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TRAUMA

# Does cumulative topical antibiotic powder use increase the risk of drug induced acute kidney injury in fracture patients?

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## Aims

There is increasing evidence to support the use of topical antibiotics to prevent surgical site infections. Although previous research suggests a minimal nephrotoxic risk with a single dose of vancomycin powder, fracture patients often require multiple procedures and receive additional doses of topical antibiotics. We aimed to determine if cumulative doses of intrawound vancomycin or tobramycin powder for infection prophylaxis increased the risk of drug-induced acute kidney injury (AKI) among fracture patients.

## Methods

This cohort study was a secondary analysis of single-centre Program of Randomized Trials to Evaluate Pre-operative Antiseptic Skin Solutions in Orthopaedic Trauma (PREP-IT) trial data. We included patients with a surgically treated appendicular fracture. The primary outcome was drug-induced AKI. The odds of AKI per gram of vancomycin or tobramycin powder were calculated using Bayesian regression models, which adjusted for measured confounders and accounted for the interactive effects of vancomycin and tobramycin.

## Results

Of the 782 included patients (mean age 48 years (SD 20); 59% male), 83% (n = 648) received at least one vancomycin dose (cumulative range 1 to 12 g). Overall, 45% of the sample received at least one tobramycin dose (cumulative range 1.2 to 9.6 g). Drug-induced AKI occurred in ten patients (1.2%). No association was found between the cumulative dose of vancomycin and drug-induced AKI (odds ratio (OR) 1.08 (95% credible interval (CrI) 0.52 to 2.14)). Additional doses of tobramycin were associated with a three-fold increase in the adjusted odds of drug-induced AKI (OR 3.66 (95% CrI 1.71 to 8.49)). Specifically, the risk of drug-induced AKI rose substantially after 4.8 g of tobramycin powder (7.5% (95% CrI 1.0 to 35.3)).

## Conclusion

Cumulative doses of vancomycin were not associated with an increased risk of drug-induced AKI among fracture patients. While the risk of drug-induced AKI remains less than 4% with three or fewer 1.2 g tobramycin doses, the estimated risk increases substantially to 8% after four cumulative doses.

**Level of evidence: Therapeutic Level III**

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## Introduction

Mounting evidence suggests that topical antibiotic powder placed in the surgical incision effectively prevents surgical site infections after fracture fixation surgery.[1-3] In contrast to intravenous antibiotics, locally applied antibiotics do not require sufficiently high systemic concentrations or

adequate blood supply to reach the target site. Thus, topical antibiotics are believed to deliver higher local concentrations to the region of interest without unnecessary systemic exposure.

Previous research suggests a minimal risk of an acute kidney injury (AKI) with a single 1,000 mg dose of intrawound vancomycin powder.[4] However, polytrauma patients often have multiple fractures treated with multiple surgeries. Subsequent doses of local antibiotics, or combinations of local antibiotics, can be given with each additional procedure.[5] It is unknown if this accumulation of local antibiotic doses increases the risk of AKI in patients with fractures. As such, the study aimed to determine if cumulative doses of intrawound vancomycin or tobramycin powder prophylaxis were associated with an increased risk of AKI among patients with an operatively treated fracture.

## Methods

**Study design.** This observational cohort study was a post-hoc secondary analysis of single-centre data from the PREP-IT trials.[6] In brief, the PREP-IT trials compare common preoperative antiseptic solutions to reduce surgical site infections in patients with operatively treated fractures of the limbs or pelvis. Data on topical antibiotic powder use were recorded as part of routine PREP-IT trial data collection. These data were combined with serum creatinine measures obtained from the hospital's medical records. The study had institutional review board approval from Advarra Inc, and all study participants provided written informed consent.

**Study participants.** We included patients admitted to the study centre, from November 2018 through July 2020, with an eligible fracture receiving surgical treatment. Eligible fractures included 1) open fractures of the limbs or pelvis, or 2) closed fractures of the lower limb or pelvis. We excluded patients with only a hand fracture. The number of eligible closed fracture patients was limited using a 1:1 random sampling strategy to reduce the overall data burden on the research staff. Surgeries that occurred after the patient had met our criteria for the primary outcome were not included towards their cumulative dose of topical antibiotics.

