	1.13 g (0.5-6 g)	6.71	G+ and G- microorganism, Fungal, Polymicrobial	-	-	NR	Not recommended
Molinari et al. [39]	Spine surgery	Partly	Deep lumbar fascia	1 g	0.99	*Staphylococcus aureus,* MRSA, *Enterococcus*	-	-	No	Recommend

IA, Intravenous administration of antibiotics; MRSA, Methicillin-resistant *Staphylococcus aureus*; MRCNS, Methicillin-resistant *coagulase-negative staphylococci species*; MSSA, Methicillin-sensitive *Staphylococcus aureus*; NR, Not reported; TVPIA, Combined application of topical vancomycin powder and intravenous administration of antibiotics.

Table 4. Bacterial spectrum of included studies

	TVPIA prophylaxis	n	IA prophylaxis	n
Gram+	*Coagulase-negative staphylococci*	7	MRSA	41
	MRSA	6	MSSA	35
	MSSA	6	*Coagulase-negative staphylococci*	27
	Staphylococcus aureus	2	MRCNS	4
	Propionibacterium	3	*Enterococcus*	9
	Corynebacterium jeikeium	2	*Staphylococcus aureus*	2
	Enterococcus	1	*Propionibacterium*	6
	Clostridium	1	*Peptostreptococcus*	6
	Diphtheroids	1	*Corynebacterium*	2
			Bacillus cereus	1
Gram-	*Escherichia coli*	4	*Pseudomonas*	9
	Enterobacter	3	*Escherichia coli*	7
	Citrobacter	3	*Proteus*	6
	Klebsiella	3	Gram-negative rods	5
	Pseudomonas	2	*Klebsiella*	3
	Proteus	2	*Serratia marcescens*	3
	Serratia marcescens	2	*Morganella*	2
	Bacteroides fragilis	1	*Enterobacter*	2
	Morganella	1	*Acinetobacter baumannii*	1
	Gram-negative rods	1		

IA, Intravenous administration of antibiotics; MRSA, Methicillin-resistant Staphylococcus aureus; MRCNS, Methicillicin-resistant coagulase-negative staphylococci species; MSSA, Methicillin-sensitive Staphylococcus aureus; TVPIA, Combined application of topical vancomycin powder and intravenous administration of antibiotics.

Sixteen studies described that the use of TVP in surgical wounds significantly reduced the incidence of SSI. These studied showed that the patient was 1.9-13.0 times more likely to have SSI with regular prophylaxis than with additional TVP. Routine use of TVP for SSI was not recommended in 4 studies [21, 27, 30, 39], including the single RCT, because no significant improvement of SSIs and vancomycin-related adverse effects were observed.

Liu et al. compared the efficacy of TVP in preventing postoperative SSI between patients with and without spinal tumor [24]. The SSI rate of nontumor patients was significantly reduced by TVP application (7.0% vs 0.7%, P = 0.011). However, this promising result was not apparent in tumor patients (8.0% vs 14.8%, P = 0.442). Thus, the authors recommend that TVP application may be beneficial for nontumor spine patients and may be less effective in tumor patients.

Pathogens

There were 15 divergent studies that reported detailed infectious pathogen outcomes (**Table 4**). *Coagulase-negative staphylococci* and *Escherichia coli* were the most common Gram-positive and Gram-negative organisms after application of TVP. The majority of documented Gram-positive and Gram-negative infections were MRSA and *Pseudomonas* without TVP.

In studies with methicillin-resistant testing, MRSA infections were found in 6 out of 12 patients with TVP (50.0%), while 45 out of 80 without TVP (56.3%) had MRSA infections. The difference in incidence was not significant (chi-squared = 0.165, P = 0.685).

The incidence of Gram-negative infections was higher in patients with TVPIA prophylaxis (43.1%) than in those with IA prophylaxis alone (22.2%) (chi-squared = 8.713, P = 0.003). Similar results were reported by Ghobrial et al. [39], namely that 66 of 981 patients were diagnosed with SSI and 51 patients had positive wound cultures with 60.7% Gram-negative infections.

Adverse events

All studies reported that there were no adverse events definitely attributable to TVP. A pro-

spective study focusing on side effects reported that no vancomycin-related adverse effects were detected [22].

Discussion

Literature review

Vancomycin derives its name from "vanquish" because this drug can kill penicillin-resistant *Staphylococcus aureus*. It is highly efficacious against Gram-positive bacteria by inhibiting cell wall synthesis. The broad antibacterial spectrum thus helps clinicians to vanquish *Staphylococcus aureus, Streptococcus pneumoniae, Clostridium, enterococci,* and so forth [16]. The application of topical antibiotics to surgical wounds is not a new concept. TVP was first used in 1989 by cardiac surgeons to decrease sternal infections after sternotomy [16]. In spine surgery, SSI prevention by TVP has been studied extensively, but without consensus.

