



CEFAZOLIN VERSUS NON-CEFAZOLIN PROPHYLAXIS IN BETA-LACTAM ALLERGY-LABELED PATIENTS UNDERGOING HIP AND KNEE ARTHROPLASTY: A SYSTEMATIC REVIEW

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ABSTRACT

Cefazolin is the preferred perioperative prophylactic antibiotic for hip and knee arthroplasty, but patients with beta-lactam allergy labels often receive second-line agents such as clindamycin or vancomycin. This practice may reduce prophylactic effectiveness despite the low likelihood of true cefazolin cross-reactivity. This systematic review evaluated the effectiveness and safety of cefazolin compared with non-cefazolin antibiotic prophylaxis in beta-lactam allergy-labeled patients undergoing hip and knee arthroplasty. PubMed, Cochrane Library, and ScienceDirect were searched for studies assessing perioperative prophylaxis in arthroplasty patients with penicillin, cephalosporin, or beta-lactam allergy labels. Outcomes included surgical site infection, periprosthetic joint infection, hypersensitivity reaction, anaphylaxis, adverse events, cefazolin utilization, and stewardship-related outcomes. Thirteen observational studies published between 2016 and 2026 were included, and findings were synthesized narratively. Cefazolin was generally associated with lower or comparable infection rates compared with non-cefazolin prophylaxis. Direct comparative studies reported lower surgical site infection and periprosthetic joint infection with cefazolin in several cohorts, while others showed no significant difference. Hypersensitivity reactions to cefazolin were rare and mostly mild. Safety was also observed among patients with reported penicillin anaphylaxis or cephalosporin allergy. Allergy testing, test-dose protocols, and multidisciplinary stewardship interventions increased cefazolin use without increasing perioperative allergic reactions. The evidence suggests that many beta-lactam allergy labels are not clinically relevant contraindications to cefazolin. Routine substitution with clindamycin or vancomycin may expose patients to inferior prophylactic coverage and avoidable adverse effects. Cefazolin should be considered for most beta-lactam allergy-labeled arthroplasty patients after structured allergy assessment, while non-cefazolin agents should be reserved for confirmed high-risk reactions.

Keywords: beta-lactam allergy; cefazolin; hip arthroplasty; knee arthroplasty; penicillin allergy

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INTRODUCTION

Total hip arthroplasty and total knee arthroplasty are among the most frequently performed and clinically successful orthopedic procedures, yet postoperative surgical site infection and periprosthetic joint infection remain among their most devastating complications. Although infection after primary arthroplasty is relatively uncommon, its consequences are substantial, including revision surgery, prolonged antimicrobial therapy, functional decline, increased cost, and reduced implant survivorship. Therefore, perioperative antibiotic prophylaxis remains a central component of infection-prevention strategies in hip and knee arthroplasty. Cefazolin is widely regarded as the preferred first-line prophylactic agent because of its favorable pharmacokinetics, narrow but appropriate antimicrobial spectrum, activity against common skin flora, ease of administration, and established efficacy in preventing postoperative infection. (Norvell et al., 2023; Sousa-Pinto et al., 2021; Wyles et al., 2019).

Despite this, many patients undergoing arthroplasty carry a documented penicillin, cephalosporin, or broader beta-lactam allergy label. These labels often lead clinicians to avoid cefazolin and

instead prescribe second-line agents such as clindamycin or vancomycin. This practice is clinically important because many reported beta-lactam allergies are unverified, remote, non-IgE-mediated, or represent intolerance rather than true allergy. Contemporary allergy evidence has also challenged the traditional concern regarding cross-reactivity between penicillin and cefazolin. Cefazolin has a unique R1 side chain that is structurally distinct from penicillins and most other cephalosporins, and modern practice parameters support the use of structurally dissimilar cephalosporins, including cefazolin, in many patients with a penicillin allergy history. (Khan et al., 2022; Sousa-Pinto et al., 2021)

Avoidance of cefazolin may not be benign. Outside arthroplasty, a reported penicillin allergy has been associated with increased surgical site infection risk, largely mediated by the use of alternative perioperative antibiotics. (Blumenthal et al., 2018) In arthroplasty populations, several observational studies have suggested that non-cefazolin prophylaxis may be associated with higher periprosthetic joint infection or surgical site infection rates, while cefazolin use in beta-lactam allergy-labeled patients appears to have a low rate of clinically significant hypersensitivity reactions. (Jones et al., 2021; Wu et al., 2020) More recent studies have extended this safety signal to higher-risk allergy histories, including patients with reported penicillin anaphylaxis or documented cephalosporin allergy, further supporting the need to reassess routine avoidance of cefazolin in this population. (Jones et al., 2021; Tan et al., 2016)

Several strategies have been proposed to address this gap, including formal preoperative allergy testing, electronic best-practice alerts, test-dose protocols, multidisciplinary antibiotic stewardship interventions, and algorithmic beta-lactam allergy triage. These approaches aim to increase appropriate cefazolin use while preserving patient safety in those with true severe beta-lactam reactions. However, the available evidence varies in design, population, allergy definitions, comparator antibiotics, and reported outcomes. Some studies directly compare cefazolin with clindamycin or vancomycin in beta-lactam allergy-labeled arthroplasty patients, whereas others evaluate allergy-label status, stewardship interventions, or safety outcomes without direct infection comparison. Therefore, a focused synthesis is needed to clarify the balance between infection prevention and hypersensitivity risk. This systematic review aims to evaluate cefazolin versus non-cefazolin antibiotic prophylaxis in beta-lactam allergy-labeled patients undergoing hip and knee arthroplasty, with emphasis on surgical site infection, periprosthetic joint infection, hypersensitivity reactions, and the role of allergy-directed stewardship strategies.

METHOD

Study design

This systematic review was conducted to evaluate the comparative effectiveness and safety of cefazolin versus non-cefazolin antibiotic prophylaxis in beta-lactam allergy-labeled patients undergoing hip and knee arthroplasty. The review was structured according to the PRISMA framework. The population of interest included adults undergoing total hip arthroplasty, total knee arthroplasty, or total joint arthroplasty with a reported or documented penicillin, cephalosporin, or beta-lactam allergy label. The intervention was perioperative cefazolin prophylaxis, while the comparator was non-cefazolin prophylaxis, including clindamycin, vancomycin, cefuroxime alternatives, or other second-line antibiotic regimens. Outcomes of interest included surgical site infection, periprosthetic joint infection, hypersensitivity reaction, anaphylaxis, adverse antibiotic-related events, and outcomes related to allergy testing or antibiotic stewardship protocols.