**Study exposures.** The study had two primary exposures of interest: intrawound vancomycin powder and intrawound tobramycin powder. Vancomycin powder was available in a 1,000 mg vial. Powdered tobramycin was available in a 1,200 mg vial. Both treatments were placed directly in the surgical wound at the time of surgery and could be used in tandem, at the discretion of the treating surgeon. All patients, regardless of receiving topical antibiotic powder, received systemic prophylactic perioperative antibiotics intravenously as well as other common infection prevention measures, such as preoperative antiseptic cleaning. In addition to our primary exposures, we recorded the cumulative dose and type of antibiotic beads received, and whether the patient received systemic vancomycin or systemic gentamicin. Our statistical models adjusted for these covariates.

**Table I.** Patient characteristics (n = 782).

| Characteristic | Value |
|---|---|
| **Mean age, yrs (SD)** | 48 (20) |
| **Male sex, n (%)** | 461 (59) |
| **Race, n (%)** | |
| White | 508 (65) |
| African-American | 253 (32) |
| Asian | 8 (1) |
| American Indian or Alaska Native | 3 (0) |
| Native Hawaiian or Other Pacific Islander | 4 (1) |
| Prefer not to answer | 5 (1) |
| **Median injury severity score (IQR)** | 9 (1 to 14) |
| **Renal disease, n (%)** | 13 (2) |
| **Liver disease, n (%)** | 6 (1) |
| **Alcohol abuse, n (%)** | 48 (6) |
| **Drug abuse, n (%)** | 95 (12) |
| **Fracture location, n (%)** | |
| Humerus | 37 (5) |
| Radius or ulna | 63 (8) |
| Femur | 227 (29) |
| Tibia | 319 (41) |
| Pelvis | 78 (10) |
| Foot | 57 (7) |
| **Open fracture, n (%)** | 348 (45) |
| **Mean number of surgeries (range)** | 2.2 (1 to 12) |
| **Antibiotic beads, n (%)** | 26 (3) |
| **Intravenous antibiotics, n (%)** | |
| Cefazolin only | 725 (93) |
| Cefazolin and vancomycin | 28 (4) |
| Cefazolin and gentamicin | 24 (3) |
| Cefazolin, vancomycin, and gentamicin | 5 (1) |

IQR, interquartile range; SD, standard deviation.

**Study outcome.** The primary outcome was a drug-induced AKI. The outcome was defined using the International Serious Adverse Event Consortium's recommendation of a two-fold or more rise in serum creatinine between 24 hours and seven days after each topical antibiotic administration.[7] Serum creatinine was measured before the surgery per protocol at our institution and served as a baseline measure, and then was typically measured daily for the remainder of the inpatient stay, up to seven days post-surgery. This AKI outcome definition is consistent with the Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) definitions of stage 2 or higher AKI.[8,9] We also measured AKI based on the AKIN criteria.[8] Additionally, the classification uses serum creatinine to distinguish AKI as stage 1 (1.5× to 1.9× increase), stage 2 (2.0× to 2.9× increase), or stage 3 (3.0× or greater increase).

