World Neurosurgery: X 24 (2024) 100397

Contents lists available at ScienceDirect

World Neurosurgery: X

journal homepage: www.journals.elsevier.com/world-neurosurgery-x

Practice preference and evidence analysis on topical use of tobramycin powder in lumbar spine surgery: A Multi-National AO spine survey with systematic review of the literature☆

Veranis Sotiris [a,1], Sathish Muthu [b,c,d,*,1], Matt Gary [e], Sam Cho [f], So Kato [g], Stephen J. Lewis [h], Ho-Joong Kim [i], Jeffrey Wang [j], Amit Jain [k], S. Tim Yoon [l], AO Spine Knowledge Forum Degenerative [m]

[a] Department of Neurosurgery, General Air Force General Staff Hospital, Athens, Greece
[b] Orthopaedic Research Group, Coimbatore, Tamil Nadu, India
[c] Department of Biotechnology, Karpagam Academy of Higher Education, Coimbatore, Tamil Nadu, India
[d] Department of Orthopaedics, Government Medical College, Karur, Tamil Nadu, India
[e] Departments of Neurosurgery and Orthopaedic Surgery, Emory University, Atlanta, GA, USA
[f] Department of Orthopedic Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[g] Department of Orthopaedic Surgery, The University of Tokyo, Tokyo, Japan
[h] UHN-Orthopedics, University of Toronto, Toronto Western Hospital, Toronto, Ontario, Canada
[i] Spine Center and Department of Orthopaedic Surgery, Seoul National University College of Medicine and Seoul National University Bundang Hospital, Seongnam, South Korea
[j] Department of Orthopaedic Surgery and Neurological Surgery, Keck School of Medicine, University of Southern California, CA, USA
[k] Department of Orthopaedic Surgery, Johns Hopkins University, Baltimore, MD, USA
[l] Department of Orthopaedics, Emory University, Atlanta, GA, USA
[m] AO Spine, AO Foundation, Davos, Switzerland

ARTICLE INFO

Keywords:
Tobramycin
Topical antibiotics
Spine surgery
Gram-negative
Surgical site infection

ABSTRACT

Study design: Cross-sectional study with systematic review of literature.
Objective: There is an increasing interest in the topical use of antibiotics to prevent infection following spine surgery. To extend the antibiotic coverage to the gram-negative spectrum, the usage of tobramycin powder is being considered. We surveyed to analyze the current practice preference on the use of topical tobramycin in lumbar spine surgery and also aimed to analyze the literature for current evidence on the same.
Methods: A multinational cross-sectional survey was conducted among AO Spine members worldwide to understand the use of topical tobramycin in 1 or 2-level open lumbar fusion surgeries. Also, an independent systematic review of four scientific databases (PubMed, Scopus, clinicaltrials.gov, Web of Science) was performed by two authors to identify relevant articles in adherence to the preferred reporting in systematic reviews and meta-analysis (PRISMA) guidelines. Studies reporting the usage of tobramycin in lumbar spine surgeries were included for analysis.
Results: Among the 231 participating surgeons, only 1.7 %($n = 4$) reported utilizing tobramycin in 1 or 2-level open lumbar fusion surgery. Upon systematic review of the literature, two studies with 484 patients were included for analysis. With the usage of tobramycin as a topical antibiotic powder, both studies noted a reduction in the incidence of infection with change in the spectrum of infective organisms.

Abbreviations: PRISMA, Preferred Reporting In Systematic reviews and Meta-Analysis; RCT, Randomised controlled Trial; SD, Standard Deviation; SSI, Surgical Site Infection.

☆ This study was organized and supported by AO Spine through the AO Spine Knowledge Forum Degenerative, a focused group of international experts. AO Spine is a clinical division of the AO Foundation, which is an independent medically-guided not-for-profit organization. Study support was provided directly through the AO Spine Research Department.

* Corresponding author. Orthopaedic Research Group, Coimbatore, 641 045, Tamil Nadu, India.
E-mail address: drsathishmuthu@gmail.com (S. Muthu).

[1] co-first author.

https://doi.org/10.1016/j.wnsx.2024.100397
Received 5 November 2023; Received in revised form 26 August 2024; Accepted 20 September 2024
Available online 26 September 2024
2590-1397/© 2024 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Conclusion: Topical Tobramycin is not the commonly preferred topical antibiotic to prevent SSI among spine surgeons worldwide. There is a lack of sufficient evidence to support the routine use of topical tobramycin in lumbar spine surgery.

1. Introduction

Surgical site infection (SSI) remains a major concern in spine surgery due to its catastrophic effects on the patient and the operating surgeon.[1] The overall incidence of SSIs in spine surgery ranges from less than 1 %–11.9 % based on the risk factors inherent to the patient and the procedure.[1–11] SSI has an impact on the medical, social, and economic sectors of patients and the hospitals treating them.[12] SSI might necessitate prolonged length of hospital stay and need for additional procedures along with extended antibiotic usage thereby increasing the cost of the procedure to the patient.[13,14] Apart from the economic burden, SSI has an emotional impact on the overall outcome of the procedure.

