Effect of Local Antibiotic Prophylaxis on Postoperative Deep Infection in Fracture Surgery: A Systematic Review and Meta-Analysis

Colin Kruse, MD,[a,b] Daniel Axelrod, MD, MSc,[b] Omar A. Al-Mohrej, MD (Hons),[b,c] Ryan Daniel, BSc,[d] and Herman Johal, MD, MPH, FRCSC[b]

Objectives: Despite the use of systemic antibiotic prophylaxis, postoperative infection after fracture surgery remains an issue. The purpose of this systematic review and meta-analysis was to evaluate the effect of locally applied antibiotics on deep infection in fracture surgery in both the open and closed fractures.

Data Sources: A comprehensive search of MEDLINE, Embase, and PubMed was performed from the date of inception to April 15, 2021, and included studies in all languages.

Study Selection: Cohort studies were eligible if they investigated the effect on the infection rate of local antibiotic prophylaxis on deep infection after fracture surgery.

Data Extraction: This study was conducted according to the Cochrane Handbook for Systematic Reviews and reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Risk of bias was assessed using version 2 of the Cochrane risk-of-bias tool for randomized trials and the Methodological Index for Nonrandomized Studies tool where applicable.

Data Synthesis: An inverse variance random-effects model was the primary analysis model because of the anticipated diversity in the evaluated populations. Univariate models were used when a single outcome was of interest.

Conclusions: The risk of deep infection was significantly reduced when local antibiotics were applied compared with the control group receiving systemic prophylaxis only. This beneficial effect was observed in open fractures but failed to reach statistical significance in closed fractures. This meta-analysis suggests that there may be a significant risk reduction in deep infection rate after fracture surgery when local antibiotics are added to standard systemic prophylaxis, particularly in open fractures. Further high-powered Level I studies are needed to support these findings.

Key Words: open fractures, closed fractures, local antibiotics, vancomycin, infection

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

(*J Orthop Trauma* 2023;37:e28–e35)

INTRODUCTION

Despite the regular use of systemic antibiotic prophylaxis, the rate of infection in orthopaedic trauma surgery remains high.[1] Depending on the type and location of the fracture and the severity of the injury, the rate of infection ranges from 5% to 30%.[1,2] In particular, deep infections are associated with substantially greater morbidity and socioeconomic costs.[3–7] Although internal fixation (ORIF) of fractures has been shown to reduce morbidity in numerous fracture patterns, the surgical management of both the open and closed fractures carries a risk of surgical site infection (SSI).[8,9] Open fractures are particularly susceptible to infection because they are regularly associated with more bone and soft-tissue injury as well as periosteal stripping and contamination.[1,10] Systemic antibiotic prophylaxis has been shown to considerably reduce the risk of subsequent infection after a fracture.[11,12] However, the delivery of intravenous antibiotics is limited by the quality of blood supply to the area.[13] The local vascular anatomy can be disrupted in acutely damaged tissues at the time of fracture making it difficult to achieve sufficient tissue concentration of antibiotics.[2]

Locally applied antibiotics may overcome this issue because they can be delivered directly to the surgical site, resulting in greater tissue concentration levels.[14] High local antibiotic concentrations can be attained even when local vasculature is disrupted, and the risk of systemic toxicity is minimized.[2] Local antibiotics may also prevent bacteria from colonizing implant or compromised tissue surfaces and prevent biofilm formation, which can make fracture-related deep infections particularly difficult to treat.[15] Although there have been emerging recommendations supporting the use of local antibiotics in open fractures[16] and despite the

Accepted for publication September 2, 2022.
From the [a]Michael G. DeGroote School of Medicine, McMaster University, Hamilton, ON, Canada; [b]Division of Orthopedic Surgery, Department of Surgery, McMaster University, Hamilton, ON, Canada; [c]Section of Orthopedic Surgery, Department of Surgery, King Abdullah Bin Abdulaziz University Hospital, Princess Nourah Bint Abdul Rahman University, Riyadh, Saudi Arabia; and [d]Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada.
The authors report no conflict of interest.
Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jorthotrauma.com).
Reprints: Colin Kruse, BSc, Division of Orthopaedic Surgery, McMaster University c/o St. Joseph's Hospital, 50 Charlton Avenue East, Room G522, Hamilton, ON L8N 4A6, Canada (e-mail: colin.kruse@medportal.ca).

DOI: 10.1097/BOT.0000000000002487

fact that their use has been adopted by some orthopaedic practices,[17] there is limited high-quality evidence surrounding their effectiveness.[2,16] The increasing emphasis on antibiotic stewardship to protect patients from harms caused by unnecessary antibiotic use and to combat antibiotic resistance underscores the importance of strong evidence regarding the use of local antibiotics in fracture management.[18,19] The purpose of this systematic review and meta-analysis was to evaluate the current literature for evidence regarding the effect of local antibiotic prophylaxis on deep infection after fracture surgery.

METHODS

This study was conducted according to the Cochrane Handbook for Systematic Reviews[20] and reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21] No funding was provided for this investigation.

Search Strategy

Embase, MEDLINE, PubMed, and Cochrane Central Register of Controlled Trials (CENTRAL) database were searched from date of inception to April 15, 2021. The search strategy, adapted to each database, included terms representing “open fractures” and antibiotic use.