**Statistical analysis.** We described the demographic and clinical characteristics of the patients using count with

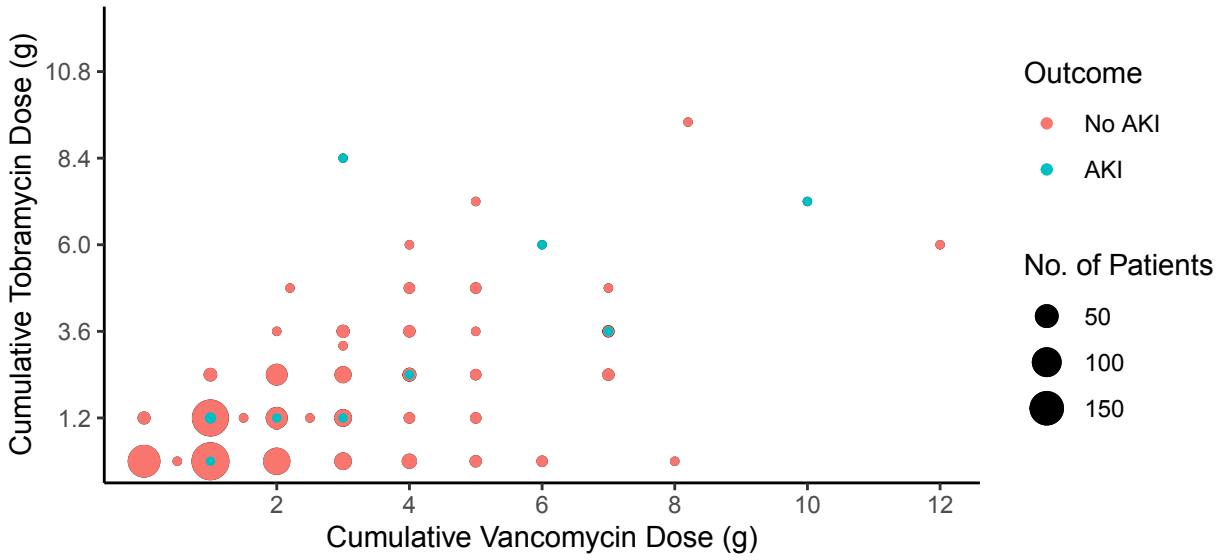


**Fig. 1**

Distribution of the intrawound vancomycin powder and intrawound tobramycin powder cumulative doses. The dot size is proportional to the number of patients it represents. Drug-induced acute kidney injury (AKI) is indicated by the green dots.

proportions and means with standard deviations (SDs) or medians with interquartile ranges (IQRs), depending on the distribution of the data. To examine the association between the cumulative dose of intrawound antibiotic powder and drug-induced AKI, we used a Bayesian regression model with a Bernoulli distribution. The model included indicators for vancomycin and tobramycin plus an interaction term to account for possible synergistic effects. The model assumed a very weak prior (mean 0 (SD 10)) with a normal distribution for all covariates, and was conditioned on patient age, sex, Injury Severity Score, the cumulative antibiotic bead dose, and whether intravenous (IV) vancomycin or gentamicin was given. While the number of surgical procedures was correlated with the number of intrawound vancomycin powder doses (ρ = 0.54) and the number of tobramycin powder doses (ρ = 0.47), its inclusion in the model did not qualitatively change our parameter estimates. As such, the number of surgical procedures covariate was not included in the final model. We used multiple imputations to impute missing covariate data.[10] We report the conditional odds of drug-induced AKI per gram of topical powder with 95% credible intervals (CrIs). The model assumes a baseline risk of drug-induced kidney injury within the study population. The estimated parameters represent the marginal change in risk with additional doses of intrawound antibiotic powder. All analyses were performed using R v. 4.0.2 (R Foundation for Statistical Computing, Austria).

## Results

The study included 782 patients who sustained a qualifying fracture and were enrolled in the PREP-IT trials at the study location between November 2018 and July 2020. The mean age of the cohort was 48 years (SD 20), and 59% (n = 461) were male (Table I). The median Injury Severity Score was 9 (IQR 1 to 14). Most patients had either a tibia (41%; n = 319) or femur (29%; n = 227) fracture, and 45% (n = 348) of the fractures were open. Of the included patients, 648 (83%) received at least one vancomycin dose, with the cumulative vancomycin dose per patient ranging from 1 g to 12 g (Figure 1). Overall, 45% (n = 350) of the sample received at least one tobramycin dose, and the cumulative tobramycin dose varied from 1.2 g to 9.6 g; 16% of the sample (n = 129) did not receive intrawound vancomycin or tobramycin; and 3% of the patients (n = 26) also received antibiotic beads mixed with vancomycin and tobramycin. The median preoperative serum creatinine was 0.80 mg/dL (IQR 0.67 to 0.97).

Ten patients (1.2%) were classified as having drug-induced AKI. In total, 21 patients (2.7%) had stage 1 AKI, seven patients (0.9%) had stage 2 AKI, and three patients (0.4%) had stage 3 AKI. The overall risk of AKI was 4.0% (95% confidence interval (CI) 2.8% to 5.6%).

