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MAJOR ARTICLE

Cefazolin vs Second-line Antibiotics for Surgical Site Infection Prevention After Total Joint Arthroplasty Among Patients With a Beta-lactam Allergy

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Background. Cefazolin is a first-line agent for prevention of surgical site infections (SSIs) after total joint arthroplasty. Patients labeled allergic to beta-lactam antibiotics frequently receive clindamycin or vancomycin perioperatively due to the perceived risk of a hypersensitivity reaction after exposure to cefazolin.

Methods. This single-system retrospective review included patients labeled allergic to penicillin or cephalosporin antibiotics who underwent a primary total hip and/or knee arthroplasty between January 2020 and July 2021. A detailed chart review was performed to compare the frequency of SSI within 90 days of surgery and interoperative hypersensitivity reactions (HSRs) between patients receiving cefazolin and patients receiving clindamycin and/or vancomycin.

Results. A total of 1128 hip and/or knee arthroplasties from 1047 patients were included in the analysis (cefazolin n = 809, clindamycin/vancomycin n = 319). More patients in the clindamycin and/or vancomycin group had a history of cephalosporin allergy and allergic reactions with immediate symptoms. There were fewer SSIs in the cefazolin group compared with the clindamycin and/or vancomycin group (0.9% vs 3.8%; $P < .001$) including fewer prosthetic joint infections (0.1% vs 1.9%). The frequency of interoperative HSRs was not different between groups (cefazolin = 0.2% vs clindamycin/vancomycin = 1.3%; $P = .06$).

Conclusions. The use of cefazolin as a perioperative antibiotic for infection prophylaxis in total joint arthroplasty in patients labeled beta-lactam allergic is associated with decreased postoperative SSI without an increase in interoperative HSR.

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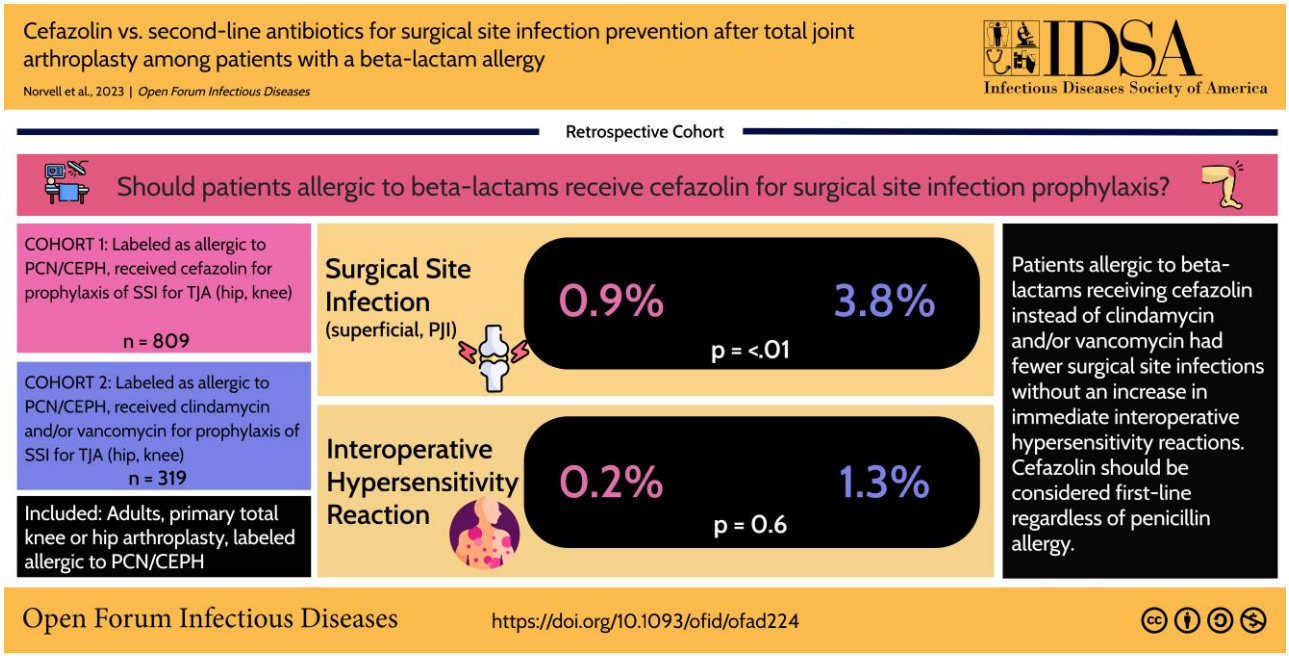
Graphical Abstract



This graphical abstract is also available at Tidbit: https://tidbitapp.io/tidbits/cefazolin-vs-second-line-antibiotics-for-surgical-site-infection-prevention-after-total-joint-arthroplasty-among-patients-with-a-beta-lactam-allergy

Keywords. antibiotic prophylaxis; hip arthroplasty; interoperative hypersensitivity reaction; knee arthroplasty; prosthetic joint infection.

