Research Article

Documented Penicillin Allergies Should Not Preclude Use of Preoperative Cefazolin in Hip and Knee Arthroplasty

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ABSTRACT

Introduction: Perioperative cefazolin administration for total joint arthroplasty is a first-line antibiotic recommended by the American Academy of Orthopaedic Surgeons (AAOS) guidelines for the prevention of periprosthetic joint infections (PJIs). We aim to analyze the clinical viability of giving patients with a documented penicillin allergy (PA) a perioperative full-strength cefazolin "test dose" under anesthesia.

Methods: This is a retrospective chart review of 2,451 total joint arthroplasties from a high-volume arthroplasty orthopaedic surgeon over a 5-year period from January 2013 through December 2017. This surgeon routinely gave patients with a documented PA a full-strength cefazolin test dose while under anesthesia instead of administrating a second-line antibiotic. The primary outcomes examined were allergic reaction and postoperative infection.

Results: Cefazolin was given to 87.1% of all patients (1,990) and 46.0% of patients with a PA (143). The total rate of allergic reactions among all patients was 0.5% (11). Only one patient with a documented PA who received cefazolin had an allergic reaction. The reaction was not severe and did not require any additional treatment. In patients who had no reported allergies and received cefazolin, 0.3% (6) had an allergic reaction. There was no statistically significant difference in the rate of allergic reaction when comparing patients with and without a PA ($P = 0.95$). Patients receiving cefazolin had an overall PJI rate of 2.9% (57) versus those patients receiving antibiotics other than cefazolin who sustained a 5.5% PJI rate (16), which was statistically significant ($P = 0.02$).

Conclusion: This study found that utilization of a full-strength test dose of cefazolin in patients with a documented PA is a feasible, safe, and effective way of increasing the rate of cefazolin administration and thus mitigating the risk of PJIs.

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None of the following authors or any immediate family member has received anything of value from or has stock or stock options held in a commercial company or institution related directly or indirectly to the subject of this article: Kurcz, Allan, Nestler, Lister, Yarnell, Delfino, Thuppal, and Horberg.

J Am Acad Orthop Surg 2023;31:e107-e117

DOI: 10.5435/JAAOS-D-22-00122

Infection after total hip arthroplasty (THA) and total knee arthroplasty (TKA) is a devastating complication and a tremendous burden on patients and the healthcare system.[1,2] Perioperative antibiotic administration is one of the cornerstones of prevention of periprosthetic joint infection (PJI). Given increasing rates of antibiotic resistance worldwide, proper antibiotic selection and stewardship is of utmost importance.[3] The AAOS guidelines include cefazolin administration for preoperative prophylaxis in total joint arthroplasty (TJA) for its optimal coverage of skin flora including gram-positive and gram-negative organisms.[4] This recommendation is based on its ease of administration, benign adverse effect profile, and low cost when compared with other recommended antibiotics, leading to a decreased infection rate comparably.[5] One of the reasons for failure to administer perioperative cefazolin is a documented penicillin allergy (PA).[6] Surgeons and anesthesiologists may use alternative antibiotics such as vancomycin or clindamycin when a patient reports a PA. In fact, cefazolin use has been reported to be 20% to 80% less in the setting of documented PA.[7] The coverage of these alternative antibiotics and their adverse effect profile may not be as good as cefazolin. The 2019 John Charnley Award–winning study by Wyles et al[8] found that patients who were administered cefazolin at the time of surgery demonstrated statistically significant increased 1-, 5-, and 10-year implant survivorship as compared with the noncefazolin group.

Studies suggest that 5% to 10% of patients have a documented allergy to penicillin (PCN) in their medical record.[9] It is sometimes unclear whether the documented reaction was Immunoglobulin E (IgE)-mediated, which only occurs in 1.16% of individuals, or non–IgE-mediated maculopapular reactions, which can be delabeled.[10] Furthermore, adverse drug reactions such as diarrhea, nausea, or emesis may be mischaracterized as allergic reactions.[11] In fact, one retrospective review of adverse events related to prophylactic cefazolin in TJA patients reporting non-IgE reactions to PCN found no allergic reactions in these patients.[12] Attributing symptoms of concomitant viral exanthems of childhood to allergic response to medication may have also complicated allergy reporting.[13] Moreover, more than 80% of patients who had an acute IgE-mediated reaction to PCN as children will no longer have detectable circulating IgE antibodies 10 years later.[12,14] The literature suggests that patients reporting a PA are substantially less likely to receive cefazolin (12%) compared with those patients without a PA (92%) and at an increased odds ratio (OR = 1.51) of sustaining a surgical site infection (SSI).[5]

Recent studies have questioned the validity of concerns regarding cross-reactivity between penicillins and cephalosporins.[15] Early concerns for cross-reactivity stemmed from similarities in the chemical structure. Both penicillins and cephalosporins contain a β-lactam ring, which confers their antimicrobial activity, and a sulfur-containing side ring. Penicillins contain a five-membered thiazolidine ring, whereas cephalosporins contain a six-membered dihydrothiazine ring. Furthermore, under physiologic conditions, the β-lactam ring in penicillin spontaneously unfolds, forming a highly antigenic and free thiazolidine ring and penicilloyl group, whereas both rings in cephalosporins rapidly degrade rendering them immunologically inert.[15] Studies reporting cross-reactivity as high as 10% between penicillin and cefazolin have been subsequently attributed to bacterial contamination and outdated preparation processes.[12] Recent clinical studies in both adult and pediatric patients have also brought the clinical relevance of cephalosporin cross-reactivity with PCN into question.[12,14,15]

