Is Penicillin Allergy a Clinical Problem? A Systematic Review of Total Joint Arthroplasty Procedures with Implications for Patient Safety and Antibiotic Stewardship

Joshua Porto, Monish Sai Lavu, Christian Joseph Hecht, Ryan McNassor, Robert John Burkhart, Atul F Kamath[1]
[1]Cleveland Clinic

INTRODUCTION:
Patients undergoing total joint arthroplasty (TJA) who report penicillin allergy (PA) are frequently administered second-line antibiotics, though recent evidence suggests this may be unnecessary and could increase infection risk. Many institutions have aimed to improve antibiotic deployment via allergy testing and screening; however, there is little standardization to this process. This review aimed to evaluate: 1) antibiotic selection in patients who report PA and assess the impact of antibiotic stewardship interventions, 2) rates of allergic reactions in patients with a reported PA, and 3) the association between reported PA and stewardship programs and odds of surgical site infection (SSI) or periprosthetic joint infection (PJI).
METHODS:
PubMed, EBSCOhost, and Google Scholar electronic databases were searched on February 4, 2023 to identify all studies published since January 1, 2000, that evaluated the impact of PA on patients undergoing TJA (PROSPERO study protocol registration: CRD42023394031). Articles were included if full-text manuscripts in English were available and the study analyzed the impact of PA and related stewardship on patients undergoing total hip or knee arthroplasty.
RESULTS: Eleven studies evaluating 1,276,663 patients were included **(Table 1)**. All six studies reporting found that PA screening and testing increase the use of first-line antibiotics **(Table 2)**. Also, the frequency of allergic reaction for patients with a reported PA receiving cephalosporins was between 0-2% **(Table 3)**. Although there were mixed findings across studies, there was a trend toward second-line antibiotic prophylaxis being associated with a slightly higher rate of SSI and PJI in PA patients **(Table 4)**.
DISCUSSION AND CONCLUSION: The studies analyzed in this review showed that patients who report PA are less likely to receive cephalosporins, are frequently categorized as high-risk for cross-reaction, and seldom demonstrate a true allergy upon testing. Furthermore, several institutions achieved demonstrable increases in cephalosporin usage following implementation of antibiotic stewardship interventions, which included check-in questionnaires, medical record screens, PA testing, perioperative "test doses" of cephalosporin agents, and institutional guideline changes. Future research on the efficacy of allergy screening and testing programs, as well as their impact on patient outcomes, can help guide decision makers in determining appropriate interventions at their institutions and inform future guidelines.

Table 1. Characteristics of studies included in the final analysis.

Study (year)	Design	Sample size (n)	Study Period	Source of Data	Procedure	Antibiotics Used	MINORS Score
Wyles et al. 2019[37]	Retrospective	29,695	2004-2017	Single Institution	THA,TKA	Cefazolin (94.9%) vs Vancomycin/Clindamycin (5.1%)	19
Goh et al. 2021[7]	Prospective	4,136	2019-2020	Single Institution	THA,TKA	Cefazolin (89.6%) vs Vancomycin/Clindamycin (10.4%)	23
Jones et al. 2021[11]	Retrospective	180	2017-2019	Single Institution	THA,TKA	Cefazolin (+/- vancomycin for MRSA risk); 72.7% vs vancomycin monotherapy; 27.3%	21
Haslam et al. 2012 [8]	Retrospective	1,962	2007-2010	Single Institution	THA,TKA	Cefazolin (87.1%) vs other (12.9%)	17
Kurcz et al. 2023 [14]	Retrospective	2,284	2014-2017	Single Institution	THA,TKA	Cefazolin (92.8%) vs other (7.2%)	18
Wu et al. 2020 [36]	Retrospective	1,197,814	2010-2018	PearlDiver	THA,TKA	N/A	19
Tan et al. 2016 [32]	Retrospective	10,391	2005-2014	Two Institutions	THA,TKA	Cefazolin (74.4%) vs Vancomycin (25.6%)	20
McDanel et al. 2017 [22]	Retrospective	363	2013-2015	Single Institution	THA,TKA	Cefazolin in regimen (84.6%) vs no cefazolin in regimen (15.4%)	20
Ponce et al. 2014 [26]	Retrospective	18,830	2005-2009	SCIP and VASQIP	THA,TKA	Cefazolin (81.9%), vancomycin (8.0%, cefazolin + vancomycin (5.6%), clindamycin (4.5%)	19
Stone et al. 2019 [31]	Retrospective	4,903	2005-2017	Single Institution	THA,TKA	Cefazolin (80.6%), clindamycin (14.0%), vancomycin (5.4%)	18
Stevoska et al. 2022 [30]	Retrospective	6,085	2011-2020	Single Institution	THA,TKA	Cefuroxime (94.0%) vs. clindamycin, ciprofloxacin, vancomycin (6.0%)	19

THA, total hip arthroplasty; TKA, total knee arthroplasty; MINORS, Methodological Index for Nonrandomized Studies; N/A, none available; SD, standard deviation

Table 2. Key findings from studies evaluating patient-reported prevalence versus actual prevalence of PA.