Prophylactic usage of systemic antibiotics has been routinely employed to prevent postoperative SSIs. Cephalosporins are the common group of antibiotics routinely used with established efficacy against staphylococcal species.[15] However, Vancomycin remains the drug of choice in high-risk individuals harboring methicillin-resistant *Staphylococcus aureus* or with known allergy to β-lactam antibiotics.[16] Despite the systemic administration of prophylactic antibiotics their penetration is limited below the minimum inhibitory concentration in the target tissue in spine surgery. Hence, local antibiotic application to the surgical sites became a common practice to ensure adequate therapeutic drug levels at surgical sites. Local antibiotic delivery has been shown to demonstrate a 10-fold reduction in the infection rate in orthopedic surgeries.[17] Further, local administration not only prevents the adverse effects due to systemic administration but also prevents the risk of antibiotic resistance.[18]

Vancomycin and tobramycin remain the safe candidate antibiotics for topical use to reduce the risk of SSIs.[19–22] With the increasing evidence, vancomycin has been commonly used topically in spine surgery in high-risk surgeries such as deformity correction in the young and multi-level surgeries and surgeries requiring instrumentation in high-risk individuals. However, vancomycin usage has resulted in an increased incidence of sepsis due to gram-negative organisms.[23] This calls us to consider tobramycin with an antibiotic spectrum against common gram-negative organisms such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*.[24–27] We surveyed the AO Spine members worldwide to understand the current intraoperative topical antibiotic usage in open lumbar fusion surgery. Hence there is a need to understand the evidence behind the usage of topical tobramycin in spine surgery.

We surveyed to analyze the current practice preference on the use of topical tobramycin in lumbar spine surgery and also aimed to analyze the literature for evidence to support the use of topical tobramycin in lumbar spine surgery and generate recommendations for its routine usage.

2. Methods

2.1. Survey design

A survey was designed and disseminated through AO Spine Knowledge Forum to analyze the perioperative surgeon practices in degenerative lumbar spine surgery. Questions ranging from topics such as perioperative antibiotic use, wound closure techniques, and suture materials used were included in the surgery along with the demographic information of the participants. Surgeons performing at least 10 cases of open 1 or 2-level fusion for adult lumbar degenerative pathologies annually were eligible to participate in the survey. Informed consent was not required since no specific patient data has been involved in the survey and ethical committee approval was not obtained given the study was a surgeon-based survey.

The survey was distributed to over 6,000 AO Spine members internationally and was conducted electronically in March 2022. Surgeon demographic information was collected including geographic region (Asia Pacific, North America, Latin America, Europe and Southern Africa, and Middle East and Northern Africa), gender, age, years of practice, specialty, and practice setting. In the antibiotic usage domain, the surgeons were asked specifically about their topical use of tobramycin, location of placement, and dosage utilized.

2.2. Literature search

The present systematic review was conducted according to the preferred reporting in systematic reviews and meta-analysis (PRISMA) guidelines.[28] Two individual researchers (S.M., S.V.) independently reviewed four scientific databases (PubMed, Scopus, clinicaltrials.gov, Web of Science) to identify relevant articles. The algorithms used for the literature search included the following keywords: "tobramycin", "lumbar spine", "surgical site infection", and "topical antibiotics". Appropriate adjustments to the algorithms were made for each of the databases using Boolean operators such as “AND”, “OR” and “NOT”. The algorithms used in one of the included databases are presented in ***Appendix 1***. The bibliographies of the identified studies were also reviewed for the identification of additional relevant studies. Any conflicts were resolved by discussion until a consensus was achieved.

Following the removal of the duplicates, the titles and abstracts of the identified studies were reviewed for relevance using the online platform www.rayyan.ai. The full texts of the possibly relevant studies were then examined against our inclusion criteria. Studies that fulfilled the following inclusion criteria were included in the systematic review:

Patient: patients undergoing lumbar spine surgery.

Intervention: use of topical tobramycin

Comparison: comparator or placebo

Study types: randomized controlled trials (RCT) or observational studies with at least 10 patients per study group

We excluded observational studies with less than 10 patients, study types such as in-vitro studies, animal studies, case reports, letters to the editor, brief reports, and conference abstracts.

2.3. Data extraction

Using an Excel form, two independent authors (S.M., S.V.) extracted the following data from the studies, if available:

Study characteristics: name of the first author, year of publication, type of study, number of participants

Patient characteristics: age, gender, comorbidities

Procedure characteristics: approach and levels of fusion, surgery type (open/minimally invasive), the dosage of antibiotic used

Outcomes: incidence of SSI and spectrum of organisms noted.

Any discrepancies between the reviewers were resolved through discussion until consensus was obtained.

2.4. Quality assessment

Quality assessment was performed using the ROB2 tool of Cochrane

Collaboration for RCTs with five domains of assessment and the ROBINS tool for non-randomized studies that have seven domains of assessment. The quality assessment was performed independently by two investigators (S.M., S.V.). Any discrepancy is resolved upon discussion until consensus was obtained.

2.5. Statistical analysis

We used mean and standard deviation (SD) to present the continuous variables and percentages for discrete data. We used Stata (Version 17, StataCorp, LLC) for all statistical analyses. We considered a p-value of 0.05 as significant for all statistical calculations.