Search strategy

A systematic literature search was performed using PubMed, Cochrane Library, and ScienceDirect. The search was designed to identify studies evaluating cefazolin, cephalosporins, or alternative perioperative prophylactic antibiotics in patients with beta-lactam allergy labels undergoing hip or knee arthroplasty. The PubMed search strategy was: ("cefazolin" OR "cephalosporin" OR

"vancomycin" OR "clindamycin") AND ("penicillin allergy" OR "beta-lactam allergy" OR "cephalosporin allergy" OR "drug allergy" OR "allergy label") AND ("total joint arthroplasty" OR "hip arthroplasty" OR "knee arthroplasty" OR "total hip arthroplasty" OR "total knee arthroplasty" OR THA OR TKA) AND ("antibiotic prophylaxis" OR "perioperative antibiotic" OR "surgical prophylaxis" OR "surgical site infection" OR "periprosthetic joint infection" OR "allergy testing" OR "antibiotic stewardship"). The Cochrane Library search strategy was: (cefazolin OR cephalosporin OR vancomycin OR clindamycin) AND ("penicillin allergy" OR "beta-lactam allergy" OR "cephalosporin allergy" OR "allergy label") AND ("total joint arthroplasty" OR "hip arthroplasty" OR "knee arthroplasty" OR THA OR TKA) AND ("antibiotic prophylaxis" OR "perioperative antibiotic" OR "surgical site infection" OR "periprosthetic joint infection" OR "allergy testing" OR stewardship). The ScienceDirect search strategy was: cefazolin AND ("penicillin allergy" OR "beta-lactam allergy" OR "cephalosporin allergy") AND ("hip arthroplasty" OR "knee arthroplasty" OR "total joint arthroplasty") AND ("antibiotic prophylaxis" OR "perioperative antibiotic"). Reference lists of eligible studies were also screened manually to identify additional relevant articles. The studies ultimately included in this review were published between 2016 and 2026; this range describes the included evidence and does not establish a publication-year restriction for the search.

Eligibility criteria

Studies were eligible for inclusion if they evaluated patients undergoing hip or knee arthroplasty and reported data on perioperative antibiotic prophylaxis in the context of penicillin, cephalosporin, or beta-lactam allergy labels. Eligible designs included retrospective cohort studies, registry-based studies, claims database analyses, chart reviews, and quasi-experimental studies evaluating antibiotic stewardship, allergy testing, or triage protocols. Studies were included if they reported at least one relevant outcome, including surgical site infection, periprosthetic joint infection, hypersensitivity reaction, anaphylaxis, cefazolin tolerance, antibiotic-related adverse events, or changes in cefazolin utilization after allergy assessment or stewardship intervention. Studies were excluded if they did not involve hip or knee arthroplasty patients, did not address beta-lactam allergy or antibiotic prophylaxis, used an inappropriate intervention regimen, lacked relevant clinical outcomes, were reviews, editorials, commentaries, case reports, animal studies, or were unavailable in full text.

Study selection

All identified records were exported and duplicates were removed before screening. Titles and abstracts were screened for relevance to the review question. Studies that appeared eligible or could not be excluded based on title and abstract alone underwent full-text review. Full-text articles were assessed according to the predefined eligibility criteria. Disagreements during study selection were resolved by reassessment of the full text and discussion until consensus was reached. The study selection process was summarized using a PRISMA flow diagram.

Data extraction

Data were extracted using a standardized table. Extracted variables included author, year of publication, country, study design, study period, study population, type of arthroplasty, allergy label or allergy definition, prophylactic antibiotic groups, sample size, follow-up or outcome period, and main findings. Outcome data included surgical site infection, periprosthetic joint infection, hypersensitivity reaction, anaphylaxis, epinephrine administration, rapid response activation, adverse antibiotic-related events, *C. difficile* infection, readmission, cefazolin utilization, allergy testing outcomes, and stewardship-related outcomes when available. For studies that included broader arthroplasty populations, hip and knee arthroplasty data were prioritized when separately available.

Risk of bias assessment

The methodological quality of included observational studies was assessed using the Newcastle-Ottawa Scale. The assessment considered selection of study groups, comparability of cohorts, and ascertainment of outcomes. For quasi-experimental stewardship or protocol-based studies, risk of bias was evaluated by considering clarity of intervention definition, comparability between preintervention and postintervention groups, consistency of outcome assessment, and completeness of follow-up. Studies were not excluded solely based on quality assessment, but risk of bias findings were considered when interpreting the strength and consistency of the evidence.

Data synthesis

A narrative synthesis was performed because of heterogeneity in study design, allergy definitions, prophylactic antibiotic regimens, comparator groups, arthroplasty types, and outcome definitions. Studies were grouped thematically according to whether they evaluated direct cefazolin versus non-cefazolin prophylaxis, allergy-label status and infection risk, cefazolin safety in penicillin or cephalosporin allergy-labeled patients, or allergy testing and antibiotic stewardship interventions. Infection outcomes were summarized using reported rates, odds ratios, hazard ratios, or comparative findings when available. Safety outcomes were summarized according to allergic reactions, hypersensitivity reactions, anaphylaxis markers, and antibiotic-related adverse events. Because included studies varied substantially in population structure and outcome reporting, no quantitative meta-analysis was performed.