According to some scholars, TVP is a promising option for additional prophylaxis against postoperative SSIs. This conclusion has gained support in recent research. A study by Schroeder and colleagues evaluated the use of intrasite vancomycin in degenerative spine surgery and found a reduction in the rate of SSIs (0.4% vs 1.3%) and irrigation and debridement procedures [19]. Devin et al. studied a cohort of 2,056 patients and compared the infection rates between those receiving and not receiving topical vancomycin from 7 spinal surgery centers across the United States, all undergoing posterior spine surgery [25]. They found that TVP reduced the risk of SSI and return to the operating room associated with SSI (2.2% vs 5.1%). Similar results were reported by Korean and Singaporean researchers. Lee et al. demonstrated that TVP application resulted in a significant decrease in SSI rates (5.5% vs 10.5%) in posterior lumbar surgical procedures [23]. Dennis et al. confirmed a decrease in the number of SSI in patients receiving TVP (6.3%) in comparison with those treated only with IA prophylaxis (0.9%) [17]. Molinari et al. and Ghobrial et al. reported low infection rates (0.99% and 6.71%) and recommended prophylactic vancomycin application to spinal wounds [40]; however, the results of these two studies were influenced by the fact that there was no control group for comparison.

Meanwhile, different messages have been sent forth. Two studies by the same team claimed that significantly reduced SSI rates after using TVP in spinal deformity [30] (5.1% and 5.3%) and posterior cervical fusion surgery [27] (5.2% and 6.9%) were not observed. However, Matin et al. pointed out that in these two studies the follow-up was only 1 month (inferred from the article) after spine operations [27, 30]. Such a short follow-up period tends to underestimate the incidence of postoperative SSIs and overlooks the potential difference between application and nonapplication of TVP. Ghobrial et al. found that prophylactic TVP in spine surgery may increase the incidence of Gram-negative or polymicrobial spinal infections [39], although again there was no direct control group for comparison in this study. The only prospective RCT by Tubaki et al. confirmed that the use of TVP in surgical wounds did not significantly reduce the incidence of spinal SSI (1.61% and 1.68%) owing to the fact that this method may not be effective when the infection rate is low [21]. As a prospective RCT study, the non-blinded trial did not evaluate preoperative body mass index, smoking, and other risk factors that may affect the SSI postoperatively. In addition, the number of subjects was insufficient to properly discern the difference in infection rates between the two groups based on the reported SSI rate.

SSI infection rates and pathogens

The present study examined the overall effectiveness of TVP in preventing SSIs in spine surgery. The pooled effects of studies following the inclusion criteria showed that TVPIA prophylaxis reduces the infection rate compared with IA prophylaxis alone (1.69% vs 4.36%, P < 0.001). We would infer that TVP is an effective approach to help decrease general SSIs in spine surgery. However, results showed unexpectedly that MRSA infections were 50.0% and 56.3% in patients with and without TVP, respectively (P = 0.685). In the present study, the methicillin-resistant testing results were obtained from only 12 and 80 infected patients with or without TVP, respectively. The small number of subjects and the lack of high-quality literature render a definitive conclusion and clinical significance contentious.

An obvious difference in the bacterial spectrum was found under two prophylaxis approaches.

Peking Union Medical College, Beijing, China. E-mail: pumchzhaoyu@sina.com

References

[1] Maruo K and Berven SH. Outcome and treatment of postoperative spine surgical site infections: predictors of treatment success and failure. J Orthop Sci 2014; 19: 398-404.

[2] Ceken S, Yavuz SS, Sensoy A and Imamoglu O. Original article epidemiology and risk factors for surgical site infections following thoracic surgery. Int J Clin Exp Med 2016; 9: 12018-12024.

[3] Gecgel SK and Demircan N. The epidemiology of pathogen microorganisms in hospital acquired infections. Int J Clin Exp Med 2016; 9: 22310-22316.

[4] Sasso RC and Garrido BJ. Postoperative spinal wound infections. J Am Acad Orthop Surg 2008; 16: 330-337.

[5] Pull ter Gunne AF and Cohen DB. Incidence, prevalence, and analysis of risk factors for surgical site infection following adult spinal surgery. Spine (Phila Pa 1976) 2009; 34: 1422-1428.

[6] Noskin GA, Rubin RJ, Schentag JJ, Kluytmans J, Hedblom EC, Jacobson C, Smulders M, Gemmen E and Bharmal M. National trends in Staphylococcus aureus infection rates: impact on economic burden and mortality over a 6-year period (1998-2003). Clin Infect Dis 2007; 45: 1132-1140.