After controlling for patient age, sex, injury severity, and other prophylactic antibiotics, we found no evidence of an association between cumulative doses of intrawound vancomycin powder and drug-induced AKI (odds ratio (OR) 1.08 (95% CrI 0.52 to 2.14)) (Figure 2). Similarly, our model suggests no synergistic risk of combining cumulative doses of vancomycin and tobramycin powder (OR 0.91 (95% CrI 0.79 to 1.03)). However, our data suggest that each additional gram of intrawound tobramycin powder is associated with a more than three-fold increase in the odds of drug-induced AKI (OR 3.66 (95% CrI 1.71 to 8.49)). Given the low baseline risk of this

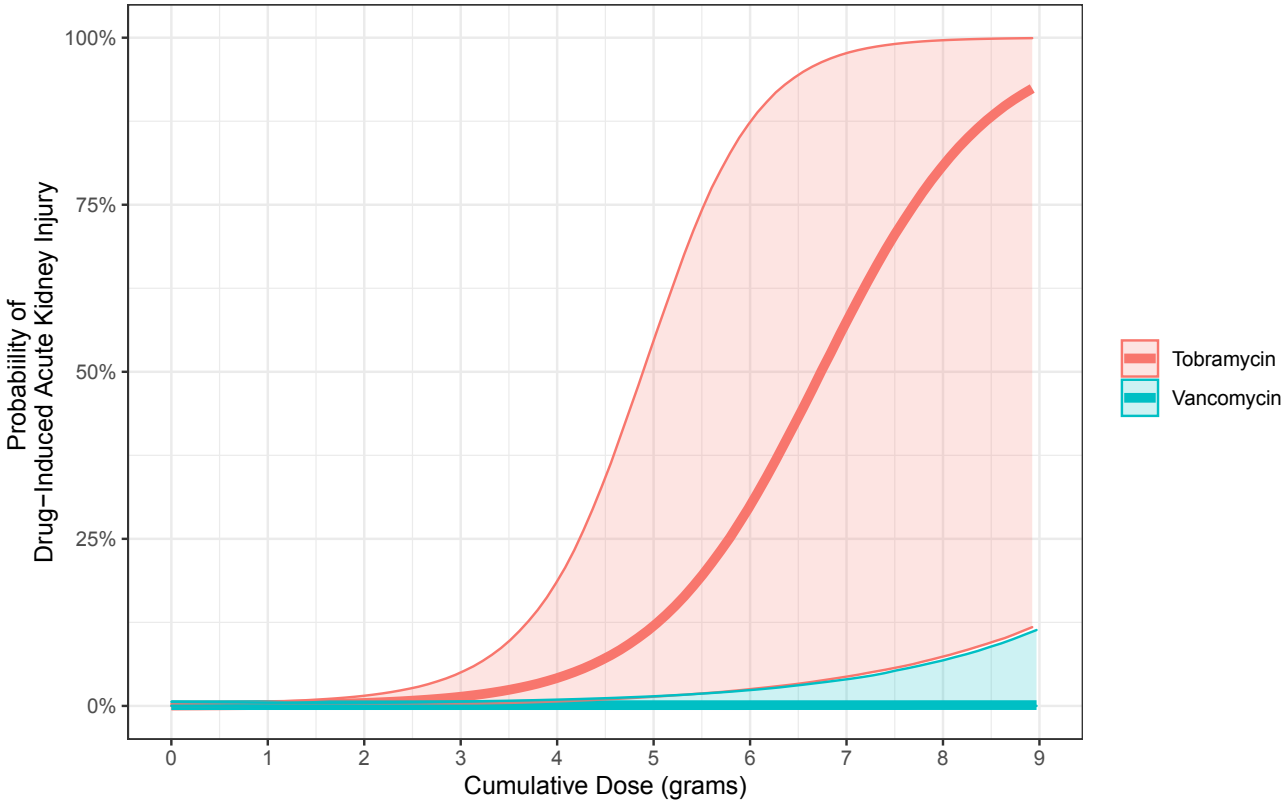


**Fig. 2**

Association of intrawound vancomycin powder and intrawound tobramycin powder cumulative doses with drug-induced acute kidney injury. The estimates were derived using Bayesian modelling conditioned on patient age, sex, and injury severity, and accounted for potential interactive effects between the two antibiotics.

outcome, the probability of drug-induced AKI with up to three doses (3.6 g) remains relatively low at 2.5% (95% CrI 0.5 to 10.6). The probability of acute drug-induced kidney injury climbs thereafter, increasing to a 7.5% risk (95% CrI 1.0% to 35.2%) with four cumulative doses (4.8 g) and a 33.8% risk (95% CrI 2.7% to 88.0%) after five cumulative doses (6.0 g).