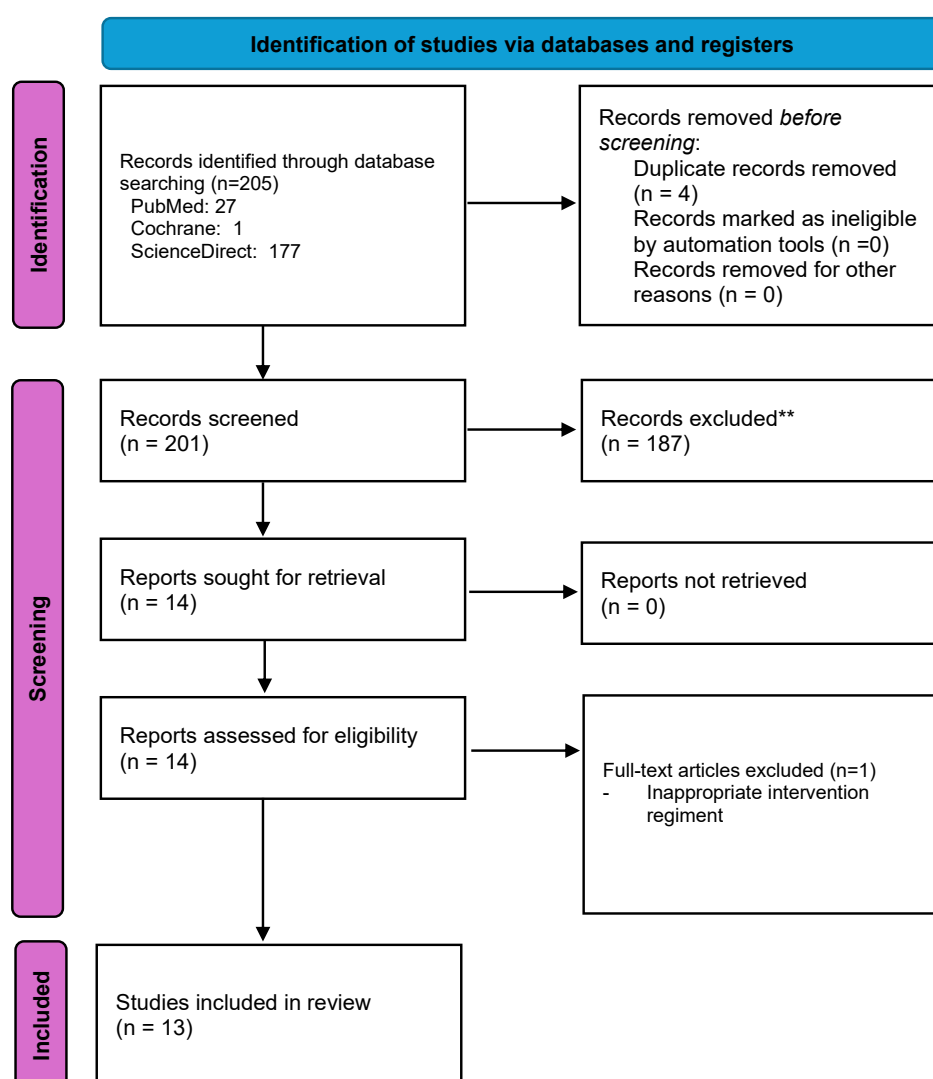


Table 1.
Characteristics and results of the included studies

Study	Country	Study design	Study period	Population	Arthroplasty type	Allergy label/definition	Prophylaxis groups	Sample size	Followup /outcome period	Summary of findings
Norvell et al., 2023	USA	Single-system retrospective chart review	January 2020 to July 2021	Adults ≥ 18 years with penicillin or cephalosporin allergy label in the electronic health record undergoing primary total joint arthroplasty	Primary THA and TKA	Beta-lactam allergy label, categorized as immediate, delayed, or undetermined based on documented reaction history	Cefazolin vs clindamycin and/or vancomycin	1128 procedures from 1047 patients, cefazolin: 809, clindamycin/vancomycin: 319	90 days after surgery	Cefazolin was associated with fewer SSI than clindamycin/vancomycin, 0.9% vs 3.8%. PJI was also lower with cefazolin, 0.1% vs 1.9%. Intraoperative hypersensitivity reactions were not significantly different, 0.2% vs 1.3%.
Wu et al., 2020	USA	Retrospective comparative study using a nationwide administrative claims database	2010 to 2017, with 1-year follow-up	Patients undergoing primary total joint arthroplasty, stratified by patient-reported penicillin allergy status	Primary THA, TKA, and total shoulder arthroplasty; hip and knee data relevant to this review	Patient-reported penicillin allergy identified using ICD-9 and ICD-10 diagnosis codes before surgery	Patient-reported penicillin allergy vs no patient-reported penicillin allergy; actual prophylactic antibiotic regimen was not directly captured	THA: 397,214, penicillin allergy: 9755, no allergy: 387,459. TKA: 800,660, penicillin allergy: 19,669, no allergy: 780,991	1 year after surgery	Patient-reported penicillin allergy was independently associated with increased PJI risk after TKA, OR 1.3, 95% CI 1.1 to 1.4, $p < 0.01$, but not after THA, OR 1.1, 95% CI 0.9 to 1.3, $p = 0.36$. The study suggested that increased infection risk may be related to second-line prophylaxis use, although antibiotic choice was not directly analyzed.
Stevoska et al., 2022	Austria	Retrospective single-center cohort study	2011 to 2020	Patients undergoing elective primary THA, TKA, or UKA in a tertiary referral hospital	Primary THA, TKA, and UKA	Patient-reported penicillin or cephalosporin allergy; prophylaxis was changed when allergy was reported	Cefuroxime vs non-cefuroxime prophylaxis, mainly clindamycin; in THA non-cefuroxime group: clindamycin 201/206, ciprofloxacin 4/206, vancomycin 1/206; in knee group: all received clindamycin	THA: cefuroxime 3213, non-cefuroxime 206. UKA/TKA: cefuroxime 2455, non-cefuroxime 211	Median follow-up, THA: 15.9 vs 15.4 months; UKA/TKA: 13.1 vs 13.5 months	No significant difference in PJI between first-line and second-line prophylaxis. PJI in UKA/TKA was 0.9% vs 1.4%, $p = 0.403$, and PJI in THA was 2.0% vs 2.9%, $p = 0.309$. No allergic reactions were reported among allergy-labeled patients who still received cefuroxime.
Wyles et al., 2019	USA	Retrospective cohort study using institutional	January 2004 to May 2017	Patients undergoing primary total knee or hip	Primary TKA and THA	Patients with historical or self-reported penicillin or	Cefazolin vs non-cefazolin antibiotics, mainly	29,695 arthroplasties from 22,705 patients,	Infection-free survivors hip	Among allergy-tested patients, 2,493 of 2,576, 97%,