Outcomes Assessed

The primary outcome assessed was the comparison of deep infection rate between the use of local antibiotics combined with systemic antibiotics to systemic antibiotic prophylaxis alone among adult patients undergoing surgical management of either open or closed fractures. Superficial infections were analyzed as a secondary outcome.

Study Selection

To maximize potentially eligible data, no restrictions were made on publication date or follow-up period. The criteria for inclusion were (1) studies comparing deep infection rate for local antibiotic prophylaxis combined with systemic antibiotics to systematic antibiotic prophylaxis alone in skeletally mature patients undergoing definitive surgical management of either closed or open fractures. The exclusion criteria were (1) studies including patients with established infections or osteomyelitis at the fracture site, (2) studies that included less than 10 patients, and (3) editorials, reviews, and conference abstracts.

Data Extraction

Two reviewers independently evaluated the systematically searched titles and abstracts using a standardized, pilot-tested form. The selection of studies was performed in a stepwise manner, first by title and abstract and then full-text review. Two reviewers then independently conducted data extraction into a data collection form designed a priori. The extracted data included study characteristics, patient demographics, injury characteristics, follow-up period, type of antibiotics used, method of local antibiotic delivery, and infection rate. Data regarding the type of local antibiotics and the type of fracture regarding open or closed status were collected to use as covariates.

Risk of Bias Assessment

Risk of bias for included randomized controlled trials was assessed using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2).[22] All other comparative studies included in this study were assessed using the Methodological Index for Nonrandomized Studies (MINORS).[21] Two reviewers assessed the quality of the studies independently.

Statistical Analysis

An inverse variance random-effects model was the primary analysis model because of the anticipated diversity in the evaluated populations.[23] Univariate models were used when a single outcome was of interest.

We estimated the between-study variance (τ^2) with the restricted maximum likelihood approach. Because some studies had a retrospective design, binary outcomes were presented as odds ratios (ORs) with 95% confidence intervals.

Statistical heterogeneity was tested using the Cochran Q test[24] and quantified with the I^2 statistic.[25] The 95% prediction interval (95% PI) was presented to facilitate the interpretation. The 95% PI indicates the expected range in the treatment effects across different patient populations and settings.[26]

We tested the difference in magnitude of treatment effects observed in randomized trials compared with those reported in retrospective studies (design interaction test). We additionally assessed publication bias and small-study bias through visual inspections of contour-enhanced funnel plots, contrasting the standard error of log ORs on the vertical axis against the point estimates on the horizontal axis.

For the summary effects, a P value < 0.05 (2-tailed) was considered statistically significant. All analyses were conducted in Stata 16 (StataCorp, TX).

RESULTS

Characteristics of the Included Studies

A total of 10 studies were included in the meta-analysis.[27–36] A PRISMA flow diagram of the screening process and study selection is illustrated in Figure 1. One study was a randomized trial, and 9 studies had a retrospective observational design. There were a total of 4643 fractures included in the analysis. The median sample size was 393 participants [interquartile range (IQR): 110–789]. Across the 10 studies, the median age was 42 years (IQR: 36–47 years). The mean follow-up period was 11.9 months. Detailed study characteristics of the included studies are presented in Table 1.

Deep Infections

The overall summary estimate for deep infections in all fractures favored local antibiotics when compared with systemic antibiotics alone (OR = 0.50; 95% CI: 0.34–0.72, $P < 0.001$) (Fig. 2). These results indicated that patients receiving local antibiotics will be, on average,