3. Results

3.1. Survey demographics

A total of 231 surgeons responded to the antibiotic usage domain of the survey on perioperative management. Respondents formed an international cohort, with the largest group from Europe and Southern Africa (35.9 %), followed by Asia Pacific (21.6 %), North America (19.5 %), Latin America (14.3 %), and Middle East and Northern Africa (8.7 %). Most respondents were orthopedic surgeons (77.1 %) and academic/university hospital affiliated (49.4 %). On the other hand, 27.7 % of surgeons were affiliated with public/military hospitals, and 22.9 % were in private practice. Finally, surgeon experiences among the respondents varied widely, and they were equally distributed across five groups ranging from <5 years of experience to >20 years of experience. Characteristics of the participating surgeons were presented in Table 1.

3.2. Tobramycin usage

Among the 231 participating surgeons, only 1.7 %($n = 4$) reported utilizing tobramycin in 1 or 2-level open lumbar fusion surgery. All of them reported sub-fascial application of the tobramycin powder. The dose of tobramycin utilized ranged from ≤1 g ($n = 1$), 1–2 g ($n = 2$), and 2–3 g ($n = 1$). The characteristics of surgeons using topical tobramycin in their practice are given in Table 1.

Table 1
Characteristics of surgeons participated in the survey and those using topical tobramycin in their current practice.

Variable	Total Surgeons	Tobramycin
	N = 231	N = 4
Gender		
Male	220 (95.2 %)	3 (75 %)
Female	11 (4.8 %)	1 (25 %)
Surgeon Age		
25–34 years	17 (7.4 %)	1 (25 %)
35–44 years	100 (43.3 %)	1 (25 %)
45–54 years	65 (28.1 %)	1 (25 %)
55–64 years	39 (16.9 %)	1 (25 %)
≥ 65 years	10 (4.3 %)	–
Region		
Asia Pacific	50 (21.6 %)	1 (25 %)
Europe and Southern Africa	83 (35.9 %)	–
Latin America	33 (14.3 %)	1 (25 %)
Middle East and Northern Africa	20 (8.7 %)	–
North America	45 (19.5 %)	2 (50 %)
Surgeon experience		
<5 years	40 (17.3 %)	1 (25 %)
05–10 years	55 (23.8 %)	–
11–15 years	47 (20.3 %)	1 (25 %)
16–20 years	34 (14.7 %)	–
>20 years	55 (23.8 %)	2 (50 %)
Speciality		
Orthopaedic Surgery	178 (77.1 %)	4 (100 %)
Neurosurgery	53 (22.9 %)	–
Institution		
Academic/University Hospital	114 (49.4 %)	3 (75 %)
Private practice	53 (22.9 %)	1 (25 %)
Public/Military Hospital	64 (27.7 %)	–

3.3. Study characteristics

We performed an independent and duplicate screening of the literature to identify studies using tobramycin in lumbar spine surgery. Following duplicate removal, 58 studies were identified from the included databases and screened for inclusion. After an initial screening of titles and abstracts, we excluded 52 studies. The full texts of the 6 remaining studies were then examined against our inclusion criteria, leading to the inclusion of 2 studies.[29,30] The characteristics of the included studies are presented in Table 2 (see Fig. 1).

3.4. Risk of bias assessment

None of the studies had a high risk of bias to warrant exclusion from the analysis as shown in Fig. 2. Of all included studies, some concerns were noted in domains accounting for confounding bias and missing data bias in one of the included studies.[29]

3.5. SSI incidence

Shapiro et al.[29] used tobramycin combined with methylmethacrylate in 65 patients undergoing cranioplasty, lumbar spinal fusion, and vertebral body replacement surgeries. They did not note any case of infection in the spinal procedures using topical tobramycin powder.

Lee et al.[30] in their study analyzed the incidence of SSI with ($n = 708$) and without ($n = 209$) the use of topical antibiotics in lumbar spine surgeries. Their topical antibiotic group had two subgroups, one vancomycin alone ($n = 489$) and the other vancomycin with tobramycin (219). The incidence of SSI noted was 5.7 %($n = 12$) in the control group whereas 2 %($n = 10$) in the vancomycin group and 1.8 %($n = 4$) in the vancomycin and tobramycin group. The difference was statistically significant compared to the control group while within the two antibiotic subgroups, they did not note any significant difference in SSI incidence.

3.6. Infective strain

Upon comparing the organisms cultured from the SSI cases in the antibiotic group in the study by Lee et al.,[30] it is noted that apart from 3 cases of methicillin-sensitive *Staphylococcus aureus* rest of all the 7 cases from the 10 SSI cases in vancomycin group were gram-negative strains, predominantly *Pseudomonas aeruginosa* and *Klebsiella pneumoniae.* Similarly, the strains from the vancomycin with tobramycin group were also due to *Pseudomonas aeruginosa* ($n = 2$), *Klebsiella pneumoniae* ($n = 1$), and *Escherichia coli* ($n = 1$).