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		arthroplasty and allergy-testing registries		arthroplasty at a single academic institution		cephalosporin allergy were eligible for preoperative allergy testing	vancomycin or clindamycin	cefazolin: 28,174, non-cefazolin: 1,521; preoperative allergy testing: 3,411 arthroplasties in 2,576 patients	reported up to 10 years	were cleared to use cephalosporins. Infection-free survivorship was higher with cefazolin than non-cefazolin antibiotics, including 98.83% vs 98.22% at 1 year and 98.15% vs 96.96% at 10 years. Cefazolin was independently associated with lower PJI risk, adjusted HR 0.68, 95% CI 0.48 to 0.96, p=0.027.
McDaniel et al., 2017	USA	Retrospective observational study evaluating a beta-lactam allergy screening program with best practice alert and Drug Allergy Clinic referral	February 2013 to May 2015	Adult orthopedic patients with a history of beta-lactam allergy identified in preoperative arthroplasty clinic	Hip or knee arthroplasty, including revision procedures	History of beta-lactam allergy based on electronic allergy record; patients were screened for possible IgE-mediated reaction and referred for formal allergy evaluation when appropriate	Drug Allergy Clinic evaluation vs no evaluation; cefazolin-containing prophylaxis vs alternative prophylaxis, including clindamycin, vancomycin, and/or gentamicin	Best practice alert fired in 363 patients; 161 appropriate patients were evaluated in the Drug Allergy Clinic. Surgical data included 154 evaluated patients, 58 consulted but not evaluated, and 54 patients in whom the alert was overridden	Perioperative prophylaxis use and perioperative allergic reactions	Penicillin skin testing was performed in 140 of 161 patients and was negative in 139, 99%. Cefazolin was deemed safe in 145 of 161, 90%. Cefazolin use in any regimen was higher among evaluated patients than non-evaluated groups, 139/154, 90%, vs 42/58, 72%, and 44/54, 81%. Alternative antibiotic use was lower after evaluation, 24/154, 16%, vs 18/58, 31%, and 13/54, 24%. No perioperative IgE-mediated reactions to cefazolin were reported.
Stone et al., 2019	USA	Single-institution retrospective chart review	January 2015 to June 2017	Consecutive patients undergoing primary unilateral total hip or knee arthroplasty, stratified by patient-reported penicillin allergy	Primary unilateral THA and TKA	Patient-reported penicillin allergy, classified into three tiers: severe reaction/hypersensitivity, side effects/intolerance, and unknown/unspecified reaction	Cefazolin vs second-line prophylaxis, mainly clindamycin or vancomycin; also compared penicillin allergy vs no penicillin allergy	1,903 patients, allergy: 4,107, penicillin allergy: 796; procedures: THA 1,777 and TKA 3,126	Acute SSI within 90 days	Patients with penicillin allergy were much less likely to receive cefazolin, 6.9% vs 94.9%, and more likely to receive clindamycin, 80.7% vs

Study	Country	Study design	Study period	Population	Arthroplasty type	Allergy label/definition	Prophylaxis groups	Sample size	Followup/outcome period	Summary of findings
										1.1%, or vancomycin, 12.4% vs 4.0%. SSI did not differ by penicillin allergy status, 0.6% vs 0.4%, $p=0.473$, or by primary antibiotic, cefazolin 0.5%, clindamycin 0.6%, vancomycin 0.0%, $p=0.479$. No patient with penicillin allergy who received cefazolin experienced an allergic reaction.
Wagner et al., 2026	USA	Retrospective cross-sectional study	July 2008 to July 2024	Adult patients undergoing elective primary THA or TKA, stratified by penicillin allergy status	Primary THA and TKA	Patients were grouped into documented penicillin anaphylaxis, documented nonanaphylactic penicillin allergy, and no documented penicillin allergy	Cefazolin vs vancomycin vs clindamycin	8,456 patients; no penicillin allergy: 7,196, nonanaphylactic penicillin allergy: 1,046, penicillin anaphylaxis: 214	Perioperative period; rapid response team activation and/or epinephrine administration were used as surrogate markers of anaphylaxis	Cefazolin did not significantly increase anaphylaxis or clinical instability among patients with documented penicillin anaphylaxis. In the penicillin-anaphylaxis cohort, only one patient receiving cefazolin had RRT/EPI, and chart review determined this was postoperative hypotension unrelated to cefazolin. Vancomycin was associated with higher odds of RRT/EPI in all patients, OR 7.2, 95% CI 4.4 to 11.7, and in patients without penicillin allergy, OR 11.6, 95% CI 6.9 to 19.7.
Guido et al., 2026	USA	Retrospective cohort study evaluating a multidisciplinary beta-lactam allergy triage	January 2024 to October 2025; protocol implemented January	Adult patients undergoing hip or knee arthroplasty, including primary and revision	Primary and revision hip or knee arthroplasty, total or partial	Algorithm classified beta-lactam allergy risk. Patients with cefazolin allergy, cephalosporin allergy, anaphylaxis/ang	Pre-protocol allergy referral strategy vs post-protocol algorithmic cefazolin triage	2,127 arthroplasties in 1,718 patients; pre-protocol: 1,685 cases, post-protocol: 442 cases	Perioperative hypersensitivity reaction and allergy referral	Cefazolin was used in 2,083 of 2,127 procedures, 97.93%. Before the protocol, 62 patients were

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		protocol	2025	procedures		ioedema, or severe delayed beta-lactam reactions were referred for allergy testing; patients with penicillin IgE-mediated reactions, including anaphylaxis, could receive cefazolin without testing			outcomes	referred for allergy testing and only 6 were advised to avoid cefazolin. After implementation, beta-lactam allergy referrals decreased to zero, cefazolin use remained high, 98.10% vs 97.23%, and no perioperative hypersensitivity reactions were reported.
Tan et al., 2016	USA	Retrospective multi-institutional cohort study	January 2005 to November 2014	Patients undergoing primary TJA, comparing beta-lactam allergy-labeled patients receiving vancomycin with nonallergic patients receiving cefazolin	Primary THA and TKA	Patient-reported penicillin or cephalosporin allergy identified from anesthesia records; vancomycin was used for allergy of any severity	Vancomycin monotherapy n beta-lactam-allergic patients vs cefazolin in patients without beta-lactam allergy	10,391 primary TJAs; vancomycin for beta-lactam allergy: 2,657, cefazolin without beta-lactam allergy: 7,734	Minimum 1-year follow-up; mean follow-up 40 months in vancomycin group and 39 months in cefazolin group	Vancomycin monotherapy was not associated with higher odds of deep SSI compared with cefazolin, adjusted OR 0.98, 95% CI 0.67 to 1.43, p=0.907. Deep SSI occurred in 48/2,657, 1.8%, with vancomycin and 152/7,734, 2.0%, with cefazolin. Vancomycin was associated with fewer Gram-positive and resistant-organism infections, but Gram-negative infection was higher in bivariate analysis.
Kurcz et al., 2023	USA	Retrospective chart review from a high-volume arthroplasty surgeon	January 2013 to December 2017	Adult patients undergoing hip or knee arthroplasty, including patients with documented penicillin allergy	Primary and revision THA and TKA	Documented penicillin or cephalosporin allergy in the medical record	Cefazolin full-strength "test dose" under anesthesia vs non-cefazolin prophylaxis	2,284 procedures analyzed; primary: 1,709, revision: 575; penicillin allergy: 310; cefazolin: 1,990, non-cefazolin: 294	Perioperative allergic reaction and postoperative PJI assessment	Cefazolin was administered to 87.1% of all patients and 46.0% of patients with documented penicillin allergy. Only 1 penicillin-allergic patient who received cefazolin had a nonsevere allergic reaction that required no additional treatment. Cefazolin use was associated with lower overall PJI