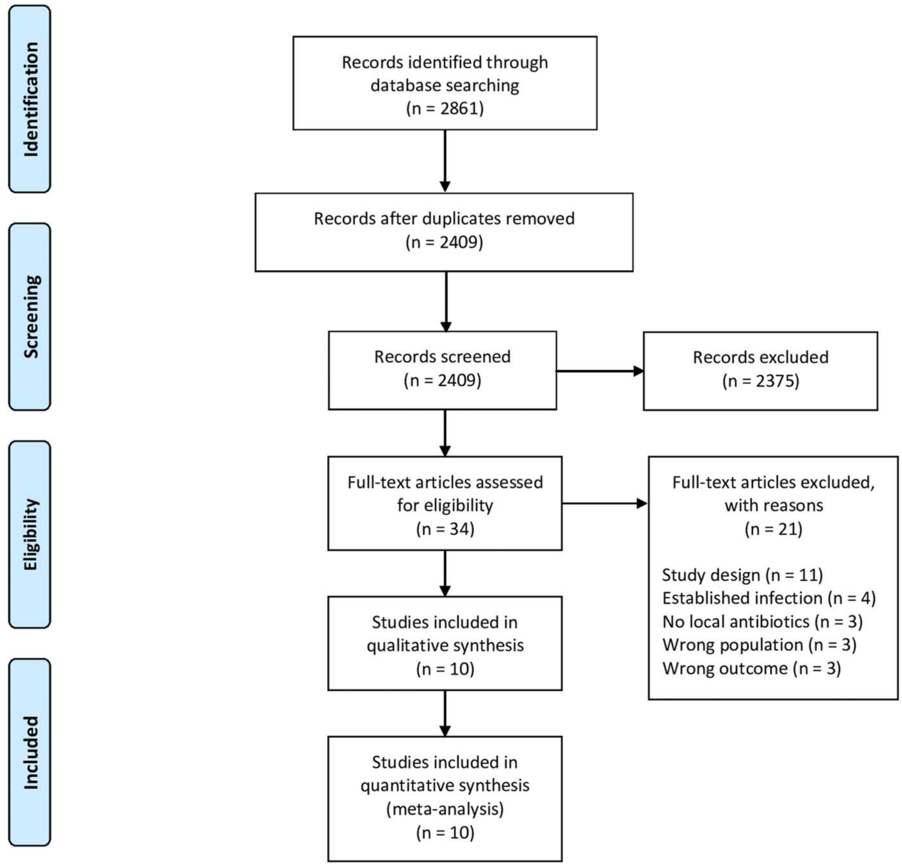

FIGURE 1. PRISMA flow diagram of the study selection process.

approximately 2 times less likely to develop deep infections compared with their counterparts receiving systemic antibiotics.

Total Deep Infections by Fracture Type

The summary estimate for infections in open fractures favored local antibiotics over systemic antibiotics (OR = 0.45;

TABLE 1. Study Characteristics

Author	Year	Study Design	Sample Size	Local Antibiotics	Delivery of Antibiotics	Fracture Type	Fracture Location
Cichos et al[35]	2021	Retrospective cohort	789	Vancomycin	Powder	Closed	Acetabular
Keating et al[27]	1996	Retrospective cohort	78	Tobramycin	Antibiotic beads	Open	Tibia
Lawing et al[28]	2015	Retrospective cohort	351	Tobramycin	Local injection	Open	Upper + lower extremity
O'Neill et al[34]	2011	Retrospective cohort	110	Vancomycin	Powder	Closed	Traumatic spine
Ostermann et al[36]	1995	Retrospective cohort	1085	Tobramycin	Antibiotic beads	Open	Upper + lower extremity
O'Toole et al[42]	2021	RCT	980	Vancomycin	Powder	Open + Closed	Tibia
Owen et al[33]	2017	Retrospective cohort	140	Vancomycin + Tobramycin	Powder	Closed	Acetabular
Qadir et al[30]	2021	Retrospective cohort	583	Vancomycin	Powder	Open + Closed	Tibia + calcaneus
Singh et al[29]	2015	Retrospective cohort	93	Vancomycin	Powder	Open + Closed	Tibia
Vaida et al[31]	2020	Retrospective cohort	434	Vancomycin	Powder	Open	Lower extremity

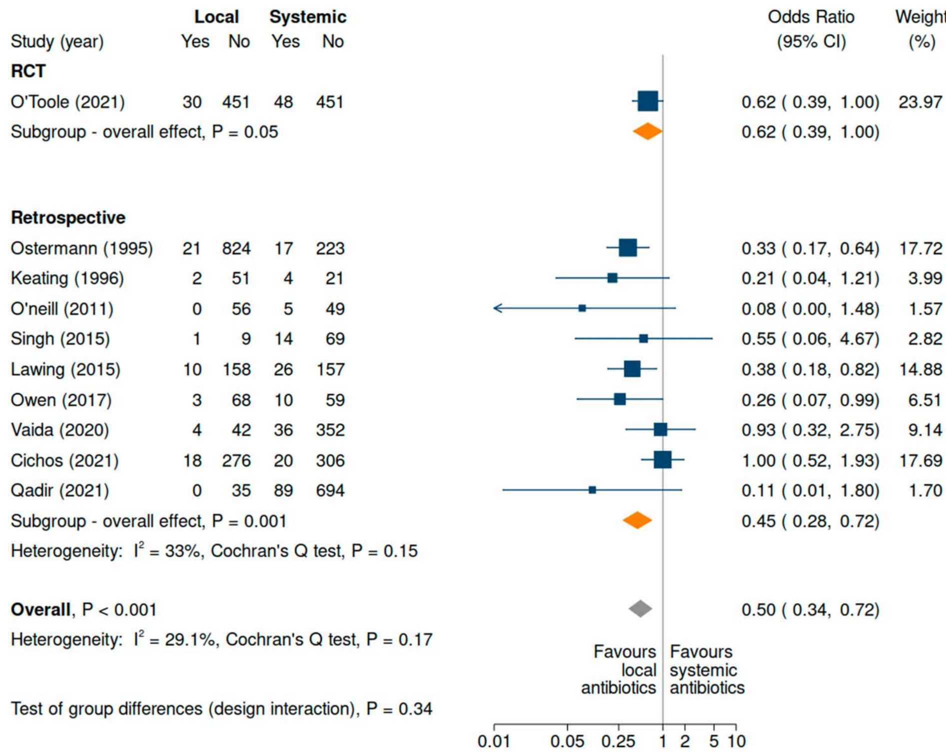

FIGURE 2. Forest plot for deep infections in all fractures. RCT denotes randomized controlled trial. The design interaction test examined the difference in the magnitude of treatment effects comparing RCTs with retrospective studies.

95% CI: 0.31–0.66, $P < 0.001$) (Fig. 3). In closed fractures, this effect on deep infection rate failed to reach statistical significance (OR = 0.59; 95% CI: 0.31–1.12, $P = 0.11$) (see **Figure**, **Supplemental Digital Content 1**, http://links.lww.com/JOT/B839, which demonstrates effect of local antibiotics in closed fractures).