Some authors have advocated for preoperative screening programs to test for cross-reactivity to cephalosporins.[1] These may not be available in all clinical settings. In addition, cephalosporin allergy skin testing for immediate hypersensitivity has not been standardized nor validated.[16] Because most cephalosporin reactions are immediate in nature occurring within one hour of administration, one promising strategy is to administer an intravenous, full-strength "test dose" while the patient is under monitored anesthesia care. Given these risk-mitigating factors and in the interest of antibiotic stewardship, we have decided to investigate whether intraoperative administration of IV cefazolin is clinically viable. We decided to investigate cephalosporin administration in patients labeled with a PA who did and did not receive a cephalosporin. We hypothesize from the current literature that those with a PA can safely be given a cephalosporin for preoperative prophylaxis in hip and knee arthroplasty in most instances. Furthermore, cefazolin administration will lead to decreased PJIs when given over second-line antibiotics.

Methods

Data from all patients older than 18 years undergoing primary and revision THA or TKA by a single

arthroplasty fellowship-trained orthopaedic surgeon over a 5-year period from January 2013 through December 2017 based on a Current Procedural Terminology (CPT) code query were included in this retrospective study. This study was approved by the Springfield Committee for Research Involving Human Subjects. Data collected included demographics, comorbidities, medication allergies, antibiotics administered during surgery, and any allergic reactions that occurred perioperatively. Postoperative infections were also identified for comparison purposes.

Data were stratified and statistically analyzed based on PA, whether the patient received cefazolin, and primary or revision surgery. The primary end points were postoperative infection and allergic reaction. Additional subgroup analysis comprised our secondary outcomes including PA related to comorbidities and cefazolin administration related to comorbidities. Independent statistical analysis was conducted using SAS v9.4. Descriptive statistics were computed for all variables. Student *t*-tests were used to test for differences in continuous variables. Comparisons between categorical variables were compared with the χ^2 test. Logistic regression was used to determine notable predictors of our outcome variables of interest. ORs with 95% confidence intervals are reported. Multivariate logistic regression was then used to adjust for covariates and potential confounders on our outcome variables. Significance was determined at the $P < 0.05$ level.

Results

Data from 2,451 procedures conducted during the 5-year period were collected; 167 patients had incomplete information leaving 2,284 procedures being included in the analysis. There were 1,709 primary procedures (880 THA, 829 TKA) and 575 revision procedures (246 THA, 329 TKA). Of the revision procedures, 441 were for aseptic reasons and 132 were for infection. There were 389 patients (17%) with a PA or cephalosporin allergy. Of those, 310 had a PA; 57 had a cephalosporin allergy; and 22 had both.

In total, 87.1% of patients (1,990/2,284) received cefazolin as preoperative prophylaxis. A larger proportion of patients who received cefazolin antibiotics were male (46% versus 35%, $P = 0.0004$) and underwent primary surgeries (77% versus 60%, $P < 0.0001$) compared with those who did not. Most of the comorbidities were similar between those who received cefazolin antibiotics compared with a second-line antibiotic; however, patients given cefazolin had a lower percentage of pulmonary comorbidities (22% versus 31%, $P = 0.0007$; Table 2). A significantly higher proportion of patients who received cefazolin were observed in the no allergy group compared with those with only a PA (1,809/1,894 and 96% versus 143/310 and 46%; $P \leq 0.0001$). Univariate regression analysis showed that PCN allergy was a significant factor in receiving cefazolin (OR 0.040; 95% CI, 0.029 to 0.055, $P < 0.0001$). When adjusting for confounders of sex, surgery type, and pulmonary comorbidities, PA remains significant (OR 0.038; 95% CI, 0.028 to 0.053, $P < 0.0001$). Sex and pulmonary comorbidity variables were also associated with PA. A higher percentage of females (65% versus 53%, $P < 0.0001$) and pulmonary comorbidities (35% versus 21% $P \leq 0.0001$) were observed in the PCN allergy population compared with the no allergy group. Age was also significantly higher in the PCN population (67 versus 65, $P = 0.0221$; Tables 1 and 2).

The total rate of allergic reactions among all patients was 0.5% (n = 11). Of those receiving cefazolin, 0.4% (8/1,988) had an allergic reaction compared with 1.02% (3/294) of those receiving second-line antibiotics; however, this was not statistically significant ($P = 0.1596$). A significantly higher rate of allergic reactions was observed in those with a PA (1.3%, n = 4/310) versus those who reported no allergies (0.3%, n = 6/1,887; $P = 0.04$). When controlling for confounders of age, sex, and pulmonary comorbidities, those with a PA still remained at increased risk of reaction versus those with no allergy (OR 4.0; 95% CI, 1.1 to 14.6). However, of the four patients with PA who had an allergic reaction, only one was given cefazolin. The reaction was not severe and did not require any additional treatment. See Figure 1 for a graphic representation of the allergic reaction rate by antibiotic type and allergy status.