Study	Method of Screening for Allergy	Key Findings	True PA/ High-Risk Rate from Reported Allergies
Wyles et al. 2019[37]	Patients reporting /cephalosporin allergy given preoperative allergy test	Out of 28,174 TJAs, 11.5% had preoperative allergy testing (3,411 patients). Among the 2,376 tested patients, only 3.2% were not cleared for cephalosporins, while 96.8% of patients and 97.0% of arthroplasties were cleared. Allergy consultation increased cefazolin use by around 27.0%, resulting in 920 more patients receiving it. Allergy testing also reduced non-cefazolin use perioperatively from 30% to 5% in this group.	3.2%
Jones et al. 2021[11]	Stewardship program; identification of high-risk patients and referral to allergy, immunology, and rheumatology	Out of 90 patients reporting allergies in the intervention group, 11 reported severe penicillin allergies. Four of them were referred to allergy, and three had their PA removed from their chart. One patient had intolerance to amoxicillin oral challenge, but all four patients received cefazolin for their procedure. After the intervention, patients were much more likely to receive first-line perioperative prophylaxis (91%) compared to before (54%).	1.1%
McDanel et al. 2017 [22]	TJA patients with reported beta-lactam allergy history were referred for skin testing via electronic alert	An electronic alert was sent for 363 patients, of which 161 (44%) patients were appropriately evaluated at the drug allergy clinic (DAC). 140 (87%) patients received penicillin skin testing, with 139 (>99%) negatives for true allergy. DAC-evaluated patients received cefazolin more often (90%) than non-DAC patients (77%), using fewer non-beta lactam antibiotics (16% vs 27%).	0.7%
Goh et al. 2021[7]	Questionnaire to determine high-risk (receive vancomycin or clindamycin) and low-risk patients (receive cefazolin) for an IgE-mediated reaction	In the protocol group with the questionnaire, 17.2% self-reported a PA, and 33.1% of those were high-risk. The control group had 17.2% of patients with reported PA in the EMR. Multivariate regression showed 3 times greater cephalosporin use in the protocol group than the control group.	33%*
Haslam et al. 2012 [8]	IgE-mediated reaction history retrospectively queried for patients reporting PA	Out of all the patients, 9.9% reported having a PA. Various allergic reactions, including IgE-mediated reactions such as anaphylaxis, urticaria, angioedema, and airway compromise, were reported by 23% of patients. Cefazolin was administered to fewer patients who reported a PA to it (27%) compared to non-allergic patients (93%).	25%*
Stone et al. 2019 [31]	Retrospective classification of PA into tiers of severity	16.2% of patients reported a PA. These allergies were classified into three tiers based on the severity of the reaction reported (1=IgE-mediated allergic response, hypersensitivity reactions, 2= side effects, 3 = unknown). 77.2% of patients were included in tier 1 and 11.2% were in tier 2. Female sex, ASA score, age, and white race were shown to be independent predictors of PA reporting.	77%*

THA = total hip arthroplasty; BMI = body mass index; TKA = total knee arthroplasty; TJA = total joint arthroplasty; PA= penicillin allergy; * indicates high-risk PA

Table 3. Key findings from studies evaluating adverse reaction rate with and without screening/intervention programs.

Study	Key Findings	Cross-Reactivity Rate
Goh et al. 2021[7]	After implementing the protocol, the rate of adverse reactions did not vary. Most allergic reactions were due to cefazolin administration. Out of the 239 patients (66.9%) placed in the low-risk category, cefazolin was administered to all. Of these patients, 236 (98.7%) tolerated the cefazolin without any problems, while three experienced allergic reactions (all grade-1). This resulted in a cross-reactivity rate of 1.3%.	1.3%
Jones et al. 2021[11]	2% (2/130) of the patients with documented PA receiving cefazolin had an adverse reaction and received diphenhydramine for itching. This was likely not related to cefazolin administration. None of the patients with documented severe PA experienced allergic reactions following cefazolin administration.	2%
Haslam et al. 2012 [8]	Cefazolin was not administered to any patient who reported an IgE-mediated reaction. Furthermore, none of the patients who were allergic to but did not have IgE-mediated reactions experienced adverse reactions after receiving cefazolin.	0%
Kurcz et al. 2023 [14]	Among all patients, 0.5% experienced allergic reactions. Of those who received cefazolin, 0.4% experienced an adverse reaction, compared to 1.02% of those who received a second-line antibiotic. This difference was not significant. Patients reporting PA had a significantly higher rate of allergic reaction (1.3% vs. 0.3%) and markedly increased odds when controlling for age, sex, and pulmonary comorbidities. Only 1 (0.7%) of 143 patients with a reported PA receiving cefazolin experienced an allergic reaction.	0.7%
Stone et al. 2019 [31]	The majority of patients who reported having a PA were administered second-line antibiotics: 80.7% were given clindamycin, 12.4% were given vancomycin, and 6.9% were given cefazolin. Among those who were given cefazolin, 54.5% had experienced a previous tier 2 or 3 penicillin reaction. Notably, none of the patients who reported a PA and received cefazolin had an allergic reaction to this medication.	0%
Stevoska et al. 2022 [30]	In the THA group, 269 patients (7.7%) reported penicillin or cephalosporin allergies, while in the TKA group, 268 patients (10.1%) reported allergies. Among those who reported allergies, 63 patients (23.4%) in the THA group and 57 patients (21.3%) in the TKA group were given cefuroxime, with no allergic reactions reported in either group. Of note, however, the majority of patients reporting PA in both groups were given second-line antibiotics.	0%

THA = total hip arthroplasty; BMI = body mass index; TKA = total knee arthroplasty; TJA = total joint arthroplasty; PA= penicillin allergy