

Selected Proceedings from the 2020 Musculoskeletal Infection Society Meeting
Guest Editor: Charalampos G. Zalavras MD, PhD

Antibiotic Stewardship Interventions Improve Choice of Antibiotic Prophylaxis in Total Joint Arthroplasty in Patients with Reported Penicillin Allergies

Raquel Jones PharmD, Katelyn S. Quartuccio PharmD, BCPS, Jessica L. Stern MD, MS, Eric V. Heintz MD, Kelly E. Pillinger PharmD, BCPS, BCIDP, Thomas G. Myers MD, MPT

Received: 29 August 2020 / Revised: 25 November 2020 / Accepted: 26 February 2021 / Published online: 14 April 2021
Copyright © 2021 by the Association of Bone and Joint Surgeons

Abstract

Background Most patients who report a penicillin allergy can tolerate cefazolin, the preferred prophylaxis in a total joint arthroplasty (TJA). Regardless, patients with a reported penicillin allergy are less likely to receive first-line perioperative antibiotics as a result of inaccurate penicillin allergy documentation and misconceptions regarding cross-reactivity between penicillin and cephalosporins. The over-reporting of penicillin allergies and the safety of cephalosporins in patients

with reported penicillin allergies have been well established throughout the evidence [13].

Questions/purposes The study sought to answer two questions: (1) Do antibiotic stewardship interventions improve adherence to appropriate prophylactic antibiotic usage in patients with a documented penicillin allergy undergoing primary TJA? (2) What is the risk of allergic or adverse reactions secondary to cefazolin use in patients with a documented penicillin allergy?

Each author certifies that neither he or she, nor any member of his or her immediate family, has funding or commercial associations (consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research*® editors and board members are on file with the publication and can be viewed on request.

Ethical approval for this study was waived by the University of Rochester Research Subjects Review Board.

R. Jones, University of Rochester Medical Center - Strong Memorial Hospital, Rochester, NY, USA

K. S. Quartuccio, University of Rochester Medical Center- Highland Hospital, Rochester, NY, USA

J. L. Stern, Allergy/Immunology & Rheumatology Division, University of Rochester Medical Center - Strong Memorial Hospital, Rochester, NY, USA

E. V. Heintz, Infectious Disease Division, University of Rochester Medical Center - Strong Memorial Hospital, Rochester, NY, USA

K. E. Pillinger, Department of Pharmacy, University of Rochester Medical Center - Strong Memorial Hospital, Rochester, NY, USA

T. G. Myers, Department of Orthopaedics, University of Rochester Medical Center - Strong Memorial Hospital, Rochester, NY, USA

T. G. Myers ✉, Department of Orthopaedics, University of Rochester Medical Center - Strong Memorial Hospital, 601 Elmwood Avenue, Box 665, Rochester, NY 14642 USA, Email: thomas_myers@urmc.rochester.edu

Methods This was a single-center, retrospective study of orthopaedic patients older than 18 years who underwent a primary elective TJA at a 261-bed community hospital. The study had two periods: the preintervention period ran from March 1, 2017 to August 30, 2017 and the post-intervention period was from March 1, 2019 to August 30, 2019. A total of 396 patients with a history of a documented penicillin allergy underwent a THA or TKA during the study periods. After reviewing every fourth patient with a history of a documented penicillin allergy who met study inclusion criteria and excluding those patients who had a codocumented cephalosporin allergy, a total of 180 patients with a documented penicillin allergy were evaluated (90 patients in the preintervention group and 90 patients in the postintervention group). To answer our first study question, regarding whether antibiotic stewardship interventions improve adherence to appropriate prophylactic antibiotic usage in patients with a documented penicillin allergy undergoing primary TJA, we evaluated appropriate antibiotic usage pre- and postintervention. To answer our second study question, concerning the risk of allergic or adverse reactions secondary to cefazolin use in patients with a documented penicillin allergy, we reviewed signs of allergic reactions in patients who received cefazolin for a primary TJA and had a documented penicillin allergy.