The periprosthetic infection rate was 3.2% of all patients (73). A significantly higher infection rate was observed in revision arthroplasties (8.9%, 51 total, 21 THA, 30 TKA) compared with that in primary arthroplasties (1.3%, 22 total, 13 THA, 9 TKA; $P < 0.0001$). The infection rate was not significantly different between those with a PA compared with no allergy (7/307 [2 primary, five revision] versus 60/1,825 [18 primary, 42 revision] $P = 0.3941$). See Figure 2 for a comparison of infection rates based on allergy status. Patients receiving cefazolin had an overall PJI rate of 2.9% (57) versus those patients receiving antibiotics other than cefazolin who sustained a 5.5% PJI rate (16), which was statistically significant ($P = 0.02$). Univariate regression

Table 1. **Demographic and Comorbidity Frequencies for PA Including *P*-values Showing Significant Differences Between Those With and Without PCN Allergy**

		Allergy			% No Allergies	% PCN	*P*
		No Allergies	PCN	Total			
Age	Mean ± SD	65.3 ± 11.2	66.9 ± 11.0				0.0221
BMI	Mean ± SD	31.7 ± 6.0	31.4 ± 5.8				0.4263
Sex	F	1,004	202	1,206	53	65	<0.0001
	M	890	108	998	47	35	
Joint	THA	947	143	1,090	50	46	0.2063
	TKA	947	167	1,114	50	54	
Type	Primary	1,437	220	1,657	76	71	0.0639
	Revision	457	90	547	24	29	
DM	No	1,523	242	1,765	81	79	0.421
	Yes	368	66	434	19	21	
PVD	No	1,841	297	2,138	97	96	0.2223
	Yes	50	12	62	3	4	
CKD	No	1,774	285	2059	94	92	0.2768
	Yes	116	24	140	6	8	
Liver	No	1,837	305	2,142	97	99	0.1123
	Yes	54	4	58	3	1	
CAD	No	1,554	243	1,797	82	79	0.1361
	Yes	337	66	403	18	21	
PULM	No	1,490	201	1,691	79	65	<0.0001
	Yes	399	108	507	21	35	
EtOH	No	1,513	260	1,773	80	84	0.0917
	Yes	377	49	426	20	16	
Tobacco	No	1,065	174	1,239	56	56	0.9899
	Yes	825	135	960	44	44	
Blood thinners	No	1,477	237	1,714	78	77	0.569
	Yes	413	72	485	22	23	

BMI = body mass index, PA = penicillin allergy, PCN = penicillin, THA = total hip arthroplasty, TKA = total knee arthroplasty, DM = diabetes mellitus, PVD = peripheral vascular disease, CKD = chronic kidney disease, CAD = coronary artery disease, PULM = Document Pulmonary Disease, EtOH = Document alcohol use.

analysis results showed decreased odds of developing a PJI when cefazolin was administered versus second-line antibiotics (OR 0.509; 95% CI, 0.288 to 0.899 $P = 0.02$). When adjusting for confounders of sex, surgery type, and pulmonary comorbidities, cefazolin administration was no longer significant in predicting PJI ($P = 0.2657$), but primary surgery still had significantly decreased odds (OR 0.144; 95% CI, 0.086 to 0.241, $P < 0.0001$) (Table 3). See Figure 3 for comparison of infection rates based on the antibiotic administered.

When looking at primary joint arthroplasty, 1.4% (22/1,525) of those receiving cefazolin developed PJI compared with those receiving other antibiotics (0%, 0/176), which was not significantly different ($P = 0.16$). For revision surgery, there was a statistically significant decrease in infection rates with cefazolin use (7.7%, 35/456) compared with other antibiotics (13.9%, 16/115) ($P = 0.04$). When separating this out even further between aseptic and septic revisions, we can see a clear difference in the infection rate when cefazolin was used in aseptic revisions. Patients undergoing aseptic revision who received cefazolin had a 6% infection rate (22/367) compared with those who received second-line antibiotics, who had a 12.3% infection rate (9/73). This

Table 2. Demographic and Comorbidity Frequencies for Cefazolin Administration Including *P*-values Showing Significant Differences Between Those Who did and did Not Receive Cefazolin as Antibiotic Prophylaxis

		Antibiotic					
		Cefazolin	Other	Total	% Cefazolin	% Other	*P*
Age	Mean ± SD	65.5 ± 11.1	65.9 ± 11.5	65.5 ± 11.2			0.5793
BMI	Mean ± SD	31.7 ± 6.0	31.9 ± 6.4	31.7 ± 6.0			0.6509
Sex	F	1,079	192	1,271	54	65	0.0004
	M	911	102	1,013	46	35	
Joint	THA	989	137	1,126	50	47	0.321
	TKA	1,001	157	1,158	50	53	
Type	Primary	1,532	177	1,709	77	60	<0.0001
	Revision	458	117	575	23	40	
DM	No	1,593	225	1,818	80	77	0.1737
	Yes	393	68	461	20	23	
PVD	No	1,934	280	2,214	97	96	0.0917
	Yes	53	13	66	3	4	
CKD	No	1,862	271	2,133	94	92	0.4092
	Yes	124	22	146	6	8	
Liver	No	1,932	290	2,222	97	99	0.0767
	Yes	55	3	58	3	1	
CAD	No	1,635	230	1,865	82	78	0.1169
	Yes	352	63	415	18	22	
PULM	No	1,540	201	1,741	78	69	0.0007
	Yes	445	92	537	22	31	
EtOH	No	1,594	248	1,842	80	85	0.0754
	Yes	392	45	437	20	15	
Tobacco	No	1,129	158	1,287	57	54	0.3462
	Yes	857	135	992	43	46	
Blood thinners	No	1,555	220	1,775	78	75	0.2161
	Yes	431	73	504	22	25	