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										than non-cefazolin antibiotics, 2.9% vs 5.5%, p=0.02, although this association was no longer significant after adjustment.
Bukowski et al., 2024	USA	Retrospective cohort study using institutional total joint registry	February 2016 to January 2022	Patients undergoing primary TJA, comparing those with reported penicillin allergy who received cefazolin, those with reported penicillin allergy who received alternatives, and those without reported penicillin allergy	Primary THA and TKA	Reported penicillin allergy documented in the electronic medical record; reactions categorized as severe IgE-mediated or nonsevere/non-IgE-mediated	Cefazolin vs alternative prophylaxis, mainly vancomycin or clindamycin	49,842 primary TJAs; reported penicillin allergy: 5,508; reported penicillin allergy + cefazolin: 4,938; reported penicillin allergy + alternative: 570; no reported penicillin allergy: 43,359	Allergic reactions within 72 hours; superficial infection, deep infection, and C. difficile infection within 90 days	Among patients with reported penicillin allergy, cefazolin was used in 89.7%. Allergic reaction occurred in 0.1% of penicillin-allergic patients receiving cefazolin vs 0.2% receiving alternatives, p=0.48. All cefazolin reactions were mild and clinically indolent. No significant differences were observed in 90-day superficial infection, deep infection, or C. difficile infection between cefazolin and alternative prophylaxis groups.
Jolissaint et al., 2026	USA	Retrospective cohort study at a high-volume academic center	February 2016 to May 2024	Patients with documented cephalosporin allergy undergoing hip or knee arthroplasty	Primary or revision THA and TKA; revisions for PJI were excluded	Documented allergy to any cephalosporin, including cefazolin, cephalexin, cefadroxil, cefaclor, cefradine, cefprozil, ceftriaxone, cefpodoxime, cefuroxime, cefdinir, cefixime, or ceftibuten	Cefazolin despite documented cephalosporin allergy vs alternative prophylaxis, mainly clindamycin or vancomycin	1,268 patients with cephalosporin allergy; cefazolin: 482, alternative prophylaxis: 786	Allergic reactions within 72 hours; PJI, C. difficile infection, readmission, and antibiotic-related adverse events within 90 days	Cefazolin use in patients with cephalosporin allergy was associated with 0.0% IgE-mediated or severe type-IV allergic reactions, compared with 0.51% in the alternative prophylaxis group, p=0.30. No significant differences were found in PJI after primary arthroplasty, 0.21% vs 0.26%, p=0.83, C. difficile

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Jones et al., 2021	USA	Single-center retrospective quasi-experimental study evaluating antibiotic stewardship interventions	Preintervention: March 2017 to August 2017; postintervention: March 2019 to August 2019	Adult patients with documented penicillin allergy undergoing elective primary TJA	Primary THA and TKA	Documented penicillin allergy; severe allergy was redefined after intervention, with hives and local swelling reclassified as nonsevere	Preintervention vs postintervention prophylaxis guideline; cefazolin-based prophylaxis for nonsevere penicillin allergy vs vancomycin for severe penicillin allergy	180 evaluated patients with documented penicillin allergy; n: 90, postintervention: 90	Allergic reactions within 72 hours; SSI and C. difficile infection within 90 days	infection, 0.0% vs 0.0%, or 90-day readmission, 3.95% vs 4.33%, p=0.75. Antibiotic stewardship interventions improved appropriate prophylactic antibiotic use from 54% to 91%, RR 1.67, 95% CI 1.37 to 2.04, p<0.01. Improvement was most marked in patients with nonsevere allergy, 47% to 96%, p<0.01. No patients had signs of allergic reaction related to cefazolin, including 8 patients with severe penicillin allergy.



Figure 2. Risk of bias assessment results of the included studies

RESULT

Study selection

The database search identified 205 records, consisting of 27 records from PubMed, 1 from Cochrane, and 177 from ScienceDirect. After removal of 4 duplicate records, 201 records were screened by title and abstract. Of these, 187 records were excluded because they were not relevant to the review question. Fourteen reports were sought for retrieval, and all were successfully retrieved. After full-text assessment of 14 reports, 1 article was excluded because of an inappropriate intervention regimen. Finally, 13 studies were included in the systematic review.

Study characteristics

The 13 included studies were published between 2016 and 2026. Most studies were conducted in the United States, while one study was conducted in Austria. All included studies used observational designs, including retrospective cohort studies, retrospective chart reviews, registry-based studies, claims database analyses, and quasi-experimental evaluations of antibiotic stewardship or allergy triage protocols. The study periods ranged from 2004 to 2025, with follow-up windows varying from perioperative hypersensitivity assessment within 72 hours to infection-free survivorship analysis up to 10 years.

The included populations consisted mainly of adults undergoing primary total hip arthroplasty and total knee arthroplasty. Several studies also included unicompartmental knee arthroplasty, total shoulder arthroplasty, or revision hip and knee arthroplasty; however, hip and knee arthroplasty data were the main focus of this review. Sample sizes varied widely, ranging from 180 evaluated patients with documented penicillin allergy to large institutional and nationwide cohorts including tens of thousands to more than one million arthroplasty procedures. The largest claims-based study analyzed 397,214 total hip arthroplasties and 800,660 total knee arthroplasties, while large institutional registry studies included 49,842 primary total joint arthroplasties and 29,695 arthroplasties.

Allergy labels and prophylactic antibiotic patterns

Most studies evaluated patients with a reported or documented penicillin allergy, beta-lactam allergy, or cephalosporin allergy. Allergy definitions varied across studies, ranging from simple patient-reported allergy labels in electronic medical records to detailed categorization of reaction severity, including IgE-mediated reactions, anaphylaxis, nonsevere reactions, side effects, intolerances, unknown reactions, and severe delayed hypersensitivity reactions. Some studies specifically evaluated penicillin-anaphylactic patients or patients with documented cephalosporin allergy.