Total knee arthroplasties (TKAs) and total hip arthroplasties (THAs) are 2 of the most common surgical procedures performed in the United States, with an estimated 498 000 total hip replacements and 1 065 000 total knee replacements completed in 2020 [1]. With numbers expected to increase by 85% by 2030, it is important to ensure that patients undergoing these procedures receive the optimal antibiotic regimens to prevent surgical site infections (SSIs) [2]. SSIs, specifically periprosthetic joint infections (PJIs), are associated with poor patient outcomes and are considered a traumatic outcome after a total joint arthroplasty [3, 4]. PJI is also associated with an increased risk of mortality, reaching up to 21% for both TKA and THA after 5 years [3, 4]. PJIs can also pose detrimental effects to the health care system as a whole, where it was estimated that PJIs related to both knees and hips will cost $1.85 billion by 2030 [5].

To decrease the risk of SSI and PJI after total joint arthroplasty, prophylactic antibiotics are indicated perioperatively [6]. The first study looking at the prevention of infection after TKA and THA from 1984 found that frequency of infection was reduced by 3- to 4-fold when antibiotics were given prophylactically [7]. A systematic review from 2008 found that despite TKA and THA being classified as clean operations, the frequency of PJI still reached 2% after a primary operation surgery [8]. This study also identified the most commonly seen organisms in each PJI, which included mainly gram-positive bacteria, specifically *Staphylococcus aureus* and *Staphylococcus epidermidis* [8]. Cephalosporins, specifically cefazolin, are the backbone of SSI prevention for many surgeries given their wide therapeutic index, activity against both gram-positive and gram-negative bacteria, and ease of administration in the perioperative setting. Neither clindamycin nor vancomycin has appreciable activity against gram-negative bacteria; they have considerably more adverse effects and require long infusion durations in the case of vancomycin [6]. Considering that 10%–15% of the US population report an allergy to penicillin antibiotics and 1%–2% report an allergy to cephalosporin antibiotics [9–11], it can be estimated that 250 000 hip or knee replacements are performed annually on patients labeled allergic to penicillins or cephalosporins. This allergy label often results in the avoidance of cefazolin and the receipt of second-line antibiotics, most frequently clindamycin and/or vancomycin.

The purpose of this study was to compare cefazolin with second-line antibiotics to evaluate the incidence of SSIs within 90 days following joint replacement surgery and interoperative HSRs among patients labeled allergic to a penicillin or cephalosporin.

METHODS

Participants

A retrospective chart review was conducted for all patients who underwent a total knee or hip arthroplasty within the

University of Colorado Health (UCHealth) system from January 1, 2020, through July 31, 2021. Patients were included if they were 18 years of age or older, underwent a primary total knee arthroplasty (TKA) or total hip arthroplasty (THA), and were labeled allergic to a penicillin or cephalosporin antibiotic in the electronic health record at the time of surgery. Patients were excluded if there was a preexisting joint infection before surgery, the patient died before the 90-day postoperative period, or the surgical procedure was a revision, secondary TKA or THA, hemiarthroplasty, or patellofemoral arthroplasty.

Data Collection and Study Design

This retrospective chart review was reviewed and approved by the Colorado Multiple Institutional Review Board (COMIRB). Data collected from the electronic health record included demographics, comorbidities, immunomodulatory medications, allergy history, perioperative medications, and laboratory test results. Patients with multiple joint replacements that occurred in separate procedures were recorded as separate encounters. Bilateral joint replacements that were conducted in the same operation were recorded as 1 encounter. Beta-lactam allergic reaction histories were categorized into immediate, delayed, or undetermined based on documented symptoms. Immediate allergic reactions included descriptions associated with anaphylaxis, respiratory distress, cardiovascular symptoms, edema, and hives. Delayed allergic reactions included descriptions associated with dermatologic findings, pruritis, organ inflammation (eg, nephritis, hepatitis), and blood cell dysfunction (eg, neutropenia, thrombocytopenia). All other allergic reaction histories were categorized as undetermined.