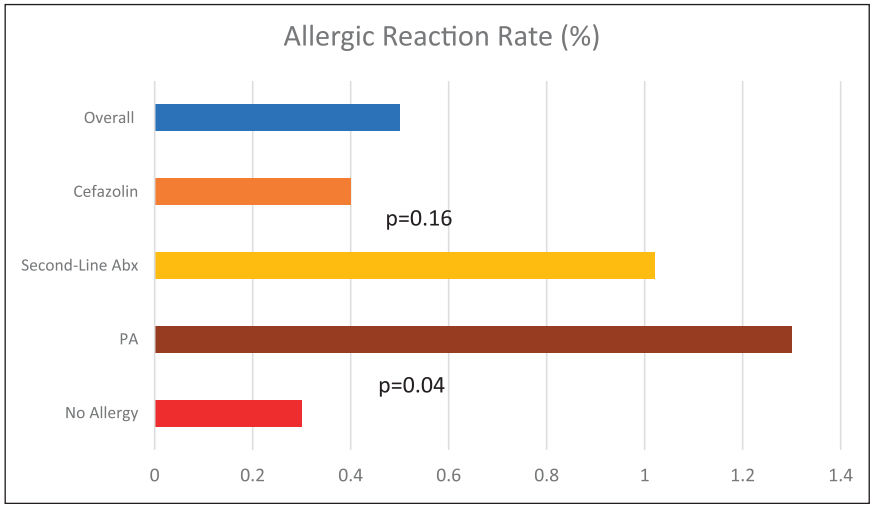
BMI = body mass index, THA = total hip arthroplasty, TKA = total knee arthroplasty

nearly approached significance with a *P*-value of 0.053. Those patients undergoing revision for infectious causes given cefazolin had a 14.8% infection rate (13/88) compared with those who received second-line antibiotics, who had a 17.1% infection rate (7/41), which was not statistically significant ($P = 0.74$). See Figure 4 for a graphic representation of the revision type and infection rate based on antibiotic choice.

Discussion

Perioperative antibiotic selection for TJA at our institutions, like many, has evolved over recent years. As evidence emerges, both demonstrating the superiority of cefazolin in preventing prosthetic joint infection and calling the risk of penicillin to cephalosporin allergic cross-reactivity into question, we have made a concerted effort to minimize the use of alternative antibiotics. It has become our practice to administer a weight-based (2 to 3 g) full-strength test dose in the operating room while monitored directly by anesthesia. This has raised safety concerns for some surgeons and anesthesia providers. The purpose of this study was to evaluate the safety of the full-strength test dose protocol in the face of penicillin and cephalosporin allergies and to assess the risk of infection for patients receiving cefazolin versus

Figure 1

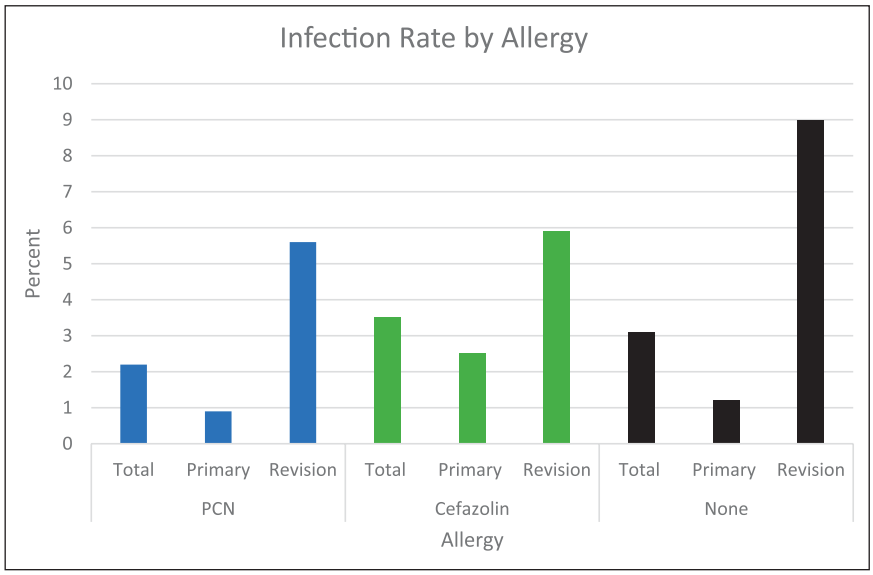


Graph showing allergic reaction rate by antibiotic administered and allergy status and related *P*-values.

alternative antibiotics in the setting of primary and revision total hip and knee arthroplasty.