Cefazolin was the main first-line prophylactic antibiotic in most included studies. Non-cefazolin comparators generally consisted of clindamycin, vancomycin, or both. One study used cefuroxime as the institutional first-line cephalosporin and compared it with non-cefuroxime prophylaxis. Several studies demonstrated that allergy labels substantially influenced prophylactic antibiotic selection. In one cohort, patients with penicillin allergy were much less likely to receive cefazolin, 6.9% versus 94.9%, and more likely to receive clindamycin, 80.7% versus 1.1%, or vancomycin, 12.4% versus 4.0%. In another cohort, cefazolin was administered to 89.7% of patients with reported penicillin allergy, including patients with severe IgE-mediated histories. In a cephalosporin-allergy cohort, 482 of 1,268 patients received cefazolin despite the documented cephalosporin allergy.

Infection outcomes

Overall, infection-related findings generally favored cefazolin or showed no significant disadvantage compared with alternative prophylaxis. In one direct comparison among beta-lactam allergy-labeled patients undergoing primary hip or knee arthroplasty, cefazolin was associated with fewer surgical site infections than clindamycin or vancomycin, 0.9% versus 3.8%, and fewer periprosthetic joint infections, 0.1% versus 1.9%. Another large arthroplasty registry study found higher infection-free survivorship with cefazolin compared with non-cefazolin antibiotics, including 98.83% versus 98.22% at 1 year and 98.15% versus 96.96% at 10 years. Cefazolin remained independently associated with lower PJI risk after adjustment, with an adjusted hazard ratio of 0.68.

Several studies found no statistically significant difference in infection outcomes between first-line cephalosporin and alternative prophylaxis. In the Austrian cohort using cefuroxime as first-line prophylaxis, PJI did not significantly differ between first-line and second-line prophylaxis in knee arthroplasty, 0.9% versus 1.4%, or hip arthroplasty, 2.0% versus 2.9%. A single-institution study of 4,903 primary hip and knee arthroplasties also found no significant difference in SSI by penicillin allergy status, 0.6% versus 0.4%, or by antibiotic prescribed, cefazolin 0.5%, clindamycin 0.6%, and vancomycin 0.0%. In a large study of patients with reported penicillin allergy undergoing primary arthroplasty, 90-day superficial infection, deep infection, and *C. difficile* infection rates were not significantly different between patients receiving cefazolin and those receiving alternative antibiotics.

Among studies evaluating alternative regimens, vancomycin monotherapy in beta-lactam allergy-labeled patients was not associated with higher odds of deep SSI compared with cefazolin in nonallergic patients, with deep SSI occurring in 1.8% versus 2.0% and an adjusted odds ratio of 0.98. However, vancomycin showed a different microbiologic pattern, with fewer Gram-positive and resistant-organism infections but a higher Gram-negative infection signal in bivariate analysis. In another study including primary and revision arthroplasty, cefazolin was associated with lower overall PJI than non-cefazolin antibiotics, 2.9% versus 5.5%, although this association was no longer statistically significant after adjustment.

Hypersensitivity and adverse reactions

Across the included studies, cefazolin administration in allergy-labeled patients was consistently associated with a very low rate of perioperative allergic or hypersensitivity reactions. In beta-lactam allergy-labeled patients, intraoperative hypersensitivity reactions did not differ significantly between cefazolin and clindamycin or vancomycin, 0.2% versus 1.3%. In patients with reported penicillin allergy, cefazolin reactions were uncommon and generally mild. One large cohort found allergic reactions in 0.1% of penicillin-allergic patients who received cefazolin compared with 0.2% of those receiving alternative prophylaxis, with all cefazolin reactions described as mild and clinically indolent.

Evidence was similar in higher-risk allergy groups. Among 214 patients with documented penicillin anaphylaxis who received cefazolin, only one patient experienced rapid response team activation or epinephrine administration, and chart review determined that this episode was postoperative hypotension unrelated to cefazolin. In contrast, vancomycin was associated with higher odds of rapid response team activation or epinephrine administration in the overall cohort and in patients without penicillin allergy. In patients with documented cephalosporin allergy, cefazolin was associated with 0.0% IgE-mediated or severe type-IV allergic reactions, compared with 0.51% in patients receiving alternative prophylaxis. No significant differences were observed in 90-day PJI, *C. difficile* infection, or readmission between cefazolin and alternative prophylaxis in this group.

Several smaller stewardship and screening studies also supported cefazolin safety. Penicillin skin testing was negative in 139 of 140 tested patients in one program, and cefazolin was deemed safe in 145 of 161 evaluated patients. No perioperative IgE-mediated reactions to cefazolin were reported. Another study using a full-strength cefazolin test dose under anesthesia found only one nonsevere reaction among penicillin-allergic patients who received cefazolin, and the reaction required no additional treatment. A stewardship intervention study found no signs of cefazolin-related allergic reaction, including among 8 patients with severe penicillin allergy.

Allergy testing, triage protocols, and stewardship outcomes

Several studies evaluated interventions designed to increase appropriate cefazolin use. Preoperative allergy testing cleared 2,493 of 2,576 allergy-tested patients, 97%, for cephalosporin use. In another drug allergy clinic program, cefazolin use in any prophylaxis regimen was higher among evaluated patients than non-evaluated groups, 90% versus 72% and 81%, while alternative antibiotic use was lower, 16% versus 31% and 24%. These findings suggested that structured allergy assessment increased access to first-line prophylaxis without increasing perioperative allergic reactions. Protocol-based approaches produced similar results. A multidisciplinary beta-lactam allergy triage protocol maintained very high cefazolin use, with cefazolin administered in 2,083 of 2,127 procedures, 97.93%. After protocol implementation, beta-lactam allergy referrals decreased to zero, cefazolin use remained high, and no perioperative hypersensitivity reactions were reported. Another antibiotic stewardship intervention improved appropriate prophylactic antibiotic use from 54% to 91%, with the greatest improvement in patients with nonsevere allergy, from 47% to 96%. Overall, the included evidence suggests that structured allergy clarification, risk stratification, test-dose strategies, and stewardship pathways can increase cefazolin utilization while maintaining a low rate of perioperative hypersensitivity reactions.