Outcomes

The primary outcome was surgical site infection, which included periprosthetic joint infection (PJI) or superficial infection, within 90 days of surgery. Infections were defined according to the definitions set forth by the Centers for Disease Control and Prevention (CDC) and National Healthcare Safety Network (NHSN) surveillance definitions for specific types of infections, with the exception of the 30-day cutoff for superficial SSI [12,13]. SSI classification was reviewed and confirmed by an orthopedic surgeon (R.K.). The secondary outcome was interoperative hypersensitivity reactions (HSRs). This was defined as hemodynamic instability (systolic blood pressure of <80 mmHg or >40% reduction), interoperative receipt of epinephrine and/or diphenhydramine, documentation of an allergic reaction in an electronic health record note (anesthesia or operative note), or a new documented allergy in the patient chart after receipt of a perioperative antibiotic. All patients who experienced hemodynamic instability during the interoperative period were subsequently reviewed for receipt of additional doses of antibiotics to assess if the hemodynamic instability experienced was due to the antibiotic or other medications received perioperatively. All patients identified as having a primary or secondary outcome were independently reviewed by 2 authors (M.J., R.K.). Discrepancies were resolved by a third author review.

Statistics

Patients were divided into 2 groups based on perioperative antibiotic received, cefazolin vs clindamycin and/or vancomycin. The study was powered for 1100 total hip/knee arthroplasties. Assuming that 25% of patients would receive a clindamycin and/or vancomycin antibiotic regimen [12], an expected SSI frequency of 4% in the clindamycin and/or vancomycin group, 1% in the cefazolin group, and an alpha of .05, the power to detect a difference would be 80%. Continuous variables were expressed as means with SDs. Categorical variables were expressed as units and percentages. Comparisons were performed using independent t tests for equality of variance for continuous variables and Fisher exact tests for categorical variables. Statistical significance was defined as $P \leq .05$. Statistical analysis was performed using SPSS software, version 27.0 (IBM, Armonk, NY, USA).

RESULTS

A total of 1182 procedures from 1100 patients were screened for inclusion, and 53 patients were excluded. Reasons for exclusion were nonprimary surgery including revision (n = 18), hemiarthroplasty (n = 15), absence of beta-lactam allergy label at time of surgery (n = 9), complex surgery beyond scope of total arthroplasty or a patellofemoral surgery (n = 4), presence of joint infection at time of surgery (n = 3), patient death before 90-day time frame (n = 3), or the patient did not receive perioperative antibiotics (n = 1).

The final cohort resulted in 1128 surgical procedures from 1047 patients. A total of 809 surgeries (71.7%) used cefazolin as the perioperative antibiotic regimen. The remaining 319 (28.3%) surgeries used clindamycin and/or vancomycin as the perioperative antibiotic regimen. Of the 319 patients, 146 received only clindamycin, 79 received only vancomycin, and 94 received both clindamycin and vancomycin perioperatively.

Patient characteristics between the cefazolin and clindamycin/vancomycin groups were similar for all characteristics except class of beta-lactam allergy, type of beta-lactam allergy, surgery duration, antibiotic irrigation use, and past medical history including cancer, asthma, and fibromyalgia (Table 1). More patients in the clindamycin and/or vancomycin group had a cephalosporin allergy history and allergic reactions associated with immediate hypersensitivity. Surgery duration was longer in the clindamycin and/or vancomycin group compared with the cefazolin group. More patients used a topical antibiotic

Table 1. Characteristics of Patients Labeled as Beta-lactam Allergic Receiving Preoperative Antibiotics for Either Total Hip and/or Total Knee Arthroplasty