Superficial Infections

There was no statistically significant difference in the summary estimate for superficial infection with or without local antibiotics (OR = 0.59; 95% CI: 0.29–1.17, $P = 0.13$) (see **Figure**, **Supplemental Digital Content 2**, http://links.lww.com/JOT/B840, which demonstrates effect of local antibiotics on superficial infection).

Fracture Location

There was substantial heterogeneity regarding fracture locations (Table 1). There were 840 (18.1%) fractures reported as "Lower Extremity," while 305 (6.6%) were reported as "Upper Extremity" fractures. One study included 110 (2.4%) traumatic spine fractures. There were 789 (17.0%) acetabular fractures, and 49 (1.1%) of fractures involving the pelvis included. There were 70 (1.5%) femur fractures. There were 2128 (45.8%) tibia fractures included, making it the most common fracture location. There were 118 (2.5%) fractures classified as ankle fractures and 231 (5.0%) foot fractures.

Type of Local Antibiotics

Regarding the type of local antibiotics, vancomycin and tobramycin were most commonly used. Six studies applied 1 g of vancomycin powder directly into the wound, with one other study using a combination of vancomycin and tobramycin powder. Three studies used tobramycin alone, either as antibiotic-impregnated beads or by local injection. The results indicate that treatment effects observed in aminoglycoside studies were significantly larger (OR = 0.34; 95% CI: 0.21–0.55, $P < 0.001$) than those observed in vancomycin studies (OR = 0.63; 95% CI: 0.41–0.98, $P = 0.04$) (Fig. 4).

Risk of Bias

Based on the quality assessment of the included randomized controlled trials (RCTs) using RoB 2, the lone RCT included had an overall rating of "Low Risk." The other 9 comparative studies were assessed using the MINORS tool (see **Table**, **Supplemental Digital Content 3**, http://links.lww.com/JOT/B841, comparative study quality assessment). The mean MINORS score across all included studies was 16 (range: 13–20) of 24.

DISCUSSION

Fracture-related infections remain a problem in orthopaedic trauma surgery despite the widespread use of systemic antibiotic prophylaxis.[12,17] This systematic review demonstrated a significantly reduced risk of deep infections in patients who were given additional local antibiotics when all fracture types were pooled. It is worth noting that although a large beneficial effect was found, most included studies were Level III evidence. Future RCTs are required to strengthen the confidence of the present findings.

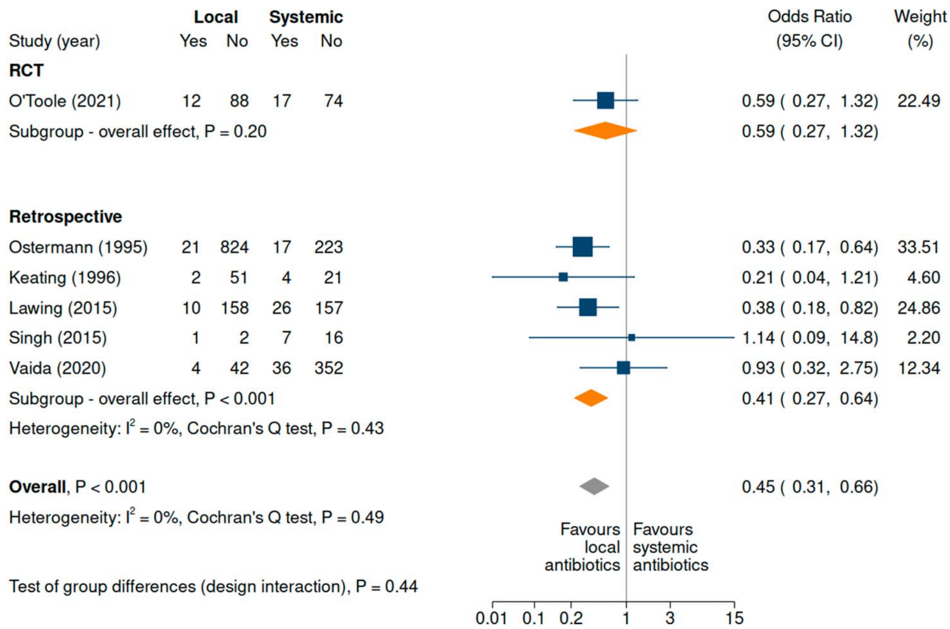

FIGURE 3. Forest plot for deep infections in open fractures. RCT denotes randomized controlled trial. The design interaction test examined the difference in the magnitude of treatment effects comparing RCTs with retrospective studies.