Figure 3 presents the daily serum creatinine values relative to the preoperative measures seven days after surgery. Of the ten patients who met the drug-induced AKI criteria, four patients were still reporting a two-fold rise in serum creatinine one week after surgery.

## Discussion

The findings suggest cumulative doses of intrawound vancomycin powder do not increase the risk of drug-induced AKI among patients with surgically treated fractures. Each cumulative dose of intrawound tobramycin powder can triple the odds of drug-induced AKI in this patient population. Although the risk of drug-induced AKI remains less than 4% with three or fewer 1.2 g doses of tobramycin, the risk increases substantially to 8% after four cumulative doses and to 34% with five cumulative doses. The clinical importance of these findings is unclear, as our outcome measure does not imply permanent disability and in many cases may just be transient elevations of creatine.

Few previous studies have investigated the association between cumulative doses of topical antibiotics and AKI. In an observational study of 534 surgical patients, Blackman et al[5] estimated that each additional gram of topical vancomycin increased the odds of AKI (OR 1.51 (95% CI 1.13 to 2.03)) but found no association between topical tobramycin powder and acute kidney injury (OR 0.89 (95% CI 0.40 to 1.92)). Although the study included orthopaedic patients, the sample primarily received nonorthopaedic treatments. In addition, the study used a more sensitive definition of AKI, including those who met the stage 1 criteria, which likely accounts for the contrasting results.

The risk of drug-induced AKI from higher concentrations and longer durations of systemic antibiotics is well established.[11,12] Current evidence suggests that topical antibiotics bear a much lower risk of AKI risks.[4,13-15] In a recent cohort of 58 fracture patients who received a single 1,000 mg dose of intraoperative vancomycin powder,[4] blood samples were obtained six to eight hours after surgery, and vancomycin levels were measured.