Variable, No. (%)	Cefazolin (n = 809)	Clindamycin and/or Vancomycin (n = 319)	*P* Value
Age, mean ± SD, y	68.1 ± 9.6	67.2 ± 10.4	.16
Sex, female	571 (70.6)	218 (68.3)	.47
Body mass index, mean ± SD, kg/m^2	30.2 ± 6.5	30.6 ± 6.4	.31
Beta-lactam allergy label			
Penicillins	743 (91.8)	267 (83.7)	<.01
Cephalosporins	91 (11.2)	117 (36.7)	<.01
Multiple beta-lactam allergies	59 (7.3)	88 (27.6)	<.01
HSR history			
Immediate reaction	290 (35.8)	190 (59.6)	<.01
Delayed reaction	279 (34.5)	87 (27.3)	.02
Indeterminate timing of reaction	241 (29.8)	44 (13.8)	<.01
Surgery type	…	…	.45
Knee	433 (53.5)	171 (53.6)	
Hip	376 (46.5)	148 (46.4)	
Bilateral	48 (5.9)	12 (3.8)	
Surgery duration, mean ± SD, min	74.7 ± 26.3	80.2 ± 25.6	<.01
Hospitalization 90 d before surgery	72 (8.9)	31 (9.7)	.65
ASA classification >2	407 (50.3)	179 (56.1)	.08
Comorbid diseases			
Depression or mood disorders	170 (21.0)	70 (21.9)	.75
Diabetes	144 (17.8)	70 (21.9)	.11
Anxiety	136 (16.8)	64 (20.1)	.20
Cancer (active or resolved)	150 (18.5)	43 (13.5)	.04
Opiate use/opiate use disorder	72 (8.9)	38 (11.9)	.15
GI disease (Crohn's/UC/IBD)	31 (3.8)	13 (4.1)	.87
Asthma	159 (19.7)	88 (27.6)	<.01
Rheumatoid arthritis	30 (3.7)	13 (4.1)	.73
Seasonal allergies or allergic rhinitis	101 (12.5)	43 (13.5)	.69
Autoimmune disease	109 (13.5)	42 (13.2)	.92
Fibromyalgia	22 (2.7)	20 (6.3)	<.01
Topical cefazolin irrigation	205 (30.6)	31 (11.8)	<.01
Topical vancomycin powder or irrigation	181 (22.4)	45 (14.1)	<.01
Given within appropriate time before cut time	778 (98.1)	249 (81.1)	

Abbreviations: ASA, American Society of Anesthesiologists; GI, gastrointestinal; HSR, hypersensitivity reaction; IBD, inflammatory bowel disease; UC, ulcerative colitis.

(either cefazolin irrigation or vancomycin powder) in the cefazolin group. Lastly, more patients in the cefazolin group had a past medication history of cancer, whereas more patients in the clindamycin and/or vancomycin group had a history of asthma and fibromyalgia.

Surgical site infections occurred less frequently in the cefazolin group than the clindamycin/vancomycin group (0.9% vs 3.8%; $P < .01$; relative risk, 4.3; 95% CI, 1.7–10.9). There were fewer superficial incisional infections in the cefazolin group (0.7% vs 1.9%) and fewer prosthetic joint infections in the cefazolin group (0.1% vs 1.9%) (Table 2). The average time from surgery to SSI was 24.3 ± 10.2 days in the cefazolin group and 21.6 + 11.0 days in the clindamycin and/or vancomycin group (Table 2).

Table 2. Ninety-Day SSI and Interoperative HSR Among Patients Labeled as Beta-lactam Allergic Receiving Total Hip and/or Total Knee Arthroplasty

Variable, No. (%)	Cefazolin (n = 809)	Clindamycin and/or Vancomycin (n = 319)	*P* Value
SSI	7 (0.9)	12 (3.8)	<.01
Superficial incisional	6 (0.7)	6 (1.9)	
Periprosthetic joint infection	1 (0.1)	6 (1.9)	
Time from surgery to SSI, mean ± SD, d	24.3 ± 10.2	21.6 ± 11.0	
Interoperative hypersensitivity reaction	2 (0.2)	4 (1.3)	.06
Airway involvement, No.	0	0	
Skin involvement, No.	1	2	
Facial/throat swelling, No.	0	0	
Hemodynamic instability, No.	0	2	
Stated in EHR note, No.	1	0	

Abbreviations: EHR, electronic health record; HSR, hypersensitivity reaction, SSI, surgical site infection.

The frequency of interoperative HSR was not different between antibiotic groups (cefazolin 0.2% vs clindamycin and/or vancomycin 1.3%; $P = .06$) (Table 2). The cefazolin group had 2 HSRs. One patient experienced skin involvement, and 1 patient self-reported an allergic reaction without supporting symptoms. Both patients had a history of penicillin allergies with no documentation of reaction history. The clindamycin and/or vancomycin group had 4 HSRs, 2 with skin involvement and 2 with hemodynamic instability. All 4 patients had a history of cephalosporin allergy, 3 with immediate allergy histories and 1 with a delayed allergy history.