[7] Calderone RR, Garland DE, Capen DA and Oster H. Cost of medical care for postoperative spinal infections. Orthop Clin North Am 1996; 27: 171-182.

[8] Graf K, Ott E, Vonberg RP, Kuehn C, Schilling T, Haverich A and Chaberny IF. Surgical site infections--economic consequences for the health care system. Langenbecks Arch Surg 2011; 396: 453-459.

[9] Kang DG, Holekamp TF, Wagner SC and Lehman RA Jr. Intrasite vancomycin powder for the prevention of surgical site infection in spine surgery: a systematic literature review. Spine J 2015; 15: 762-770.

[10] Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pollock DA and Fridkin SK. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the national healthcare safety network at the centers for disease control and prevention, 2006-2007. Infect Control Hosp Epidemiol 2008; 29: 996-1011.

[11] Huiras P, Logan JK, Papadopoulos S and Whitney D. Local antimicrobial administration for prophylaxis of surgical site infections. Pharmacotherapy 2012; 32: 1006-1019.

[12] Reichman DE and Greenberg JA. Reducing surgical site infections: a review. Rev Obstet Gynecol 2009; 2: 212-221.

[13] Mera RM, Suaya JA, Amrine-Madsen H, Hogea CS, Miller LA, Lu EP, Sahm DF, O'Hara P and Acosta CJ. Increasing role of Staphylococcus aureus and community-acquired methicillin-resistant Staphylococcus aureus infections in the united states: a 10-year trend of replacement and expansion. Microb Drug Resist 2011; 17: 321-328.

[14] Xiong L, Pan Q, Jin G, Xu Y and 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.

[15] Ueng SW, Lin SS, Wang IC, Yang CY, Cheng RC, Liu SJ, Chan EC, Lai CF, Yuan LJ and Chan SC. Efficacy of vancomycin-releasing biodegradable poly (lactide-co-glycolide) antibiotics beads for treatment of experimental bone infection due to Staphylococcus aureus. J Orthop Surg Res 2016; 11: 52.

[16] Abdullah KG, Chen HI and Lucas TH. Safety of topical vancomycin powder in neurosurgery. Surg Neurol Int 2016; 7: S919-S926.

[17] Hey HW, Thiam DW, Koh ZS, Thambiah JS, Kumar N, Lau LL, Liu KG, Wong HK. Is intraoperative local vancomycin powder the answer to surgical site infections in spine surgery? Spine (Phila Pa 1976) 2017; 42: 267-274.

[18] Gaviola ML, McMillian WD, Ames SE, Endicott JA and Alston WK. A retrospective study on the protective effects of topical vancomycin in patients undergoing multilevel spinal fusion. Pharmacotherapy 2016; 36: 19-25.

[19] Schroeder JE, Girardi FP, Sandhu H, Weinstein J, Cammisa FP and Sama A. The use of local vancomycin powder in degenerative spine surgery. Eur Spine J 2016; 25: 1029-1033.

[20] 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.

[21] Tubaki VR, Rajasekaran S and 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.

[22] Murphy EP, Curtin M, Shafqat A, Byrne F, Jadaan M and Rahall E. A review of the application of vancomycin powder to posterior spinal fusion wounds with a focus on side effects and infection. A prospective study. Eur J Orthop Surg Traumatol 2017; 27: 187-191.

[23] Lee GI, Bak KH, Chun HJ and Choi KS. Effect of using local intrawound vancomycin powder in addition to intravenous antibiotics in posterior

lumbar surgery: midterm result in a single-center study. Korean J Spine 2016; 13: 47-52.

[24] Liu N, Wood KB, Schwab JH, Cha TD, Puhkan RD, Osler PM and Grottkau BE. Comparison of intrawound vancomycin utility in posterior instrumented spine surgeries between patients with tumor and nontumor patients. Spine (Phila Pa 1976) 2015; 40: 1586-1592.

[25] Devin CJ, Chotai S, McGirt MJ, Vaccaro AR, Youssef JA, Orndorff DG, Arnold PM, Frempong-Boadu AK, Lieberman IH, Branch C, Hedayat HS, Liu A, Wang JC, Isaacs RE, Radcliff KE, Patt JC and Archer KR. Intrawound vancomycin decreases the risk of surgical site infection after posterior spine surgery-a multicenter analysis. Spine (Phila Pa 1976) 2018; 43: 65-71.

[26] Heller A, McIff TE, Lai SM and Burton DC. Intrawound vancomycin powder decreases staphylococcal surgical site infections after posterior instrumented spinal arthrodesis. J Spinal Disord Tech 2015; 28: E584-589.

