Cefazolin and the R-1 Side Chain: Why Your Joint Arthroplasty Patients With Cephalosporin Allergy Can Safely Be Given Cefazolin

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INTRODUCTION:

Cefazolin, a first-generation cephalosporin, is the standard of care for perioperative antibiotic prophylaxis in hip and knee arthroplasty patients. Research has shown that prosthetic joint infection (PJI) rates, length of stay, and healthcare costs are significantly higher when non-cefazolin antibiotics are used for perioperative TKA and THA prophylaxis. Recent literature has demonstrated that the antigenic determinant of all cephalosporin and penicillin antibiotics is not the beta lactam ring which they share, but the R1 side chain. Cefazolin possesses a unique R1 side chain is not shared by and has not shown cross reactivity with any other cephalosporin or penicillin antibiotic. Despite these data, the declaration of a cephalosporin allergy causes uncertainty regarding the optimal antibiotic choice in these patients. Reflex substitution to alternative antibiotic prophylaxis potentially places patients at undue risk of PJI. The purpose of this study was to determine the safety of administering perioperative cefazolin in patients with a documented cephalosporin allergy undergoing total joint arthroplasty.

METHODS:

We identified every patient with a documented cephalosporin allergy that underwent primary or revision total hip and total knee arthroplasty at a single high-volume academic institution from February 2016 to May 2024. We compared patients who received perioperative cefazolin despite the presence of a cephalosporin allergy to patients who received alternative antibiotic prophylaxis The primary outcome measure was the incidence of IgE mediated allergic reactions or “severe” type IV delayed hypersensitivity reaction with end organ dysfunction within the first 72 hours postoperatively. Secondary outcomes included 90-day complication rates including PJI, *C. difficile* infection, adverse events and readmission. Statistical analysis included chi-square or Fisher exact tests for categorical variables, and t-tests or Mann-Whitney U tests for continuous variables.

RESULTS:

89,993 hip and knee arthroplasty patients from 2016–2024 were identified from our institutional database. Of these, 1,267 had a documented cephalosporin allergy. The incidence of allergic reaction in cephalosporin allergic patients who received cefazolin was 0.0% (0/481) compared to 0.51% (4/786) in patients who received alternative antibiotics prophylaxis (p=0.12). There were no significant differences in the incidences of PJI (0.23% vs. 0.30%; p=0.83), *C. difficile* infection (0.0% vs. 0.0%; p=1) or readmission (3.95% vs. 4.34%; p=0.75) within 90 days. There was one adverse event related to cefazolin administration which was urethral irritation and was self-limited. There were four adverse events related to alternative antibiotic prophylaxis including cutaneous manifestations, GI distress, pancreatitis, and headache in a patient with prior drug induced idiopathic intracranial hypertension. All four allergic reactions in the alternate antibiotic prophylaxis group were secondary to administration of vancomycin and required supportive treatment with IV corticosteroids and antihistamines.

DISCUSSION AND CONCLUSION:

This is the first study to evaluate prophylactic cefazolin in hip and knee arthroplasty patients with a documented cephalosporin allergy and resulted in a 0.0% incidence of IgE mediated or “severe” Type IV allergic reactions. These data and the fact that cefazolin’s unique R1 side chain is not shared by any other cephalosporins suggests that cefazolin can safely be administered to most patients with a documented cephalosporin allergy.

Cephalosporin Allergy	Total Count	% Total
Cephalexin	699	55.14%
Cefazolin	108	8.52%
Ceftriaxone	99	7.81%
Cefuroxime	89	7.02%
Cefdinir	74	5.83%
Cefadroxil	66	5.21%
Cefprozil	56	4.42%
Cefpodoxime	14	1.11%
Cefixime	5	0.39%
Ceftibuten	1	0.08%
Cephradine	1	0.08%

Outcome	Cefazolin Group (n=481)	Alternative Antibiotic Group (n=787)	p Value
Immediate or severe delayed allergic reaction, no. (%)	0 (0.0%)	4 (0.51%)	0.18
Prosthetic joint infection, no. (%)	1 (0.23%)	2 (0.30%)	0.83
C. difficile infection, no. (%)	0 (0.0%)	0 (0.0%)	—
90-day readmission, no. (%)	19 (3.95%)	34 (4.34%)	0.75
Adverse events attributed to antibiotic, no. (%)	1 (0.21%)	5 (0.64%)	0.42

Note: Immediate allergic reactions include IgE-mediated events such as urticaria, angioedema, bronchospasm, hypotension, and anaphylaxis. Severe delayed hypersensitivity reactions include T-cell mediated syndromes such as severe cutaneous adverse reactions (e.g., Stevens-Johnson syndrome, AGEP