The original reports of penicillin cross-reactivity with first-generation cephalosporins suggested a rate of 3% to 18%. However, in the infancy of these cephalosporins, manufacturing techniques caused trace amounts of penicillin to be included in the drug. With today's standards, there is no longer any penicillin in cephalosporin antibiotics, and they have shown a much lower cross-reactivity rate at less than 0.1%.[12] Furthermore, recent literature has shown that the structural difference between penicillin and cefazolin side chains makes them dissimilar enough to not indicate any cross-reactivity at all, although allergic reactions to one beta-lactam can confer an allergic reaction to other beta-lactams as an independent hypersensitivity.[15] This was shown in a study by Romano et al[16] where 3.2% of patients with a IgE-mediated reaction to penicillin also had positive skin test results to cephalosporins despite completely different side chains. They also found that of 130 skin prick test–positive PA patients, one patient had not only a cephalosporin allergy but also an allergy to all beta-

Figure 2



Graph showing PJI rate (%) of all patients/procedures reporting (1) PA, (2) cephalosporin allergy, and (3) no allergy. PA = penicillin allergy, PJI = periprosthetic joint infection

Table 3. **Multivariate Analysis Results Show OR of Infection Based on Cefazolin Administration Versus Second-Line Antibiotics and Associated Patient Comorbidities**

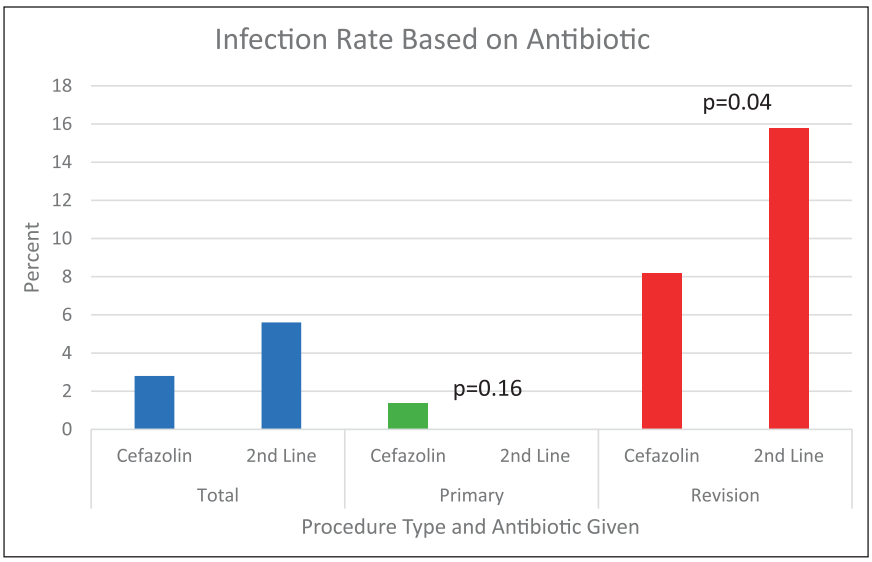
Multivariate Analysis-Infection	OR	95% CI	*P*
Antibiotics—cefazolin vs other	0.716	0.397-1.29	0.2657
Sex—F vs M	0.758	0.47-1.224	0.2573
Type—primary vs revision	0.144	0.086-0.241	<0.0001
PULM—yes vs No	1.338	0.803-2.229	0.2632

OR = odds ratio

lactam antibiotics, which shows the possibility of a different moiety causing a reaction besides the R side chains.

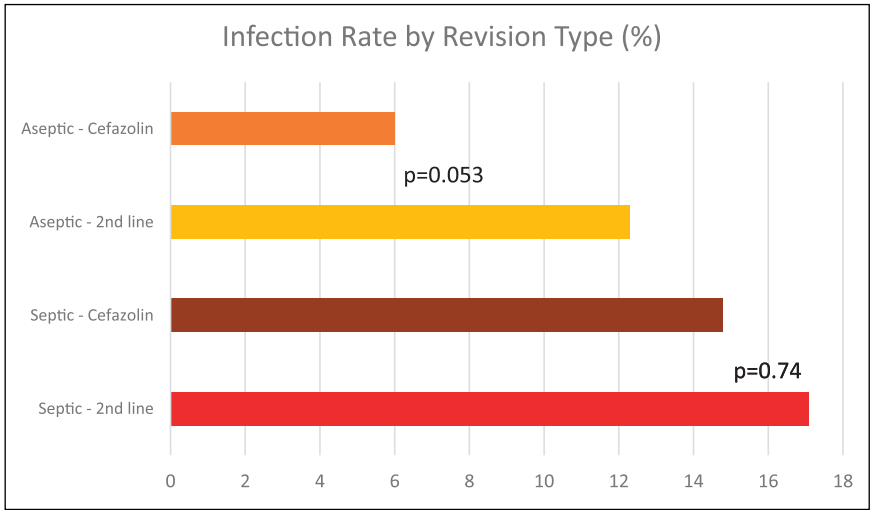
Despite this, some guidelines recommend administration of IV vancomycin or IV clindamycin in patients with a documented major reaction to PCN.[17] These agents carry their own adverse effects, and their overuse is associated with the emergence of resistant organisms.[13] Clindamycin has been associated with *Clostridium difficile* infection while vancomycin administration must be started before incision but given slowly, which sometimes does not correlate with full administration before incision. Vancomycin also carries risk of nephrotoxicity and red man syndrome. Cefazolin presents a lower risk to patients overall and offers more specific microbe coverage compared with the recommended alternatives vancomycin and/or clindamycin. Minimizing the overuse of broad-spectrum antibiotics in favor of targeted antibiotics is better antibiotic stewardship. In light of newer studies questioning penicillin-cephalosporin cross-reactivity, the use of these agents in all patients with documented PA may be unnecessary. In a study assessing the use of clindamycin and vancomycin in shoulder arthroplasty, clindamycin exhibited a hazard ratio of 3.45 when compared with cefazolin administration for postoperative infection, whereas vancomycin did not show a statistically significant increased risk of infection.[18] A similar study focusing on vancomycin-only administration in arthroplasty surgery showed no difference in deep SSI infection, a reduced odds of infection with gram-positive organisms (OR 0.25) and antibiotic-resistant organisms (OR 0.10), but an increased risk of infection with gram-negative organisms (OR 2.42).[19] The reporting of penicillin allergies in a study by Blumenthal et al[5] has shown a 23% increased odds of Clostridium difficile infection, 30% increased odds of vancomycin-resistant enterococcus