A recent systematic review by Morgenstern et al[2] suggested a large beneficial effect from the addition of local antibiotics in the management of open limb fractures. However, the authors noted that their results should be interpreted with caution as the quality of the included studies was limited. In subsequent years, there have been further cohort studies published investigating the use of local antibiotics in fracture surgery,[30–32,35] including a highly powered RCT by O'Toole et al.[32] Furthermore, the systematic review by Morgenstern et al analyzed the total infection rate as their primary outcome but did not separate superficial and deep infections. There is a lack of reliability in the diagnosis of superficial infections, and they have a relatively lower clinical relevance.[37,38] In comparison, deep infections are more accurately diagnosed and have a greater impact on patient outcomes and cost of treatment.[6,7,38] The present meta-analysis analyzed deep infections as the primary outcome and found that local antibiotics showed a significant beneficial effect in the prevention of deep infections in open fractures. When a superficial infection rate was analyzed as a separate outcome, no significant difference was found with the addition of local antibiotics. In open fractures, deep infections can be caused by the attachment of bacteria to implants and compromised bone and deep tissue, with resultant biofilm formation.[39,40] High concentrations of antibiotics are effective against biofilms,[41] and the use of local antibiotics allows delivery of high concentrations of antibiotics while minimizing the risk of systemic toxicity.[14,42] The most common bacteria encountered in open fracture sites are gram-positive staphylococci and gram-negative rods.[43] Vancomycin has established efficacy against the most common pathogens in patients with orthopaedic trauma, particularly methicillin-resistant *Staphylococcus aureus* and other gram-positive bacteria.[44] Complications or side effects associated with the use of local vancomycin are rare,[45,46] and it has been shown to reduce the costs of care in spinal surgery.[47] Although concerns have been raised over the potential development of vancomycin-resistant organisms, the use of intrawound vancomycin during spine surgery was not associated with the development of any such organisms.[18] Six studies in the included analysis used vancomycin as local antibiotic prophylaxis, and the results showed a significantly decreased risk of infection (OR = 0.63; 95% CI: 0.41–0.98, $P = 0.04$). Interestingly, there was a more robust protective effect seen in studies that used aminoglycosides, such as gentamicin or tobramycin (OR = 0.34; 95% CI: 0.21–0.55, $P < 0.001$). Aminoglycosides have gram-negative coverage, and although they are usually not first-line treatment for staphylococcal infections, they can also be used for this purpose.[43] Their bactericidal activity is concentration dependent, and local administration achieves high concentrations[48] without the same toxicity associated with systemic aminoglycosides.[49] Although there are in vitro studies that have shown that sufficiently high concentrations of aminoglycosides can have a detrimental effect on osteocytes, there are no known reports of clinical adverse effects on these cells.[50] In keeping with previous literature, 5 included studies that reported nonunion rates found no significant differences in patients who received local antibiotics and no study found any negative effect on kidney function[33,35] or any adverse reactions. There are currently 2 major clinical trials ongoing that are investigating the effect of locally applied aminoglycosides in open fractures.[51,52] A recently published survey of current practice and recommendations on antibiotic prophylaxis in open fractures showed that less than 25% of orthopaedic practices reported local antibiotic use in open limb fractures.[17] The present findings suggest that more widespread adoption of local antibiotic prophylaxis may decrease the rates of deep infection after open fractures, without increasing the risk of nonunion or nephrotoxicity.

Unsurprisingly, the effect of local antibiotics was attenuated in closed fractures. Local antibiotics were not

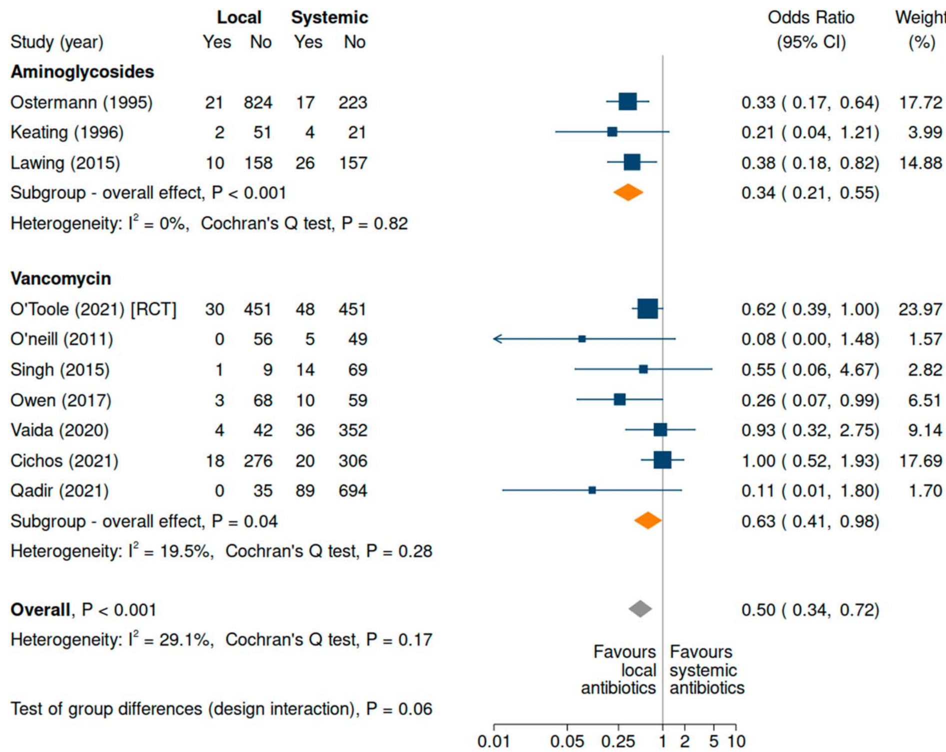

FIGURE 4. Forest plot for deep infections by drug type. RCTs are highlighted within squared brackets.