3.7. Risk factors

Lee et al.[30] analyzed the risk factors contributing to SSI in the patients analyzed. They noted that smoking ($p < 0.001$) significantly contributed to the risk of SSI. They also noted that the age of the patient ($p = 0.07$), alcohol consumption ($p = 0.05$), and comorbidities of the patient ($p = 0.07$) did not contribute to the risk of SSI in their cohort.

4. Discussion

SSI remains a devastating complication following any surgery and spinal surgeries with instrumentation make it difficult to eradicate them once it occurs.[3] The risk factors involved in the development of SSI include surgical factors such as instrumentation, levels of surgery, revision surgery, and blood loss; and patient factors such as obesity, diabetes, and immunocompromised state.[31–34] Anderson et al.[35]

Table 2
Characteristics of studies included in the systematic review.

First author (year)	Study Type	Sample size	Age (Mean)	Female	Follow-up (Mean)	Antibiotic used	Infected Cases	Organism Cultured
Shapiro et al (1991)[29]	Prospective	65	NA	NA	32.2 months	Tobramycin	0	None
Lee et al (2018)[30]	Retrospective	419	53	136	66 months	Vancomycin + Tobramycin	4	*Pseudomonas aeruginosa* (2), *Escherichia coli* (1), Coagulase negative Staphylococcus, *Klebsiella pneumoniae* (1)

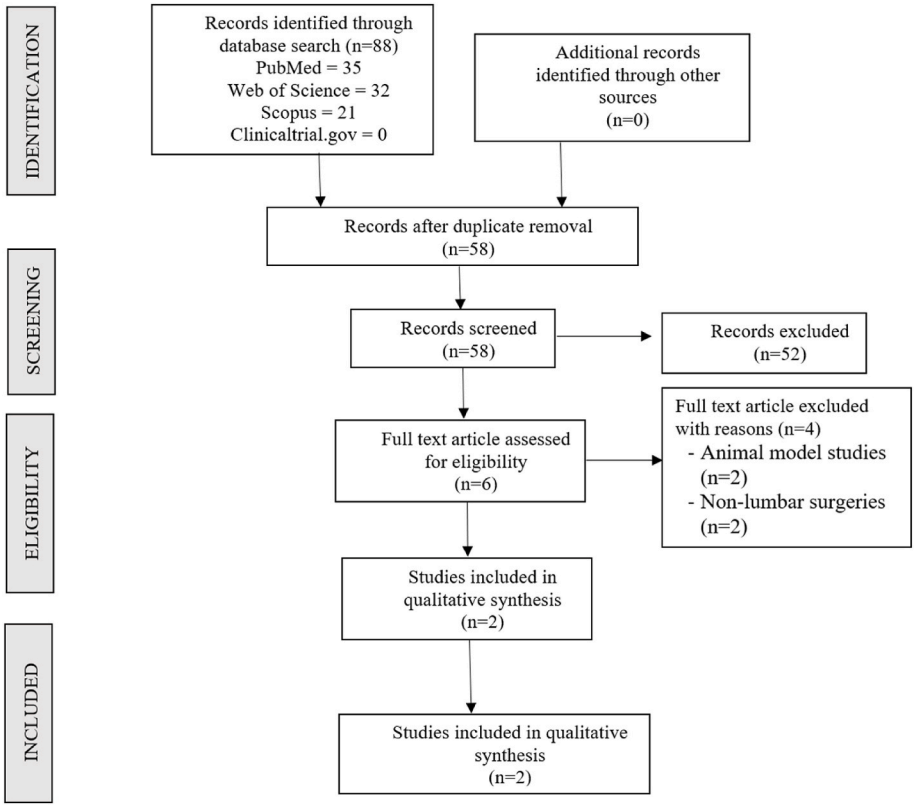

Fig. 1. PRISMA Flow diagram for selection of studies.

demonstrated that 60 % of the SSIs could be prevented, and with the increasing number of spine surgeries performed to date in the aging population, the impact of SSI must not be underestimated.[36,37]

Local administration of antibiotics has been considered a viable treatment strategy to prevent SSI with bactericidal concentrations at the surgical site with promising outcomes.[7,38–41] Topical application of vancomycin has been shown to eradicate gram-positive wound contamination thereby making it a routine practice of spine surgeons.[23,42–45] *Staphylococcus aureus* remains the common organism isolated from spinal SSI. But there has been a shift in the strain of pathogens from classic skin flora to more aggressive methicillin-resistant *Staphylococcus aureus* (MRSA) and gram-negative bacteria.[37,46]

The addition of topical vancomycin powder before wound closure has been shown to reduce the incidence of SSI from 5.7 % to 2 %. Further, the combined use of topical vancomycin with tobramycin reduced the SSI to 1.8 %.[30] Analysis behind the topical use of antibiotics has shown that whether used independent or in combination, vancomycin and tobramycin are economically justifiable in preventing SSI.[12] Recent literature analysis denotes that 30 % of spinal SSI and almost 50 % of pediatric SSI are due to gram-negative bacteria.[47] The change noted in the strain of infective organisms may be attributed to the common use of prophylactic antibiotics with gram-positive coverage resulting in selective progression of gram-negative strains.