The most common pathogens isolated from SSIs in the cefazolin group were methicillin-susceptible *Staphylococcus* spp., *Streptococcus canis* (Group G), *Cutibacterium avidum*, and *Proteus mirabilis*. The most common pathogens for the clindamycin and/or vancomycin group were methicillin-susceptible *Staphylococcus aureus*, *Enterococcus* spp., and *Klebsiella pneumoniae*. There was a higher frequency of gram-negative infections seen in the clindamycin and/or vancomycin group compared with the cefazolin group (Table 3).

DISCUSSION

This study evaluated the 90-day incidence of surgical site infections and interoperative hypersensitivity reactions in patients with a beta-lactam allergy who underwent a total knee or hip arthroplasty. Overall, cefazolin was shown to have a significantly lower frequency of SSI compared with clindamycin and/or vancomycin without an increased risk of HSR.

Similar to what this study found, Wyles et al. demonstrated that second-line antibiotics used for SSI prevention have been

Table 3. Microbiology of Postoperative Surgical Site Infections After Total Hip and/or Total Knee Arthroplasty Among Patients Labeled as Beta-lactam Allergic

Variable, No.	Cefazolin (n = 7)	Clindamycin and/or Vancomycin (n = 12)
Polymicrobial infection	1	4
No culture data available	3	3
Negative cultures	0	0
Gram-positive		
Staphylococcus spp.	2	8
MSSA	1	5
S. lugdunensis	0	1
S. pseudointermedius	0	1
S. epidermidis	1	1
Enterococcus spp.	0	0
E. faecalis	0	3
E. avium	0	1
Streptococcus canis (Group G)	1	0
Cutibacterium avidum	1	0
Gram-negative		
Klebsiella pneumoniae	0	3
Enterobacter cloacae	0	1
Proteus mirabilis	1	0

Abbreviation: MSSA, methicillin-susceptible *Staphylococcus aureus*.

associated with decreased efficacy regarding prevention of SSI in previous studies [14]. They evaluated all patients who underwent primary TKA or THA and found that infection-free survivorship was significantly higher in patients who received cefazolin compared with noncefazolin regimens ($P < .001$). This team estimated that 6098 1-year postoperation PJIs could be prevented if cefazolin were used instead of second-line agents. Robertsson et al. assessed the rate of revision surgeries required due to infection in patients who had a TKA [15]. The results of this study showed an increased risk of revisions needed due to infection in patients who received clindamycin compared with those who received cloxacillin as their perioperative antibiotic regimen (risk ratio [RR], 1.5; 95% CI, 1.2–2.0). Kheir et al. described rates of PJI after any primary total joint arthroplasty [16]. This study showed an increased risk of PJI after vancomycin was used as perioperative prophylaxis compared with cefazolin (adjusted odds ratio, 1.587; $P = .048$). Clindamycin and/or vancomycin had a higher frequency of gram-negative infections compared with cefazolin. This is likely based on cefazolin's activity against gram-negative bacteria comparted with clindamycin and vancomycin, which have negligible coverage against gram-negative bacteria.

Though the cefazolin group had a lower frequency of interoperative HSRs compared with the clindamycin and/or vancomycin group, it is important to consider that these results are likely due to the differences in allergic reaction history between antibiotic groups. More patients in the clindamycin and/or vancomycin group had a history of immediate reactions to a beta-lactam. Patients with immediate allergic reactions are more likely to have immediate allergic reactions to other medications regardless of chemical structure [17]. This increased risk of immediate HSR could explain the higher frequency of HSRs in the clindamycin/vancomycin group compared with the cefazolin group. Alternatively, it is important to realize that cefazolin also has a low risk of causing HSR in patients with other beta-lactam allergies due to its unique chemical structure. Contemporary data have established that cross-reactivity between penicillins and cephalosporins is primarily based on the R1 side chain, not the shared beta-lactam structure [18, 19]. Cefazolin does not share an R1 side chain with other penicillins or cephalosporins, so it should be safe to administer in patients with a beta-lactam allergy, regardless of reported allergy severity [20]. Fosnot et al. assessed immediate hypersensitivity reactions to perioperative antibiotics in patients with a labeled allergy to penicillin [12]. Among 690 patients, the 15 immediate hypersensitivity reactions were similar for patients receiving clindamycin (2.4%), vancomycin (2.2%), and cefazolin (1.7%).