Figure 3



Graph showing PJI rate (%) in relation to (1) all procedures, (2) primary arthroplasty, and (3) revision arthroplasty and related *P*-values.
PJI = periprosthetic joint infection

Figure 4



Graph showing infection rate based on revision type—(1) aseptic and (2) septic—compared between administered antibiotics and related *P*-values.

infection, and an OR of 1.5 for SSI simply based on the choice of the physician to use an alternative to a beta-lactam antibiotic.

Among prescribing physicians, the knowledge of the extremely low allergic cross-reactivity between penicillins and cephalosporins has been very low. One survey showed that as many as 43% to 59% did not know the correct cross-reactivity and that only 78% to 82% of physicians prescribed a cephalosporin in patients with a nonanaphylactic reaction to penicillin.[6] The 2019 John Charnley Award–winning study suggested improved infection-free survivorship at 1, 5, and 10 years for patients receiving cefazolin. Many studies have centered around how to manage the patient labeled with a PA. This "allergy" can vary from an adverse effect, mild reaction, anaphylaxis, to severe delayed reaction including toxic epidermal necrosis and Steven-Johnson syndrome. Greater than 95% of patients labeled with a PCN allergy can tolerate penicillin, and 99% of people who undergo skin testing and oral challenge tests have a negative result.[11,20] This supports the claim that many PCN allergies are miscategorized or incorrectly reported. Furthermore, the allergic effect of PCN has waned over 10 years after exposure in greater than 80% of patients.[21,22] Combining this with the fact that severe reactions to PCN only occur 0.5% to 2% of the time and that the R1 side chain of PCN and cefazolin differs markedly brings the cross-reactivity down to less than 2% and makes the overall chance of severe reaction extremely low.[20] In our study especially, we focused on cefazolin administration in light of PA because of misnomers of allergic reaction, type of reaction, and agreement among other team members, it was given only 44.6% of the time in a patient with listed PA. This is may be much higher than some institutions but still lower than desired, which may be a weakness of this study to identify total risk of allergic reaction and cross-reactivity.

Preoperative allergy testing can reduce the cost burden of PJI; however, it is difficult to do preoperative allergy testing in some areas because of availability or physician knowledge.[23] Alternatively, a questionnaire validation system has been developed that can quantify those at risk of a severe reaction and in need of preoperative testing versus those that can undergo a cefazolin test dose intraoperatively.[24] This includes the Penicillin Allergy Decisional Rule (PEN-FAST) questionnaire, which can be used to produce a score that determines the patient's relative risk of reaction. The questions include (1) PA, (2) reactions in past 5 years, (3) anaphylactic reactions, (4) severe cutaneous reactions, and (5) treatment of reactions. A score of three or more gave a 70.7% sensitivity, 78.5% specificity, and 96.3% negative predictive value. This can then be used to determine who is safe for a challenge test to cefazolin.

Despite limitations, formal allergy testing can still play an important role. Some studies recommend testing all patients with reported PA. A joint task force comprising the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology reported that a negative PCN skin test is sufficient for cephalosporin administration without additional testing whether the underlying concern was

the presence of a PCN allergy.[25] Allergy testing can be costly and time consuming because of the limited specialists, limited availability of testing, and patient monitoring that needs to take place during the tests. The cost has been estimated at $225.71, which pales in comparison with PJI that can cost on average $27,870 for TKA and $34,445 for THA. Some authors suggested there would only need to be a 0.61% and 0.66% absolute risk reduction for TKA and THA, respectively, to confer cost benefit of testing all patients with PA.[23] Other studies, however, have contradicted this suggesting that the number needed to treat to prevent one infection would need to be between 112 and 124, which brings the cost of testing almost equal to that of one PJI.[5] Regardless of the cost, greater than 96% of patients who undergo skin testing test negative. This in turn influences antibiotic administration and increases the use of cefazolin considerably, which in and of itself decreases the risk of PJI.