A synergism has been noted with the combined use of vancomycin and tobramycin in-vitro.[48] However, their combined usage did not result in clinically demonstrable SSI reduction in the study by Lee et al.[30] and the possible explanation given for the lack of synergism was due to under-dosing of the tobramycin component. However, one must carefully consider antibiotic dosing since it carries the risk of more virulent organisms with the addition of more topical antibiotic volume along with changes in the noted spectrum of SSI and the risk of nephrotoxicity in higher doses.[30,49] Further, usage of such increased dosages is questioned in the pediatric population undergoing spine surgery.[50]

The study has some significant limitations worth acknowledging. The survey results could be influenced by the working conditions of the participating surgeons and the local availability of the antibiotic. Further, the responses might not be representative of the current practice preference given the low response rate. Hence, the results of the survey must be interpreted with caution. Regarding the systematic review, the number of available studies using tobramycin in lumbar spine surgery is limited. Given the limited number of available studies using tobramycin in spine surgery, no definite conclusion on its effectiveness could be ascertained. Hence, we recommend future high-quality randomized controlled trials be conducted to arrive at a definite conclusion to develop recommendations for its routine usage in lumbar spine surgeries.

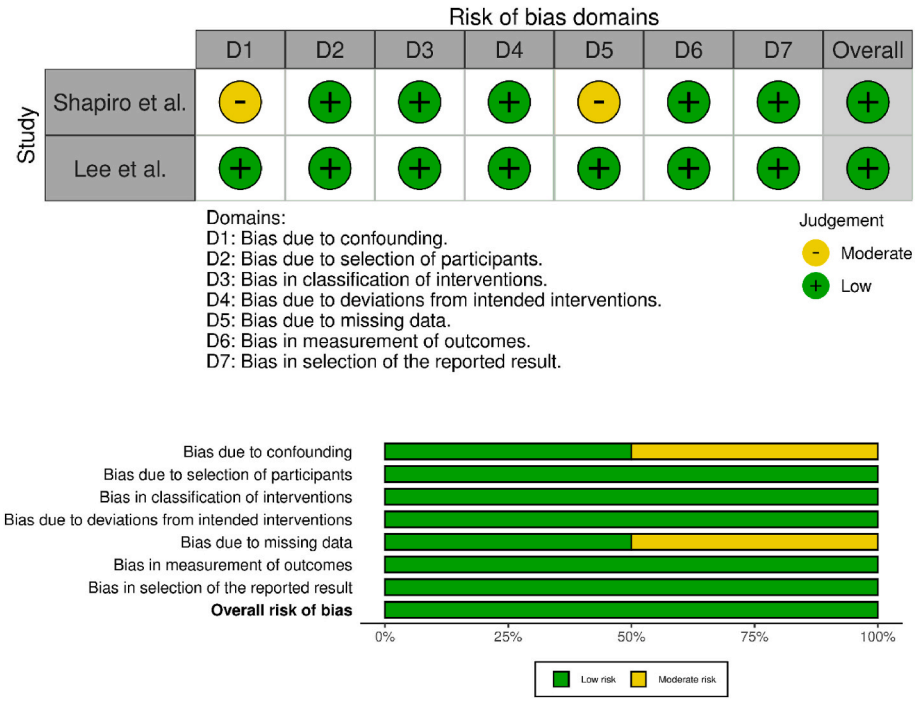

Fig. 2. Risk of bias assessment of the included studies using ROBINS-I tool of Cochrane Collaboration.

5. Conclusion

Topical Tobramycin is not the commonly preferred topical antibiotic to prevent SSI among spine surgeons worldwide. There is a lack of sufficient evidence to support the routine use of topical tobramycin in lumbar spine surgery. We recommend future high-quality randomized controlled trials to investigate the utility of tobramycin in this regard to develop recommendations on its routine usage.

CRediT authorship contribution statement

Veranis Sotiris: Writing – review & editing, Writing – original draft, Project administration, Investigation, Data curation, Conceptualization. **Sathish Muthu:** Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Matt Gary:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Sam Cho:** Writing – review & editing, Supervision, Resources, Project administration, Formal analysis. **So Kato:** Writing – review & editing, Project administration, Investigation, Data curation. **Stephen J. Lewis:** Writing – review & editing, Supervision, Methodology, Data curation. **Ho-Joong Kim:** Writing – review & editing, Supervision, Investigation, Data curation. **Jeffrey Wang:** Writing – review & editing, Supervision, Formal analysis, Conceptualization. **Amit Jain:** Writing – review & editing, Supervision, Formal analysis, Conceptualization. **S. Tim Yoon:** Writing – review & editing, Supervision, Resources, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix

Search strategy used in PubMed database

Search Topic	#	Search Terms
Population: Patients undergoing lumbar spine surgery	#1	("lumbar vertebrae"[Mesh]) OR (lumbar spine [All Fields]) OR (lumbar[All Fields])
	#2	("fusion surgery"[All Fields]) OR ("decompression surgery"[All Fields])
	#3	#1 AND #2
Intervention: Tobramycin antibiotic powder usage	#4	("tobramycin"[Mesh]) OR ("antibiotic prophylaxis"[Mesh]) OR ("antibiotic prophylaxis"[All Fields]) OR ("topical tobramycin"[All Fields]) OR ("antibiotic powder"[All Fields]) OR ("topical antibiotic"[All Fields])
	#5	#3 AND #4
Study design: Prospective and retrospective studies	#6	("clinical trial"[All Fields] OR "clinical trials as topic"[MeSH Terms] OR "clinical trials"[All Fields] OR "randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields] OR ("randomized"[All Fields] AND "controlled"[All Fields] AND "trials"[All Fields]) OR "randomized controlled trial"[All Fields]) OR ("randomized controlled trial"[Publication Type] OR "randomised controlled trial"[All Fields] OR "controlled clinical trial"[Publication Type] OR "controlled clinical trials as topic"[MeSH Terms] OR "controlled clinical trial"[All Fields])) OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "randomization"[All

(*continued on next page*)

(*continued*)

Search Topic	#	Search Terms
		Fields] OR "randomized"[All Fields] OR "random"[All Fields] OR "randomize"[All Fields] OR "randomizing"[All Fields] OR "randomizations"[All Fields] OR "randomize"[All Fields] OR "randomizes"[All Fields] OR "randomizing"[All Fields] OR "randomness"[All Fields] OR "randoms"[All Fields] OR "trials"[All Fields] OR ("prospective studies"[MeSH Terms] OR ("prospective"[All Fields] AND "studies"[All Fields]) OR "prospective studies"[All Fields] OR ("prospective"[All Fields] AND "studies"[All Fields]) OR "prospective studies"[All Fields] OR "retrospective studies"[MeSH Terms] OR ("retrospective"[All Fields] AND "studies"[All Fields]) OR "retrospective studies"[All Fields])
	#7	#5 AND #6
	#8	("biography"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lecture"[Publication Type] OR "legal case"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular work"[Publication Type] OR "congress"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "practice guideline"[Publication Type]) OR "Review"[Publication Type])
	#9	#7 NOT #8