Previous studies also investigated the risks of cross-reactivity in patients with a beta-lactam allergy regarding perioperative antibiotic choice. Grant et al. conducted a pre- and postintervention evaluation after a system-wide change that transitioned to using cefazolin in patients with penicillin allergy histories [21]. This study showed that there was no increased risk of allergic reactions, surgical site infections, or adverse events when patients received cefazolin compared with other antibiotics. Collins et al. conducted a similar pre- and postintervention study design, but they implemented a new allergy assessment process with widespread dissemination of a side-chain-based cross-reactivity chart for reference to help determine the appropriate perioperative antibiotic to use in patients with a reported beta-lactam allergy [22]. After the intervention, significantly fewer patients received a beta-lactam alternative agent (84.9% vs 15.1%; $P < .001$). They also found no difference in HSR.

This study has important limitations to consider, including the retrospective design and lack of randomization. Determining the presence of HSR was especially difficult due to the nature of medication administration in the operating room (ie, all medications are given together or in close succession). Many anesthesia medications naturally affect hemodynamics (eg, neuromuscular blockers, propofol, opioids), which made it difficult to ascertain whether drops in blood pressure were due to an HSR caused by the perioperative antibiotic or other medications used. To negate this limitation, patients with interoperative hemodynamic instability were reviewed for subsequent episodes of decreases in blood pressure after additional antibiotic doses. Additional limitations include the type of surgery analyzed. This study only assessed patients who underwent TKA and THA, making it difficult to generalize to other surgery types, especially to those surgery types that are deemed to be contaminated (eg, gastrointestinal, trauma). Lastly, the 2 study groups were not balanced at baseline, which could affect the results shown, especially regarding HSR. In

addition to differences surrounding beta-lactam allergy history, patients in the clindamycin and/or vancomycin group had increased incidence of asthma, a disease state known to be associated with increased immune response. This imbalance could mean that patients in the clindamycin and/or vancomycin group were at an increased risk of having an HSR to any medication they received based on their baseline immunologic response. Additionally, the cefazolin group received more topical antibiotics (ie, cefazolin irrigation and vancomycin powder), which indicates that these patients had additional antimicrobial protection compared with the clindamycin and/or vancomycin group. A meta-analysis of 4500 patients compared the frequency of SSIs after hip or knee arthroplasty between patients receiving topical vancomycin powder as part of their perioperative prophylactic antibiotic regimen. The use of vancomycin powder was shown to decrease the risk of SSIs (RR, 0.40; 95% CI, 0.27–0.61) [23]. Of note, a larger and more recent retrospective study of patients undergoing total knee arthroplasty (n = 11 550) compared the risk of PJI between patients who received cefazolin and topical vancomycin and patients who received second-line antibiotics and topical vancomycin. Patients receiving cefazolin had fewer PJIs (0.5% vs 1%; $P = .01$). After controlling for confounding variables, the use of cefazolin remained the key variable for preventing PJI regardless of use of topical vancomycin [24].

Overall, this study showed that beta-lactam allergic patients receiving cefazolin experienced fewer SSIs without an increase in HSR. The 2013 guidelines and protocols currently available are archived, but they are still used in the absence of published updates [6]. These guidelines recommend avoiding cefazolin in patients with beta-lactam allergies, but they should be reevaluated given the results of this study.

CONCLUSIONS

Our investigation demonstrates that the use of cefazolin as a perioperative antibiotic for infection prophylaxis in total joint arthroplasty in patients labeled beta-lactam allergic is associated with decreased postoperative SSIs without an increase in interoperative HSRs. The lack of safety concerns regarding the potential of cross-reactivity between cefazolin and other beta-lactams combined with the increased risk of SSIs associated with second-line antibiotic regimens should encourage surgeons, anesthesiologists, and other clinicians involved in the selection of perioperative antibiotics to use cefazolin for SSI prophylaxis.

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Potential conflicts of interest. All authors: no reported conflicts.

Author contributions. All authors contributed to the preparation of the final manuscript. M.R.N. was involved with protocol development, data collection, and data analysis. M.P. and M.H.R. helped with data analysis. R.C.K., C.A.H., E.B., and M.W. provided clinical expertise and helped with protocol development. M.N.J. oversaw the project and provided guidance and input at all steps of the process.

Patient consent. This study does not include factors necessitating patient consent.

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