An even more simplified approach that has been suggested and rarely described, which is the suggestion of this study, is to give nearly all patients with a PCN allergy cefazolin preoperatively while monitored by the anesthesia team. This allows for prompt and adequate treatment of any anaphylactic reactions including bronchodilators, antihistamines, and oxygen to supportively treat a severe reaction. Those patients with a history of a severe delayed-type reaction with multiple organ involvement should carry a high suspicion; should ideally be identified in the clinic; and may benefit from preoperative skin testing, oral challenge, and desensitization if necessary. This strategy increases cefazolin use, without the time and expense of preoperative testing while providing an optimal antibiotic regimen to prevent SSI/PJI.

Overall, our cohorts of patients with and without PA and those who did and did not receive cefazolin were very equally matched for risk factors of perioperative complications. The overall primary arthroplasty infection rate of 1.3% is in accordance with US norms, and that for revision arthroplasty was 8.9%. Our study shows decreased infection risks among TJA surgery when cefazolin was given compared with second-line antibiotics with 2.9% and 5.5% rates of infection, respectively (P = 0.02). Although significance was lost with a multivariate analysis, there was still a decreased OR of infection with cefazolin administration of 0.144 compared with second-line antibiotics. We think that the high number of patients receiving cefazolin in our study compared with those receiving second-line antibiotics led to relatively low power to detect a notable difference in the rate of infection when multivariate analysis was taken into account. Revision surgery is where cefazolin administration affected infection rates the most where 8.3% had an PJI when given cefazolin versus 15.8% with second-line antibiotics (P = 0.05). When taking into account aseptic versus infection revision cases, there was near significance in administration of cefazolin for aseptic cases with a reduced infection rate of 6.0% compared with 12.3% for second-line antibiotics (P = 0.053). This concludes us to suggest that patients at increased risk of infection and limited chances for success may benefit from being given cefazolin as often as possible. Allergic reaction among all comers was 0.5%. Overall, patients with a PA were more prone to an allergic reaction (OR 4.0), regardless of the antibiotic type administered, with only one of the four patients having a PA and allergic reaction to antibiotic at the time of surgery receiving cefazolin. Interestingly, when cefazolin was administered to people with no listed allergies, there was a 0.4% rate of allergic reaction, compared with a 1.2% rate of reaction with second-line antibiotics (P = 0.15). This shows that second-line antibiotic administration may not be any safer than cefazolin administered preoperatively, sharing a similar allergic reaction risk. Potential benefits may be seen in reduced rates of infection and improved patient satisfaction, outcomes, cost, and healthcare burden.

Limitations to this study include the shared decision making in antibiotic administration at the time of surgery between surgeon and anesthesia team. Because only 42.4% of patients with a documented PA received cefazolin, this could be in part by misunderstanding of actual cross-reactivity of the members part of the multidisciplinary team or lack of prior identification of allergic reaction specifics in the preoperative period. This study focused on patients with a PA; however, there were some patients with a cefazolin allergy as well; although this was not within the scope of this study, these patients may need to undergo further testing before surgery to be administered the best possible antibiotic in the fight against PJI. This may be the focus of a future study.

Conclusion

A notable number of arthroplasty patients present with a history of PA. Often, they are unaware of the inciting event when it was diagnosed of the type of reaction, and it is often unclear whether the reaction was IgE-mediated at all. Although there may be small risk of cross-reactivity to cephalosporins in patients with a PA, newer studies are

showing this not to be true. Owing to this clinically insignificant and misunderstood risk of allergic reaction, second-line antibiotics are given frequently in place of cefazolin during TJA. This is concerning because the antibiotics have less efficacy against common infective flora responsible for acute postoperative joint infections. This study redemonstrates the increased risk of infection in patients receiving second-line antibiotics versus cefazolin for perioperative antibiotic prophylaxis. A postoperative infection rate of 2.9% versus 5.5% when cefazolin versus second-line antibiotics were used, respectively, was statistically significant in our study (P = 0.02). Although statistical significance was lost with a multivariate analysis, a reduced OR of infection of 0.144 was still maintained for cefazolin administration over second-line antibiotics. Revision surgery can cause increased susceptibility to infection; in aseptic revisions, cefazolin administration showed decreased infection risk as well, which nearly approached statistical significance (6.0% versus 12.3%, P = 0.053). Furthermore, among patients given cefazolin despite documented PA, only 1 (0.3%) had an allergic reaction, which was self-limited and required no further care. This study supports the superior protection against postoperative infection in TJA of cefazolin over second-line antibiotics. Despite PA, administration of cefazolin preoperatively is safe and does not pose a notable risk of adverse reactions for most patients. Identifying important factors in a patient's previous allergic reaction to PCN in the form of preoperative questionnaires and history can indicate which patients are safe for preoperative administration of cefazolin with anesthesia monitoring and those who require further workup. Our study shows that nearly half of the patients (42.4%) with a PA were given cefazolin safely. However, there still exists a dilemma in administration of cefazolin in all patients with a PA because of multidisciplinary teams in the operating room, shared decision making, and hesitance based on allergic reaction history. From this, we conclude that the benefits of cefazolin administration in patients with a PA outweigh the risk of allergic reaction or increased risk of infection associated with the administration of an alternative antibiotic and most patients can undergo safe cefazolin administration without additional workup.

References

1. Pagani FD: Commentary: Understanding the relationship between acute kidney injury and durable ventricular assist device implantation: Is it a preoperative or postoperative event? *J Thorac Cardiovasc Surg* 2020;159:489-490.