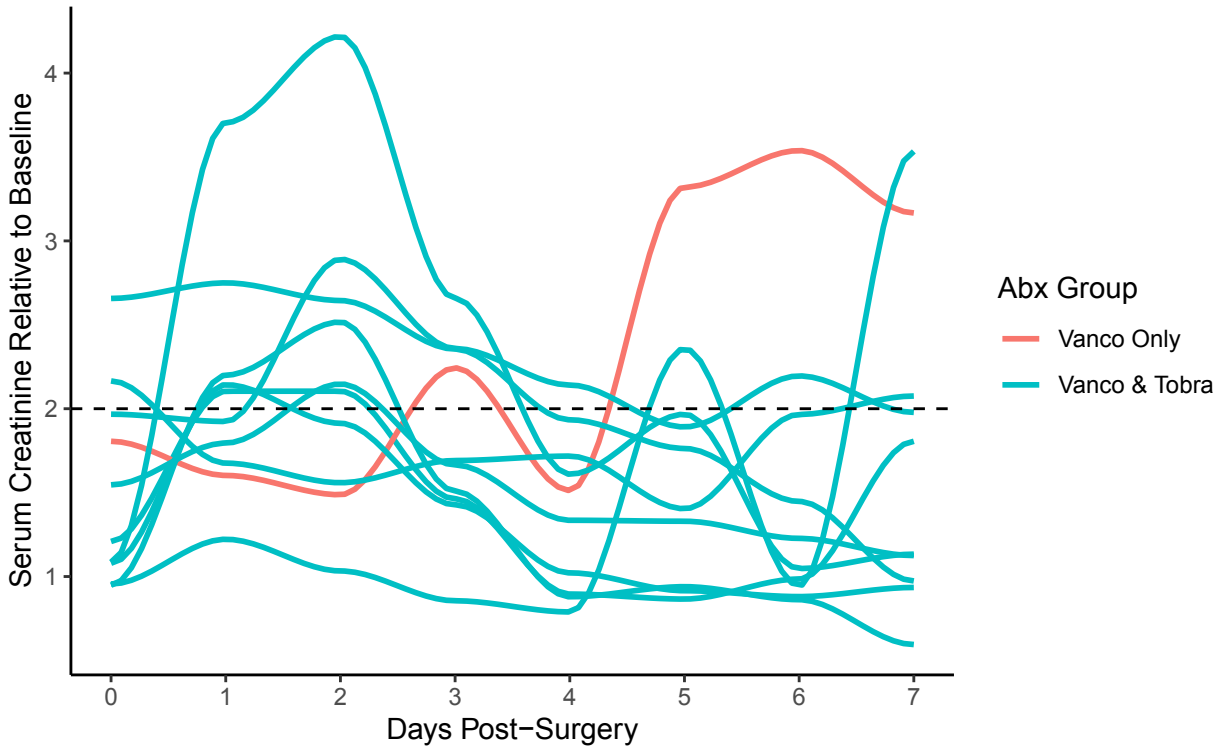


**Fig. 3**

Daily serum creatinine values relative to baseline in patients with drug-induced kidney injury. The dashed line indicates the threshold for drug induced acute kidney injury.

The vancomycin levels in all patients remained within or below the recommended therapeutic levels of vancomycin, and correlated with their IV antibiotic regimen. In addition, three studies of single intrawound vancomycin doses in spine surgery patients similarly reported no evidence of nephrotoxicity.[13,15,16] These data support the hypothesis of minimal systemic absorption from single doses of topical antibiotics and, therefore, reduce the plausibility of drug-induced AKI.[12]

Optimal dosing for patients can be defined as dosing that produces the desired pharmacological effect while avoiding or minimizing toxicities, and remains a fundamental objective of medication therapy management.[17] A growing literature recognizes the consequences of imprecise dosing on public health related to both cost and adverse outcomes.[14,18] Unfortunately, optimal dosing guidance for topical antibiotics to prevent surgical site infections in fracture patients is lacking. This study provides much-needed data on the dose-exposure risk, particularly of intrawound tobramycin powder, critical to the development of optimal dosing recommendations.

The study had several limitations. First, AKI is a complex disorder with no singular definition.[19] However, our definition of drug-induced AKI aligns with the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) Classification definition and AKIN Stage 2 or Stage 3 criteria.[8,20] Second, our serum creatinine was not prospectively collected, and the duration of measurements varied within the sample. However, we assume that patients presenting with symptoms consistent with AKI would have more serum creatinine measurements, providing specificity on the primary outcome. The low event rate limits the statistical power of our analysis. Very few patients had more than four doses of each antibiotic powder, adding uncertainty to our risk estimates at the higher cumulative doses. We encourage additional studies and meta-analyses on this important clinical question to increase the precision of these estimates.[21]

Cumulative doses of intrawound antibiotic powder are correlated with many known AKI risk factors, such as more severe injuries, more surgeries, and exposure to other conditions, medications, and tests.[5] Although we used advanced modelling to standardize the sample, we cannot rule out residual confounding that might drive the observed effects. The occurrence of AKI after more cumulative doses of intrawound tobramycin powder, and not intrawound vancomycin powder, might be explained by the pharmacokinetic properties of the drugs. The typical topical vancomycin dose of 1 g is similar to half the daily dose of IV vancomycin. In comparison, the topical tobramycin dose of 1.2 g is approximately three to four times the daily dose of IV tobramycin.

The evidence to support the use of topical antibiotics to prevent surgical site infections in fracture patients

continues to build.[2-4] Yet, some concern regarding nephrotoxicity from high-dose topical antibiotics in multiple surgeries persists. The results of this study suggest that, among patients with fractures, cumulative doses of local vancomycin powder do not increase the drug-induced AKI. Further, the risk of drug-induced AKI remains less than 3% when patients receive 3.6 g or less of intrawound tobramycin powder. However, clinicians should be cognizant that the risk of drug-induced AKI substantially increases with or more doses of intrawound tobramycin powder. Surgeons should limit the cumulative exposure of intrawound tobramycin powder in patients requiring multiple surgical procedures.

## Take home message

- To our knowledge, this is the first study to investigate the acute kidney injury (AKI) risks associated with cumulative doses of topical antibiotics in fracture patients.
- Based on our data, cumulative doses of intrawound vancomycin powder did not increase the risk of drug-induced AKI in surgically treated fracture patients.
- However, cumulative doses of intrawound tobramycin powder may substantially increase AKI risk.