DISCUSSION

This systematic review found that cefazolin was generally associated with favorable infection prevention outcomes and a very low rate of clinically significant hypersensitivity reactions among beta-lactam allergy-labeled patients undergoing hip and knee arthroplasty. Across the included studies, cefazolin either reduced surgical site infection and periprosthetic joint infection compared with second-line antibiotics or showed no significant safety disadvantage when used in patients with reported penicillin, cephalosporin, or broader beta-lactam allergy labels. These findings

support the growing view that a beta-lactam allergy label alone should not automatically preclude cefazolin prophylaxis in arthroplasty patients. (Norvell et al., 2023; Sousa-Pinto et al., 2021; Wyles et al., 2019)

The infection-related findings are biologically and clinically plausible. Cefazolin provides strong activity against common arthroplasty-related skin flora, including methicillin-susceptible staphylococci and streptococci, while also preserving some gram-negative coverage. In contrast, clindamycin and vancomycin have important limitations, including narrower coverage, bacteriostatic activity in the case of clindamycin, longer infusion requirements for vancomycin, and potential gaps in gram-negative protection. (Tan et al., 2016) These differences may explain why several included studies observed higher infection risk or lower infection-free survivorship among patients receiving non-cefazolin prophylaxis. Even in studies that did not show statistically significant infection differences, cefazolin did not appear inferior, suggesting that avoiding cefazolin solely because of an unverified allergy label may offer limited benefit while potentially compromising prophylactic effectiveness. (Stevoska et al., 2022)

The safety findings were also consistent across different allergy-risk groups. Cefazolin reactions were rare among patients with reported penicillin allergy, and reported reactions were generally mild, self-limited, or not clearly attributable to cefazolin. Importantly, newer data extended this safety signal to patients with histories traditionally considered higher risk, including documented penicillin anaphylaxis and cephalosporin allergy. (Jones et al., 2021; Mannarino et al., 2023; Stevoska et al., 2022; Tan et al., 2016; Wu et al., 2020) This is consistent with contemporary immunologic understanding that cefazolin has a unique R1 side chain and does not share the main allergenic determinants responsible for most clinically relevant cross-reactivity with penicillins or many other cephalosporins. (Khan et al., 2022; Sousa-Pinto et al., 2021) Therefore, the historical practice of substituting clindamycin or vancomycin for cefazolin in most patients with a penicillin allergy label appears increasingly unsupported.

Nevertheless, the findings should not be interpreted as meaning that cefazolin is appropriate for every patient with a beta-lactam allergy history. The most important clinical distinction is between unverified, nonsevere, remote, or intolerance-type reactions and true severe delayed immune-mediated reactions. Severe cutaneous adverse reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, serum sickness-like reactions, organ injury, or severe delayed hypersensitivity remain clinically important situations where beta-lactam avoidance or specialist evaluation is appropriate. (Guido et al., 2026; Khan et al., 2022; Mannarino et al., 2023) The practical implication is not indiscriminate cefazolin use, but rather structured allergy clarification and risk stratification that separates low-risk labels from true high-risk reactions.

Several included studies showed that stewardship-based approaches can improve cefazolin utilization without increasing hypersensitivity events. Allergy testing, drug allergy clinic referral, electronic alerts, perioperative test-dose protocols, and multidisciplinary triage algorithms all increased appropriate first-line prophylaxis or reduced unnecessary second-line antibiotic use. (Guido et al., 2026; Mannarino et al., 2023; McDanel et al., 2017; Sousa-Pinto et al., 2021) These interventions are particularly relevant in arthroplasty because infection prevention is highly protocol-dependent and small differences in prophylaxis quality may translate into meaningful differences in periprosthetic joint infection burden at population level. A simple preoperative allergy history that distinguishes anaphylaxis, delayed severe reactions, mild rash, intolerance, remote childhood events, and prior beta-lactam tolerance may be a feasible first step even in centers without immediate access to formal allergy testing. The findings also highlight the need to reconsider the role of second-line antibiotics. Vancomycin and clindamycin remain necessary in selected patients, such as those with confirmed severe beta-lactam reactions or specific

microbiologic indications. However, routine substitution may expose patients to avoidable risks, including inferior prophylactic coverage, infusion-timing problems, nephrotoxicity, antimicrobial resistance pressure, and *C. difficile*-related concerns. (Stevoska et al., 2022; Tan et al., 2016) In the arthroplasty setting, the decision to use vancomycin should ideally be driven by clear indications such as MRSA colonization or institutional microbiologic risk rather than by a vague or unverified penicillin allergy label alone. Similarly, clindamycin use should be cautious in settings with high resistance rates or when better-tolerated beta-lactam options are clinically reasonable.

This review has several limitations. Most included studies were retrospective, and no randomized controlled trial directly compared cefazolin versus non-cefazolin prophylaxis specifically among beta-lactam allergy-labeled hip and knee arthroplasty patients. Confounding by indication is likely because patients receiving alternative antibiotics often had more severe reported allergy histories, greater comorbidity burden, MRSA-related risk factors, or provider-level concerns that were not always fully captured. Allergy definitions were heterogeneous, ranging from simple electronic allergy labels to detailed reaction phenotyping, and some studies relied on administrative codes or patient-reported allergy histories. Outcome definitions and follow-up windows also varied, particularly for surgical site infection, periprosthetic joint infection, hypersensitivity reaction, and anaphylaxis markers. In addition, several studies provided indirect evidence, such as comparisons between allergy-labeled and nonallergic patients, cefuroxime versus non-cefuroxime prophylaxis, or stewardship interventions rather than direct cefazolin-versus-alternative comparisons in the target population.

Despite these limitations, the direction of evidence was clinically coherent. Cefazolin was consistently safe in most beta-lactam allergy-labeled arthroplasty patients and was frequently associated with equal or better infection-related outcomes compared with non-cefazolin prophylaxis. The available evidence supports a shift from automatic cefazolin avoidance toward allergy-informed prophylaxis selection. Future studies should use standardized allergy phenotyping, clearly separate IgE-mediated and severe delayed reactions, report antibiotic timing and dosing, and compare infection and safety outcomes in prospective multicenter cohorts. Until stronger comparative trials are available, multidisciplinary stewardship pathways may represent the most practical strategy to optimize both infection prevention and perioperative allergy safety in hip and knee arthroplasty.