2. Wildeman P, Rolfson O, Soderquist B, Wretenberg P, Lindgren V: What are the long-term outcomes of mortality, quality of life, and hip function after prosthetic joint infection of the hip? A 10-year follow-up from Sweden. *Clin Orthop Relat Res* 2021;479:2203-2213.

3. Huemer M, Mairpady Shambat S, Brugger SD, Zinkernagel AS: Antibiotic resistance and persistence-Implications for human health and treatment perspectives. *EMBO Rep* 2020;21:e51034.

4. Tubb CC, Polkowksi GG, Krause B: Diagnosis and prevention of periprosthetic joint infections. *J Am Acad Orthop Surg* 2020;28:e340-e348.

5. Blumenthal KG, Ryan EE, Li Y, Lee H, Kuhlen JL, Shenoy ES: The impact of a reported penicillin allergy on surgical site infection risk. *Clin Infect Dis* 2018;66:329-336.

6. Pettett BJ, Eskildsen SM, Huang KX, Ostrum RF: Despite the safety of preoperative cefazolin for patients with non-anaphylactic penicillin allergy, 20% of practitioners avoid its use. *Orthopedics* 2019;42:e437-e442.

7. Kuruvilla M, Sexton M, Wiley Z, Langfitt T, Lynde GC, Wolf F: A streamlined approach to optimize perioperative antibiotic prophylaxis in the setting of penicillin allergy labels. *J Allergy Clin Immunol Pract* 2020;8:1316-1322.

8. Wyles CC, Hevesi M, Osmon DR, et al: 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. *Bone Jt J* 20192019;101-B(6 supple B):9-15.

9. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ: Antibiotic allergy. *Lancet* 2019;393:183-198.

10. Vyles D, Antoon JW, Norton A, et al: Children with reported penicillin allergy: Public health impact and safety of delabeling. *Ann Allergy Asthma Immunol* 2020;124:558-565.

11. McDanel DL, Azar AE, Dowden AM, et al: Screening for beta-lactam allergy in joint arthroplasty patients to improve surgical prophylaxis practice. *J Arthroplasty* 2017;32:S101-S108.

12. Haslam S, Yen D, Dvirnik N, Engen D: Cefazolin use in patients who report a non-IgE mediated penicillin allergy: A retrospective look at adverse reactions in arthroplasty. *Iowa Orthop J* 2012;32:100-103.

13. Har D, Solensky R: Penicillin and beta-lactam hypersensitivity. *Immunol Allergy Clin North Am* 2017;37:643-662.

14. Beltran RJ, Kako H, Chovanec T, Ramesh A, Bissonnette B, Tobias JD: Penicillin allergy and surgical prophylaxis: Cephalosporin cross-reactivity risk in a pediatric tertiary care center. *J Pediatr Surg* 2015;50:856-859.

15. Zagursky RJ, Pichichero ME: Cross-reactivity in beta-lactam allergy. *J Allergy Clin Immunol Pract* 2018;6:7281.e71.

16. Romano A, Valluzzi RL, Caruso C, Zaffiro A, Quaratino D, Gaeta F: Tolerability of cefazolin and ceftibuten in patients with IgE-mediated aminopenicillin allergy. *J Allergy Clin Immunol Pract* 2020;8:1989-1993.e1982.

17. Bosco JA, Bookman J, Slover J, Edusei E, Levine B: Principles of antibiotic prophylaxis in total joint arthroplasty: Current concepts. *J Am Acad Orthop Surg* 2015;23:e27-e35.

18. Yian EH, Chan PH, Burfeind W, Navarro RA, Singh A, Dillon MT: Perioperative clindamycin use in penicillin allergic patients is associated with a higher risk of infection after shoulder arthroplasty. *J Am Acad Orthop Surg* 2020;28:e270-e276.

19. Tan TL, Springer BD, Ruder JA, Ruffolo MR, Chen AF: Is vancomycin-only prophylaxis for patients with penicillin allergy associated with increased risk of infection after arthroplasty? *Clin Orthop Relat Res* 2016;474:1601-1606.

20. Shenoy ES, Macy E, Rowe T, Blumenthal KG: Evaluation and management of penicillin allergy: A review. *JAMA* 2019;321:188-199.

21. Blumenthal KG, Huebner EM, Fu X, et al: Risk-based pathway for outpatient penicillin allergy evaluations. *J Allergy Clin Immunol Pract* 2019; 7:2411-2414.e2411.

22. Kleris R, Tang M, Radojicic C, Lugar PL: Pricking away at penicillin allergy with a dedicated outpatient clinic. *J Allergy Clin Immunol Pract* 2019;7:1358-1359.e1351.

23. Pagani NR, Moverman MA, Puzzitiello RN, Menendez ME, Barnes CL, Kavolus JJ: Preoperative allergy testing for patients reporting penicillin and cephalosporin allergies is cost-effective in preventing infection after total knee and hip arthroplasty. *J Arthroplasty* 2021;36:700-704.

24. Trubiano JA, Vogrin S, Chua KYL, et al: Development and validation of a penicillin allergy clinical decision rule. *JAMA Intern Med* 2020;180: 745-752.

25. Vorobeichik L, Weber EA, Tarshis J: Misconceptions surrounding penicillin allergy: Implications for anesthesiologists. *Anesth Analg* 2018; 127:642-649.