References

1. Abdul-Jabbar A, Takemoto S, Weber MH, et al. Surgical site infection in spinal surgery: description of surgical and patient-based risk factors for postoperative infection using administrative claims data. *Spine*. 2012;37(15):1340–1345. https://doi.org/10.1097/BRS.0b013e318246a53a.
2. Smith JS, Shaffrey CI, Sansur CA, et al. Rates of infection after spine surgery based on 108,419 procedures: a report from the scoliosis Research society morbidity and mortality committee. *Spine*. 2011;36(7):556–563. https://doi.org/10.1097/BRS.0b013e3181eadd41.
3. Abbey DM, Turner DM, Warson JS, Wirt TC, Scalley RD. Treatment of postoperative wound infections following spinal fusion with instrumentation. *J Spinal Disord*. 1995;8(4):278–283. https://doi.org/10.1097/00002517-199508040-00003.
4. Glassman SD, Dimar JR, Puno RM, Johnson JR. Salvage of instrumental lumbar fusions complicated by surgical wound infection. *Spine*. 1996;21(18):2163–2169. https://doi.org/10.1097/00007632-199609150-00021.
5. Keller RB, Pappas AM. Infection after spinal fusion using internal fixation instrumentation. *Orthop Clin N Am*. 1972;3(1):99–111.
6. Roberts FJ, Walsh A, Wing P, Dvorak M, Schweigel J. The influence of surveillance methods on surgical wound infection rates in a tertiary care spinal surgery service. *Spine*. 1998;23(3):366–370. https://doi.org/10.1097/00007632-199802010-00016.
7. Stall AC, Becker E, Ludwig SC, Gelb D, Poelstra KA. Reduction of postoperative spinal implant infection using gentamicin microspheres. *Spine*. 2009;34(5):479–483. https://doi.org/10.1097/BRS.0b013e318197e96c.
8. Levi AD, Dickman CA, Sonntag VK. Management of postoperative infections after spinal instrumentation. *J Neurosurg*. 1997;86(6):975–980. https://doi.org/10.3171/jns.1997.86.6.0975.
9. Sponseller PD, LaPorte DM, Hungerford MW, Eck K, Bridwell KH, Lenke LG. Deep wound infections after neuromuscular scoliosis surgery: a multicenter study of risk factors and treatment outcomes. *Spine*. 2000;25(19):2461–2466. https://doi.org/10.1097/00007632-200010010-00007.
10. Rechtine GR, Bono PL, Cahill D, Bolesta MJ, Chrin AM. Postoperative wound infection after instrumentation of thoracic and lumbar fractures. *J Orthop Trauma*. 2001;15(8):566–569. https://doi.org/10.1097/00005131-200111000-00006.
11. Borkhuu B, Borowski A, Shah SA, Littleton AG, Dabney KW, Miller F. Antibiotic-loaded allograft decreases the rate of acute deep wound infection after spinal fusion in cerebral palsy. *Spine*. 2008;33(21):2300–2304. https://doi.org/10.1097/BRS.0b013e31818786ff.
12. Kirchner GJ, Smith NP, Garner MR. Intra-wound vancomycin and tobramycin powder for infection prophylaxis in orthopaedic trauma surgery: economically justifiable? *Injury*. 2021;52(11):3340–3343. https://doi.org/10.1016/j.injury.2021.08.028.
13. Calderone RR, Garland DE, Capen DA, Oster H. Cost of medical care for postoperative spinal infections. *Orthop Clin N Am*. 1996;27(1):171–182.
14. Whitehouse JD, Friedman ND, Kirkland KB, Richardson WJ, Sexton DJ. The impact of surgical-site infections following orthopedic surgery at a community hospital and a university hospital: adverse quality of life, excess length of stay, and extra cost. *Infect Control Hosp Epidemiol*. 2002;23(4):183–189. https://doi.org/10.1086/502033.
15. Crader MF, Varacallo M. Preoperative antibiotic prophylaxis. In: *StatPearls Treasure Island (FL)*. StatPearls Publishing; 2023.
16. Li S, Rong H, Zhang X, et al. Meta-analysis of topical vancomycin powder for microbial profile in spinal surgical site infections. *Eur Spine J*. 2019;28(12):2972–2980. https://doi.org/10.1007/s00586-019-06143-6. Official Publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.
17. Sweet FA, Forsthoefel CW, Sweet AR, Dahlberg RK. Local versus systemic antibiotics for surgical infection prophylaxis in a rat model. *J Bone Jt Surg Am Vol*. 2018;100(18):e120. https://doi.org/10.2106/JBJS.18.00105.
18. Pais GM, Liu J, Avedissian SN, et al. Lack of synergistic nephrotoxicity between vancomycin and piperacillin/tazobactam in a rat model and a confirmatory cellular model. *J Antimicrob Chemother*. 2020;75(5):1228–1236. https://doi.org/10.1093/jac/dkz563.
19. Ishida W, Perdomo-Pantoja A, Elder BD, et al. Effects of intraoperative intrawound antibiotic administration on spinal fusion: a comparison of vancomycin and tobramycin in a rat model. *J Bone Jt Surg Am Vol*. 2019;101(19):1741–1749. https://doi.org/10.2106/JBJS.18.00988.
20. Edelstein AI, Weiner JA, Cook RW, et al. Intra-articular vancomycin powder eliminates methicillin-resistant S. aureus in a rat model of a contaminated intra-articular implant. *J Bone Jt Surg Am Vol*. 2017;99(3):232–238. https://doi.org/10.2106/JBJS.16.00127.
21. Haimoto S, Schär RT, Nishimura Y, Hara M, Wakabayashi T, Ginsberg HJ. Reduction in surgical site infection with suprafascial intrawound application of vancomycin powder in instrumented posterior spinal fusion: a retrospective case-control study. *J Neurosurg Spine*. 2018;29(2):193–198. https://doi.org/10.3171/2017.12.SPINE17997.
22. Slane J, Gietman B, Squire M. Antibiotic elution from acrylic bone cement loaded with high doses of tobramycin and vancomycin. *J Orthop Res: Official Publication of the Orthopaedic Research Society*. 2018;36(4):1078–1085. https://doi.org/10.1002/jor.23722.
23. Khanna K, Valone F, Tenorio A, et al. Local application of vancomycin in spine surgery does not result in increased vancomycin-resistant bacteria-10-year data. *Spine Deformity*. 2019;7(5):696–701. https://doi.org/10.1016/j.jspd.2019.01.005.
24. Palser S, Smith S, Nash EF, Agarwal A, Smyth AR. Treatments for preventing recurrence of infection with Pseudomonas aeruginosa in people with cystic fibrosis. *Cochrane Database Syst Rev*. 2019;12(12), CD012300. https://doi.org/10.1002/14651858.CD012300.pub2.
25. Martí-Carvajal AJ, Dayer M, Conterno LO, Gonzalez Garay AG, Martí-Amarista CE. A comparison of different antibiotic regimens for the treatment of infective endocarditis. *Cochrane Database Syst Rev*. 2020;5(5):CD009880. https://doi.org/10.1002/14651858.CD009880.pub3.
26. Vrabec G, Stevenson W, Elguizaoui S, Kirsch M, Pinkowski J. What is the intraarticular concentration of tobramycin using low-dose tobramycin bone cement in TKA: an in vivo analysis? *Clin Orthop Relat Res*. 2016;474(11):2441–2447. https://doi.org/10.1007/s11999-016-5006-x.
27. Laratta JL, Shillingford JN, Hardy N, et al. Intrawound tobramycin powder eradicates surgical wound contamination: an in vivo rabbit study. *Spine*. 2017;42(24):E1393–E1397. https://doi.org/10.1097/BRS.0000000000002187.
28. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. https://doi.org/10.1136/bmj.n71.
29. Shapiro SA. Cranioplasty, vertebral body replacement, and spinal fusion with tobramycin-impregnated methylmethacrylate. *Neurosurgery*. 1991;28(6):789.
30. Lee Y-P, Farhan S-D, Pendi A, et al. Does addition of tobramycin powder reduce infection rates after spine surgery? *Global Spine J*. 2018;8(8):816–820. https://doi.org/10.1177/2192568218776609.
31. Lieber B, Han B, Strom RG, et al. Preoperative predictors of spinal infection within the national surgical quality inpatient database. *World Neurosurgery*. 2016;89:517–524. https://doi.org/10.1016/j.wneu.2015.12.085.
32. Olsen MA, Nepple JJ, Riew KD, et al. Risk factors for surgical site infection following orthopaedic spinal operations. *J Bone Jt Surg Am Vol*. 2008;90(1):62–69. https://doi.org/10.2106/JBJS.F.01515.
33. Olsen MA, Mayfield J, Lauryssen C, et al. Risk factors for surgical site infection in spinal surgery. *J Neurosurg*. 2003;98(2 Suppl):149–155.
34. Fang A, Hu SS, Endres N, Bradford DS. Risk factors for infection after spinal surgery. *Spine*. 2005;30(12):1460–1465. https://doi.org/10.1097/01.brs.0000166532.58227.4f.
35. Anderson DJ, Podgorny K, Berríos-Torres SI, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol*. 2014;35(Suppl 2):S66–S88. https://doi.org/10.1017/s0899823x00193869.
36. van Middendorp JJ, Pull ter Gunne AF, Schuetz M, et al. A methodological systematic review on surgical site infections following spinal surgery: part 2: prophylactic treatments. *Spine*. 2012;37(24):2034–2045. https://doi.org/10.1097/BRS.0b013e31825f6652.