## References


1. **O'Toole RV**, **Joshi M**, **Carlini AR**, **et al**. Effect of intrawound vancomycin powder in operatively treated high-risk tibia fractures: a randomized clinical trial. *JAMA Surg*. 2021;156(5):e207259.
2. **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(1):23–28.
3. **Qadir R**, **Costales T**, **Coale M**, **Zerhusen T**, **Joshi M**, **O'Toole RV**. Topical vancomycin powder decreases the proportion of Staphylococcus aureus found in culture of surgical site infections in operatively treated fractures. *J Orthop Trauma*. 2021;35(1):17–22.
4. **O'Toole RV**, **Degani Y**, **Carlini AR**, **et al**. Systemic absorption and nephrotoxicity associated with topical vancomycin powder for fracture surgery. *J Orthop Trauma*. 2021;35(1):29–34.
5. **Blackman AL**, **Joshi M**, **Doub J**, **et al**. Evaluation of intraoperative topical vancomycin and the incidence of acute kidney injury. *Surg Infect (Larchmt)*. 2021;22(8):810–817.
6. **Slobogean GP**, **Sprague S**, **Wells J**, **et al**. Effectiveness of iodophor vs chlorhexidine solutions for surgical site infections and unplanned reoperations for patients who underwent fracture repair: the PREP-IT Master Protocol. *JAMA Netw Open*. 2020;3(4):e202215.
7. **Mehta RL**, **Awdishu L**, **Davenport A**, **et al**. Phenotype standardization for drug-induced kidney disease. *Kidney Int*. 2015;88(2):226–234.
8. **Mehta RL**, **Kellum JA**, **Shah SV**, **et al**. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11(2):R31.
9. **Khwaja A**. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120(4):c179-84.
10. **van BS**, **Groothuis-Oudshoorn K**. Mice: multivariate imputation by chained equations in R. *J Stat Softw*. 2010;1–68.
11. **Schentag JJ**, **Cerra FB**, **Plaut ME**. Clinical and pharmacokinetic characteristics of aminoglycoside nephrotoxicity in 201 critically ill patients. *Antimicrob Agents Chemother*. 1982;21(5):721–726.
12. **Pannu N**, **Nadim MK**. An overview of drug-induced acute kidney injury. *Crit Care Med*. 2008;36(4 Suppl):S216-23.
13. **Sweet FA**, **Roh M**, **Sliva C**. Intrawound application of vancomycin for prophylaxis in instrumented thoracolumbar fusions: efficacy, drug levels, and patient outcomes. *Spine (Phila Pa 1976)*. 2011;36(24):2084–2088.
14. **Agrawal S**, **Heiss MS**, **Fenter RB**, **et al**. Impact of CYP2C9-interacting drugs on warfarin pharmacogenomics. *Clin Transl Sci*. 2020;13(5):941–949.
15. **Gans I**, **Dormans JP**, **Spiegel DA**, **et al**. Adjunctive vancomycin powder in pediatric spine surgery is safe. *Spine (Phila Pa 1976)*. 2013;38(19):1703–1707.
16. **Armaghani SJ**, **Menge TJ**, **Lovejoy SA**, **Mencio GA**, **Martus JE**. Safety of topical vancomycin for pediatric spinal deformity: nontoxic serum levels with supratherapeutic drain levels. *Spine (Phila Pa 1976)*. 2014;39(20):1683–1687.
17. **Maxfield K**, **Zineh I**. Precision dosing: a clinical and public health imperative. *JAMA*. 2021;325(15):1505–1506.
18. **Watanabe JH**, **McInnis T**, **Hirsch JD**. Cost of prescription drug-related morbidity and mortality. *Ann Pharmacother*. 2018;52(9):829–837.
19. **Awdishu L**, **Mehta RL**. The 6R's of drug induced nephrotoxicity. *BMC Nephrol*. 2017;18(1):1–12.
20. **Cruz DN**, **Ricci Z**, **Ronco C**. Clinical review: RIFLE and AKIN--time for reappraisal. *Crit Care*. 2009;13(3):211.
21. **Hernán MA**. Causal analyses of existing databases: no power calculations required. *J Clin Epidemiol*. 2021.



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**Ethical review statement:**

- The study had institutional review board approval from Advarra Inc, and all study participants provided written informed consent.

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