associated with a significant reduction in deep infections, although the results suggest that there may be a trend toward a beneficial effect (OR = 0.59; 95% CI: 0.31–1.12, *P* = 0.11). Given the relative lack of environmental contamination and lesser soft-tissue injury in comparison with open fractures, the rate of surgical site infections after surgery for closed fractures is predictably lower with the rates of SSI after closed fractures range from 1% to 4%.[53,54] It has been reported that local antibiotics may reduce infection after internal fixation of acetabular fractures[33] and established literature has shown that topical vancomycin is effective at reducing the risk of SSI after spinal surgery.[45] However, in comparison with local antibiotics and open fractures, the evidence is limited. As such, currently there are no published guidelines for the use of local antibiotic prophylaxis in closed fractures. To the best of our knowledge, this is the first meta-analysis that evaluates the effect of local antibiotics in closed fracture surgery. The findings of this study are inconclusive; however, there were only 5 studies included in the analysis, with significant heterogeneity among anatomical fracture locations. Further controlled trials of sufficient statistical power are required to determine whether there is a beneficial effect.

There are several limitations to this study. Among the included studies, there is large variability between study designs, fracture locations, follow-up intervals, and definitions of infection. The fracture locations reported included open tibial fractures, traumatic spinal fractures, and acetabular fractures. Some of the included studies did not specify fracture locations. Different fracture patterns and anatomical locations can result in significantly different rates of infection.[55] A subanalysis based on fracture location was not performed because of large heterogeneity of the included locations. Only 3 studies used an established definition for deep infection, mainly the Centers for Disease Control and Prevention (CDC) guidelines for surgical site infection.[28,30,32] Four other studies defined deep infection as an infection that required irrigation and debridement, which is in keeping with the CDC's definition.[27,29,31,33] However, the CDC's definition for surgical site infections is not exclusively intended for fracture-related infections and has limitations when applied to patients undergoing fracture surgery.[56] Three studies provided incomplete and imprecise definitions for deep infection.[34–36] The issue of variable definitions for infection is not unique to this review because a recent systematic review found that only 2% of fracture management trials reported a recognized definition of infection.[56,57] This systematic review analyzed deep infections as the primary outcome because they are more accurately diagnosed than superficial infections.[38] In regard to follow-up period, 4 included studies reported a minimum follow-up period of less than 6 months.[28,31,34,35] Postoperative infection can present in a subacute or chronic fashion,[58] and it is possible that local antibiotics delay the presentation of infection. However, 9 of the included studies reported a mean follow-up period of greater than 6 months, suggesting a sufficient surveillance timeframe for infection. A further limitation was the lack of data reported by the included studies regarding the timing of local antibiotic administration relative to the time of injury. Multiple studies have demonstrated that the efficacy of systemic antibiotics with open fractures is improved when given earlier after injury occurrence.[59,60] It is unknown whether local antibiotics would have a similar time dependency and whether their added benefit could be influenced by the timing of systemic antibiotic administration after open fracture. This is an area of research that could benefit from future studies.

CONCLUSIONS

In summary, this meta-analysis found a significant risk reduction for postoperative deep infection after fracture surgery when local antibiotic prophylaxis was used. In regard to fracture type, this beneficial effect was found for open fractures but did not persist in closed fractures. These findings suggest that the addition of local antibiotics in fracture surgery, particularly in open fractures, may be a potential cost-effective and low-risk intervention that may reduce deep infections; however, further high-powered Level I studies are needed to corroborate this effect.