CONCLUSION

Cefazolin appears to be a safe and clinically favorable perioperative prophylactic option for most beta-lactam allergy-labeled patients undergoing hip and knee arthroplasty. Across included studies, cefazolin was associated with either lower or comparable rates of surgical site infection and periprosthetic joint infection compared with non-cefazolin alternatives, while clinically significant hypersensitivity reactions were rare, even among patients with reported penicillin anaphylaxis or cephalosporin allergy. The available evidence supports moving away from automatic cefazolin avoidance based solely on allergy labels and toward structured allergy clarification, risk stratification, and antibiotic stewardship pathways. Non-cefazolin prophylaxis should be reserved for patients with confirmed high-risk beta-lactam reactions or specific microbiologic indications.

REFERENCES

- Allan, L. P., Silvera-Tawil, D., Cameron, J., Li, J., Varnfield, M., Smallbon, V., Bomke, J., Olaiya, M. T., Lannin, N. A., & Cadilhac, D. A. (2024). Novel Multicomponent Digital Care Assistant and Support Program for People After Stroke or Transient Ischaemic Attack: A Pilot Feasibility Study. *Sensors*, 24(22). <https://doi.org/10.3390/s24227253>
- Anderson, J. A., Kimmel, B., Sansgiry, S., Venkatasubba Rao, C. P., Ovalle, A. P., Cerra-Stewart, C. A., & Kent, T. A. (2022). Using Mobile Video-Teleconferencing to Deliver Secondary Stroke Prevention Interventions: A Pilot Study. *Telemedicine Reports*, 3(1), 175–183.

- Blumenthal, K. G., Ryan, E. E., Li, Y., Lee, H., Kuhlen, J. L., & Shenoy, E. S. (2018). The impact of a reported penicillin allergy on surgical site infection risk. *Clinical Infectious Diseases*, 66(3), 329–336. <https://doi.org/10.1093/cid/cix794>
- Guido, J. M., Hudock, N. L., Frye, B. M., Parrish, K. L., Lastinger, A. M., Howard, C. A., Matyus, V. L., Leadman, K. M., Pincavitch, J. D., & Peppers, B. P. (2026). Standardizing safe cefazolin use in total joint arthroplasty: A multidisciplinary triage protocol. *The Journal of Arthroplasty*, 41(10S1), S133–S138. <https://doi.org/10.1016/j.arth.2026.03.100>
- Jones, R., Quartuccio, K. S., Stern, J. L., Heintz, E. V., Pillinger, K. E., & Myers, T. G. (2021). Antibiotic stewardship interventions improve choice of antibiotic prophylaxis in total joint arthroplasty in patients with reported penicillin allergies. *Clinical Orthopaedics and Related Research*, 479(7), 1484–1494. <https://doi.org/10.1097/CORR.0000000000001739>
- Khan, D. A., Banerji, A., Blumenthal, K. G., Phillips, E. J., Solensky, R., White, A. A., Bernstein, J. A., Chu, D. K., Ellis, A. K., Golden, D. B. K., Greenhawt, M. J., Horner, C. C., Ledford, D., Lieberman, J. A., Oppenheimer, J., Rank, M. A., Shaker, M. S., Stukus, D. R., Wallace, D., & Wang, J. (2022). Drug allergy: A 2022 practice parameter update. *Journal of Allergy and Clinical Immunology*, 150(6), 1333–1393. <https://doi.org/10.1016/j.jaci.2022.08.028>
- Mannarino, M., Montreuil, J., Tanzer, M., & Hart, A. (2023). Local tissue concentrations of cefazolin during total joint arthroplasty: A systematic review. *Canadian Journal of Surgery*, 66(4), E415–E421. <https://doi.org/10.1503/cjs.019621>
- McDanel, D. L., Azar, A. E., Dowden, A. M., Murray-Bainer, S., Noiseux, N. O., Willenborg, M., Clark, C. R., Callaghan, J. J., & Haleem, A. (2017). Screening for beta-lactam allergy in joint arthroplasty patients to improve surgical prophylaxis practice. *The Journal of Arthroplasty*, 32(9), S101–S108. <https://doi.org/10.1016/j.arth.2017.01.012>
- Norvell, M. R., Porter, M., Ricco, M. H., Koonce, R. C., Hogan, C. A., Basler, E., Wong, M., & Jeffres, M. N. (2023). Cefazolin vs second-line antibiotics for surgical site infection prevention after total joint arthroplasty among patients with a beta-lactam allergy. *Open Forum Infectious Diseases*, 10(6), ofad224. <https://doi.org/10.1093/ofid/ofad224>
- Sousa-Pinto, B., Blumenthal, K. G., Courtney, L., Mancini, C. M., & Jeffres, M. N. (2021). Assessment of the frequency of dual allergy to penicillins and cefazolin: A systematic review and meta-analysis. *JAMA Surgery*, 156(4), e210021. <https://doi.org/10.1001/jamasurg.2021.0021>
- Stevoska, S., Behm-Ferstl, V., Zott, S., Stadler, C., Schieder, S., Luger, M., Gotterbarm, T., & Klasan, A. (2022). The impact of patient-reported penicillin or cephalosporin allergy on the occurrence of the periprosthetic joint infection in primary knee and hip arthroplasty. *Antibiotics*, 11(10), 1345. <https://doi.org/10.3390/antibiotics11101345>
- Tan, T. L., Springer, B. D., Ruder, J. A., Ruffolo, M. R., & Chen, A. F. (2016). Is vancomycin-only prophylaxis for patients with penicillin allergy associated with increased risk of infection after arthroplasty? *Clinical Orthopaedics and Related Research*, 474(7), 1601–1606. <https://doi.org/10.1007/s11999-015-4672-4>
- Wu, V. J., Iloanya, M. C., Sanchez, F. L., Billings, C. R., O'Brien, M. J., Savoie, F. H., III, & Sherman, W. F. (2020). Is patient-reported penicillin allergy independently associated with increased risk of prosthetic joint infection after total joint arthroplasty of the hip, knee, and shoulder? *Clinical Orthopaedics and Related Research*, 478(12), 2699–2709. <https://doi.org/10.1097/CORR.0000000000001497>
- Wyles, C. C., Hevesi, M., Osmon, D. R., Park, M. A., Habermann, E. B., Lewallen, D. G., Berry, D. J., & Sierra, R. J. (2019). 2019 John Charnley Award: Increased risk of prosthetic joint infection following primary total knee and hip arthroplasty with the use of alternative antibiotics to cefazolin: The value of allergy testing for antibiotic prophylaxis. *The Bone & Joint Journal*, 101-B(6_Supple_B), 9–15. <https://doi.org/10.1302/0301-620X.101B6.BJJ-2018-1407.R1> <https://doi.org/10.1089/tmr.2022.0026>