[27] Martin JR, Adogwa O, Brown CR, Kuchibhatla M, Bagley CA, Lad SP and Gottfried ON. Experience with intrawound vancomycin powder for posterior cervical fusion surgery. J Neurosurg Spine 2015; 22: 26-33.

[28] Hill BW, Emohare O, Song B, Davis R and Kang MM. The use of vancomycin powder reduces surgical reoperation in posterior instrumented and noninstrumented spinal surgery. Acta Neurochir (Wien) 2014; 156: 749-754.

[29] Theologis AA, Demirkiran G, Callahan M, Pekmezci M, Ames C and Deviren V. Local intrawound vancomycin powder decreases the risk of surgical site infections in complex adult deformity reconstruction: a cost analysis. Spine (Phila Pa 1976) 2014; 39: 1875-1880.

[30] Martin JR, Adogwa O, Brown CR, Bagley CA, Richardson WJ, Lad SP, Kuchibhatla M and Gottfried ON. Experience with intrawound vancomycin powder for spinal deformity surgery. Spine (Phila Pa 1976) 2014; 39: 177-184.

[31] Caroom C, Tullar JM, Benton EG Jr, Jones JR and Chaput CD. Intrawound vancomycin powder reduces surgical site infections in posterior cervical fusion. Spine (Phila Pa 1976) 2013; 38: 1183-1187.

[32] Kim HS, Lee SG, Kim WK, Park CW and Son S. Prophylactic intrawound application of vancomycin powder in instrumented spinal fusion surgery. Korean J Spine 2013; 10: 121-125.

[33] Pahys JM, Pahys JR, Cho SK, Kang MM, Zebala LP, Hawasli AH, Sweet FA, Lee DH and Riew KD. Methods to decrease postoperative infections following posterior cervical spine surgery. J Bone Joint Surg Am 2013; 95: 549-554.

[34] Strom RG, Pacione D, Kalhorn SP and Frempong-Boadu AK. Decreased risk of wound infection after posterior cervical fusion with routine local application of vancomycin powder. Spine (Phila Pa 1976) 2013; 38: 991-994.

[35] Strom RG, Pacione D, Kalhorn SP and Frempong-Boadu AK. Lumbar laminectomy and fusion with routine local application of vancomycin powder: decreased infection rate in instrumented and non-instrumented cases. Clin Neurol Neurosurg 2013; 115: 1766-1769.

[36] Sweet FA, Roh M and Sliva C. Intrawound application of vancomycin for prophylaxis in instrumented thoracolumbar fusions: efficacy, drug levels, and patient outcomes. Spine (Phila Pa 1976) 2011; 36: 2084-2088.

[37] O'Neill KR, Smith JG, Abtahi AM, Archer KR, Spengler DM, McGirt MJ and Devin CJ. Reduced surgical site infections in patients undergoing posterior spinal stabilization of traumatic injuries using vancomycin powder. Spine J 2011; 11: 641-646.

[38] Okafor R, Molinari W, Molinari R and Mesfin A. Intrawound vancomycin powder for spine tumor surgery. Global Spine J 2016; 6: 207-211.

[39] Ghobrial GM, Thakkar V, Andrews E, Lang M, Chitale A, Oppenlander ME, Maulucci CM, Sharan AD, Heller J, Harrop JS, Jallo J and Prasad S. Intraoperative vancomycin use in spinal surgery: single institution experience and microbial trends. Spine (Phila Pa 1976) 2014; 39: 550-555.

[40] Molinari RW, Khera OA and Molinari WJ 3rd. Prophylactic intraoperative powdered vancomycin and postoperative deep spinal wound infection: 1,512 consecutive surgical cases over a 6-year period. Eur Spine J 2012; 21 Suppl 4: S476-482.

[41] Horan TC, Gaynes RP, Martone WJ, Jarvis WR and Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol 1992; 13: 606-608.

[42] Mariappan R, Manninen P, Massicotte EM and Bhatia A. Circulatory collapse after topical application of vancomycin powder during spine surgery. J Neurosurg Spine 2013; 19: 381-383.

[43] Youssef JA, Orndorff DG, Scott MA, Ebner RE and Knewitz AP. Sterile seroma resulting from multilevel xlif procedure as possible adverse effect of prophylactic vancomycin powder: a case report. Evid Based Spine Care J 2014; 5: 127-133.

[44] Duewelhenke N, Krut O and Eysel P. Influence on mitochondria and cytotoxicity of different antibiotics administered in high concentrations on primary human osteoblasts and cell lines. Antimicrob Agents Chemother 2007; 51: 54-63.

[45] Edin ML, Miclau T, Lester GE, Lindsey RW and Dahners LE. Effect of cefazolin and vancomycin on osteoblasts in vitro. Clin Orthop Relat Res 1996; 245-251.