REFERENCES

1. Cook GE, Markel DC, Ren W, et al. Infection in orthopaedics. *J Orthop Trauma*. 2015;29(suppl 12):S19–S23.
2. Morgenstern M, Vallejo A, Mcnally MA, et al. The effect of local antibiotic prophylaxis when treating open limb fractures a systematic review and meta-analysis. *Bone Joint Res*. 2018;7:447–456.
3. Tribble DR, Conger NG, Fraser S, et al. Infection-associated clinical outcomes in hospitalized medical evacuees after traumatic injury: trauma infectious disease outcome study. *J Trauma*. 2011;71(suppl 1):S33–S42.
4. Metsemakers WJ, Smeets B, Nijs S, et al. Infection after fracture fixation of the tibia: analysis of healthcare utilization and related costs. *Injury*. 2017;48:1204–1210.
5. Lerner RK, Esterhai JL, Polomano RC, et al. Quality of life assessment of patients with posttraumatic fracture nonunion, chronic refractory osteomyelitis, and lower-extremity amputation. *Clin Orthop Relat Res*. 1993; 295:28–36.
6. Partanen J, Syrjala H, Vahanikkila H, et al. Impact of deep infection after hip fracture surgery on function and mortality. *J Hosp Infect*. 2006;62: 44–49.
7. Edwards C, Counsell A, Boulton C, et al. Early infection after hip fracture surgery: risk factors, costs and outcome. *J Bone Joint Surg. Br*. 2008;90:770–777.
8. Harris AM, Althausen PL, Kellam J, et al; Lower Extremity Assessment Project LEAP Study Group. Complications following limb-threatening lower extremity trauma. *J Orthop Trauma*. 2009;23:1–6.
9. Gillespie WJ, Walenkamp GH. Antibiotic prophylaxis for surgery for proximal femoral and other closed long bone fractures. *Cochrane database Syst Rev*. 2010;17:CD000244.
10. Papakostidis C, Kanakaris NK, Pretel J, et al. Prevalence of complications of open tibial shaft fractures stratified as per the Gustilo-Anderson classification. *Injury*. 2011;42:1408–1415.
11. Boxma H, Broekhuizen T, Patka P, et al. Randomised controlled trial of single-dose antibiotic prophylaxis in surgical treatment of closed fractures: the Dutch trauma trial. *Lancet*. 1996;347:1133–1137.
12. Gosselin RA, Roberts I, Gillespie WJ. Antibiotics for preventing infection in open limb fractures. *Cochrane database Syst Rev*. 2004;4: CD003764.
13. O'Toole Rv, Joshi M, Carlini AR, et al; METRC. Local antibiotic therapy to reduce infection after operative treatment of fractures at high risk of infection: a multicenter, randomized, controlled trial (VANCO study). *J Orthop Trauma*. 2017;31:S18–S24.
14. ter Boo GJA, Grijpma DW, Moriarty TF, et al. Antimicrobial delivery systems for local infection prophylaxis in orthopedic- and trauma surgery. *Biomaterials*. 2015;52:113–125.
15. Craig J, Fuchs T, Jenks M, et al. Systematic review and meta-analysis of the additional benefit of local prophylactic antibiotic therapy for infection rates in open tibia fractures treated with intramedullary nailing. *Int Orthop*. 2014;38:1025–1030.
16. Haggard W, Nana A. Is there a role for a combination of local and systemic antibiotic delivery systems to treat open fractures with overlying contaminated wounds? *Int Consens Meet*. 2018;46. doi: 10.1016/j.ocl.2015.06.010
17. Chang Y, Bhandari M, Zhu KL, et al. Antibiotic prophylaxis in the management of open fractures: a systematic survey of current practice and recommendations. *JBJS Rev*. 2019;7:e1.
18. Chotai S, Wright PW, Hale AT, et al. Does intrawound vancomycin application during spine surgery create vancomycin-resistant organism? *Neurosurgery*. 2017;80:746–753.
19. Norton TD, Skeete F, Dubrovskaya Y, et al. Orthopedic surgical site infections: analysis of causative bacteria and implications for antibiotic stewardship. *Am J Orthop*. 2014;43:E89–E92.
20. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane, 2022. Available at www.training.cochrane.org/handbook. Accessed August 23, 2022.
21. Moher D, Liberati A, Tetzlaff J, et al; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8:336–341.
22. Sterne AC, Savović J, Page MJ, et al. Revised Cochrane risk of bias tool for randomized trials (RoB 2.0). *BMJ*. 2019;366:l4898.
23. Borenstein M, Hedges Lv, Higgins JPT, et al. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synthesis Methods*. 2010;1:97–111.
24. Pereira Tv, Patsopoulos NA, Salanti G, et al. Critical interpretation of Cochran's Q test depends on power and prior assumptions about heterogeneity. *Res Synthesis Methods*. 2010;1:149–161.
25. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558.
26. Inthout J, Ioannidis JPA, Rovers MM, et al. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open*. 2016;6:10247.
27. Keating JF, Blachut PA, O'Brien PJ, et al. Reamed nailing of open tibial fractures: does the antibiotic bead pouch reduce the deep infection rate? *J Orthop Trauma*. 1996;10:298–303.
28. Lawing CR, Lin FC, Dahners LE. Local injection of aminoglycosides for prophylaxis against infection in open fractures. *J Bone Joint Surg Am*. 2015;97:1844–1851.
29. Singh K, Bauer JM, LaChaud GY, et al. Surgical site infection in high-energy peri-articular tibia fractures with intra-wound vancomycin powder: a retrospective pilot study. *J Orthop Traumatol*. 2015;16: 287–291.
30. Qadir R, Costales T, Coale M, et al. Vancomycin powder use in fractures at high risk of surgical site infection. *J Orthop Trauma*. 2021;35: 23–28.
31. Vaida J, Conti ADB, Ray JJ, et al. Evaluating the efficacy of topical vancomycin powder in the treatment of open lower extremity fractures. *Trauma*. 2020;24. doi: 10.1177/1460408620978142
32. Major Extremity Trauma Research Consortium METRC, O'Toole RV, Joshi M, Murray CK, et al. Effect of intrawound vancomycin powder in operatively treated high-risk tibia fractures: a randomized clinical trial. *JAMA Surg*. 2021;156:e207259.
33. Owen MT, Keener EM, Hyde ZB, et al. Intraoperative topical antibiotics for infection prophylaxis in pelvic and acetabular surgery. *J Orthop Trauma*. 2017;31:589–594.
34. O'Neill KR, Smith JG, Abtahi AM, et al. Reduced surgical site infections in patients undergoing posterior spinal stabilization of traumatic injuries using vancomycin powder. *Spine J*. 2011;11:641–646.
35. Cichos KH, Spitler CA, Quade JH, et al. Intrawound antibiotic powder in acetabular fracture open reduction internal fixation does not reduce surgical site infections. *J Orthop Trauma*. 2021;35:198–204.
36. Ostermann PA, Seligson D, Henry SL. Local antibiotic therapy for severe open fractures: a review of 1085 consecutive cases. *J Bone Joint Surg Br*. 1995;77:93–97.
37. Bonnevialle P, Bonnomet F, Philippe R, et al; SOFCOT. Early surgical site infection in adult appendicular skeleton trauma surgery: a multicenter prospective series. *Orthop Traumatol Surg Res*. 2012;98: 684–689.
38. Henriksen NA, Meyhoff CS, Wetterslev J, et al; PROXI Trial Group. Clinical relevance of surgical site infection as defined by the criteria of the Centers for Disease Control and Prevention. *J Hosp Infect*. 2010;75: 173–177.