37. Lee J, Singletary R, Schmader K, Anderson DJ, Bolognesi M, Kaye KS. Surgical site infection in the elderly following orthopaedic surgery. Risk factors and outcomes. *J Bone Jt Surg Am Vol.* 2006;88(8):1705–1712. https://doi.org/10.2106/JBJS.E.01156.
38. Hanssen AD. Local antibiotic delivery vehicles in the treatment of musculoskeletal infection. *Clin Orthop Relat Res.* 2005;437:91–96. https://doi.org/10.1097/01.blo.0000175713.30506.77.
39. Yarboro SR, Baum EJ, Dahners LE. Locally administered antibiotics for prophylaxis against surgical wound infection. An in vivo study. *J Bone Jt Surg Am Vol.* 2007;89(5):929–933. https://doi.org/10.2106/JBJS.F.00919.
40. Cavanaugh DL, Berry J, Yarboro SR, Dahners LE. Better prophylaxis against surgical site infection with local as well as systemic antibiotics. An in vivo study. *J Bone Jt Surg Am Vol.* 2009;91(8):1907–1912. https://doi.org/10.2106/JBJS.G.01237.
41. Stewart S, Barr S, Engiles J, et al. Vancomycin-modified implant surface inhibits biofilm formation and supports bone-healing in an infected osteotomy model in sheep: a proof-of-concept study. *J Bone Jt Surg Am Vol.* 2012;94(15):1406–1415. https://doi.org/10.2106/JBJS.K.00886.
42. Bakhsheshian J, Dahdaleh NS, Lam SK, Savage JW, Smith ZA. The use of vancomycin powder in modern spine surgery: systematic review and meta-analysis of the clinical evidence. *World Neurosurgery*. 2015;83(5):816–823. https://doi.org/10.1016/j.wneu.2014.12.033.
43. Horii C, Yamazaki T, Oka H, et al. Does intrawound vancomycin powder reduce surgical site infection after posterior instrumented spinal surgery? A propensity score-matched analysis. *Spine J*. 2018;18(12):2205–2212.
44. Kang DG, Holekamp TF, Wagner SC, Lehman RA. Intrasite vancomycin powder for the prevention of surgical site infection in spine surgery: a systematic literature review. *Spine J*. 2015;15(4):762–770. https://doi.org/10.1016/j.spinee.2015.01.030.
45. Luo H, Ren Y, Su Y, Xue F, Hong Z. Intraoperative vancomycin powder to reduce surgical site infections after posterior spine surgery: a systematic review and meta-analysis. *EFORT Open Reviews*. 2022;7(2):109–121. https://doi.org/10.1530/EOR-21-0077.
46. Mruk AL, Record KE. Antimicrobial options in the treatment of adult staphylococcal bone and joint infections in an era of drug shortages. *Orthopedics*. 2012;35(5):401–407. https://doi.org/10.3928/01477447-20120426-07.
47. Croft LD, Pottinger JM, Chiang H-Y, Ziebold CS, Weinstein SL, Herwaldt LA. Risk factors for surgical site infections after pediatric spine operations. *Spine*. 2015;40(2):E112–E119. https://doi.org/10.1097/BRS.0000000000000693.
48. Han W, Zhang L, Yu L, Wang J. Effect of local delivery of vancomycin and tobramycin on bone regeneration. *Orthop Surg*. 2021;13(5):1654–1661. https://doi.org/10.1111/os.13020.
49. Mohsen S, Dickinson JA, Somayaji R. Update on the adverse effects of antimicrobial therapies in community practice. *Can Fam Physician*. 2020;66(9):651–659.
50. Sathish M, Girinivasan C. Is use of topical vancomycin in pediatric spine surgeries a safe option in the prevention of surgical site infections? A meta-analysis and systematic review of the literature. *Global Spine J*. 2021;11(5):774–781. https://doi.org/10.1177/2192568220937286.