39. Metsemakers WJ, Kuehl R, Moriarty TF, et al. Infection after fracture fixation: current surgical and microbiological concepts. *Injury*. 2018;49:511–522.
40. Morgenstern M, Post V, Erichsen C, et al. Biofilm formation increases treatment failure in Staphylococcus epidermidis device-related osteomyelitis of the lower extremity in human patients. *J Orthop Res*. 2016;34:1905–1913.
41. Castaneda P, McLaren A, Tavaziva G, et al. Biofilm antimicrobial susceptibility increases with antimicrobial exposure time. *Clin Orthop Relat Res*. 2016;474:1659–1664.
42. O'Toole Rv, Degani Y, Carlini AR, et al; METRC. Systemic absorption and nephrotoxicity associated with topical vancomycin powder for fracture surgery. *J Orthop Trauma*. 2021;35:29–34.
43. Carsenti-Etesse H, Doyon F, Desplaces N, et al. Epidemiology of bacterial infection during management of open leg fractures. *Eur J Clin Microbiol Infect Dis*. 1999;18:315–323.
44. Torbert JT, Joshi M, Moraff A, et al. Current bacterial speciation and antibiotic resistance in deep infections after operative fixation of fractures. *J Orthop Trauma*. 2015;29:7–17.
45. Chiang HY, Herwaldt LA, Blevins AE, et al. Effectiveness of local vancomycin powder to decrease surgical site infections: a meta-analysis. *Spine J*. 2014;14:397–407.
46. Bakhsheshian J, Dahdaleh NS, Lam SK, et al. The use of vancomycin powder in modern spine surgery: systematic review and meta-analysis of the clinical evidence. *World Neurosurg.* 2015;83:816–823.
47. Godil SS, Parker SL, O'Neill KR, et al. Comparative effectiveness and cost-benefit analysis of local application of vancomycin powder in posterior spinal fusion for spine trauma: clinical article. *J Neurosurg Spine*. 2013;19:331–335.
48. Agence francaise de securite sanitaire des produits de sante. Update on good use of injectable aminoglycosides, gentamycin, tobramycin, netilmycin, amikacin. Pharmacological properties, indications, dosage, and mode of administration, treatment monitoring. *Med Maladies Infect*. 2012;42:301–308.
49. Wahl P, Livio F, Jacobi M, et al. Systemic exposure to tobramycin after local antibiotic treatment with calcium sulphate as carrier material. *Archives Orthop Trauma Surg*. 2011;131:657–662.
50. Bistolfi A, Massazza G, Verné E, et al. Antibiotic-loaded cement in orthopedic surgery: a review. *ISRN Orthop*. 2011;2011:290851–290858.
51. Major Extremity Trauma Research Consortium. *Topical Antibiotic Therapy to Reduce Infection after Operative Treatment of Fractures at High Risk of Infection: TOBRA—A Multicenter Randomized Controlled Trial*. ClinicalTrials.gov NCT04597008.
52. Arun Aneja, University of Kentucky. *Does Prophylactic Local Tobramycin Injection Lower Open Fracture Infection Rates?*. ClinicalTrials.gov NCT04964947.
53. Guideline for prevention of surgical site infection. *Bull Am Coll Surg*. 2000;85:23–29.
54. Malik MHA, Harwood P, Diggle P, et al. Factors affecting rates of infection and nonunion in intramedullary nailing. *J Bone Joint Surg Br*. 2004;86:556–560.
55. Patzakis MJ, Wilkins J. Factors influencing infection rate in open fracture wounds. *Clin Orthop Relat Res*. 1989;243:36–40.
56. Metsemakers WJ, Morgenstern M, McNally MA, et al. Fracture-related infection: a consensus on definition from an international expert group. *Injury*. 2018;49:505–510.
57. Metsemakers WJ, Kortram K, Morgenstern M, et al. Definition of infection after fracture fixation: a systematic review of randomized controlled trials to evaluate current practice. *Injury*. 2018;49:497–504.
58. Zimmerli W. Clinical presentation and treatment of orthopaedic implant-associated infection. *J Intern Med*. 2014;276:111–119.
59. Roddy E, Patterson JT, Kandemir U. Delay of antibiotic administration greater than 2 hours predicts surgical site infection in open fractures. *Injury*. 2020;51:1999–2003.
60. Lack WD, Karunakar MA, Angerame MR, et al. Type III open tibia fractures: immediate antibiotic prophylaxis minimizes infection. *J Orthop Trauma*. 2015;29:1–6.