Results Postintervention antibiotic use was more appropriate (91% [82 of 90] versus 54% [49 of 90], risk ratio 1.67 [95% confidence interval 1.37 to 2.04]; $p < 0.01$), particularly in patients with nonsevere allergy (preintervention: 47% [36 of 76] versus postintervention: 96% [76 of 79]; $p < 0.01$). No patients had signs of an allergic reaction related to cefazolin, including eight patients with severe penicillin allergy.

Conclusion A multifaceted antibiotic stewardship intervention increased the appropriateness of antibiotic prophylaxis in elective primary TJA. Patients with nonsevere penicillin allergies, even those reporting hives or local swelling, tolerated cefazolin. Antibiotic stewardship interventions can be implemented across institutions to expand cephalosporin use in patients with a reported penicillin allergy within orthopaedic TJA patients.

Level of Evidence Level III, therapeutic study.

Introduction

Beta-lactam antibiotics, specifically narrow-spectrum cephalosporins, are the mainstay of surgical antibiotic prophylaxis in total joint arthroplasty (TJA). The International Consensus on Orthopedic Infections (ICM) recommends a first- or second-generation cephalosporin as the most appropriate perioperative prophylactic antibiotic in patients undergoing a primary TJA (super majority, strong consensus) [1]. Notably, cefazolin has a unique side

chain resulting in an extremely low rate ($< 1\%$) of cross-reactivity with penicillin [3, 7, 13]. However, patients with a reported penicillin allergy are less likely to receive first-line perioperative antibiotics as a result of inaccurate penicillin allergy documentation and misconceptions regarding cross-reactivity between penicillin and cephalosporins, directly impeding antibiotic stewardship efforts [2, 7, 13].

Previous studies have examined delabeling penicillin allergies before surgery; however, to our knowledge, there is only one report in the evidence that evaluated changes to institutional prophylaxis guidelines for patients with a penicillin allergy that also provided evidence for safely reducing the use of second-line antibiotics [9]. Furthermore, the effect on the orthopaedic population was not detailed in this study [9]. Therefore, our current study specifically evaluated the impact of antibiotic stewardship interventions to improve guideline adherence in patients with a reported penicillin allergy who were undergoing a TJA. By improving guideline adherence, appropriate first-line perioperative antibiotic prophylaxis should improve as well. Before the guideline updates, a penicillin allergy reaction of hives or local swelling was classified as a severe allergy, and clindamycin or vancomycin were recommended as second-line prophylaxis. Updated guidelines redefined severe allergy (removed hives and local swelling) and streamlined second-line prophylaxis to vancomycin only based on high rates of *Staphylococcal* resistance to clindamycin. Additionally, the ordering of prophylactic antibiotics was centralized to a limited number of providers on the perioperative care team, which minimized variation and increased compliance to the revised guidelines. We also aimed to add to current evidence by establishing the safety and efficacy of cefazolin in the TJA population. By assessing the risk of allergic or adverse reactions secondary to cefazolin use we can advocate for the safe use of first-line perioperative antibiotics in penicillin-allergic orthopaedic patients.

Therefore, we asked two questions: (1) Do antibiotic stewardship interventions improve adherence to appropriate prophylactic antibiotic usage in patients with a documented penicillin allergy undergoing primary TJA? (2) What is the risk of allergic or adverse reactions secondary to cefazolin use in patients with a documented penicillin allergy?

Patients and Methods

Study Design

This single-center, retrospective, quasi-experimental study evaluated all orthopaedic patients older than 18 years who underwent a primary elective THA or TKA for osteoarthritis at our institution from March 1, 2017 to August 30,

2017 (preintervention) and from March 1, 2019 to August 30, 2019 (postintervention).

Data were collected through November 30, 2019. Patient demographics included age, sex, race/ethnicity, BMI, reported penicillin allergy and reaction severity (any patient reporting both a nonsevere and a severe reaction was documented and analyzed as severe allergy only), risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA), smoking history, history of controlled or uncontrolled diabetes mellitus, and immunosuppressive status (see Appendix 1; Supplemental Digital Content 1, <http://links.lww.com/CORR/A535>). Procedure data included procedure type, surgery length, estimated blood loss, need for transfusion, and tranexamic acid use. Antibiotic data included perioperative antibiotic, appropriateness of dose and timing of perioperative antibiotic, and use of postoperative antibiotics within and beyond 24 hours of the procedure. Appropriate antibiotics included the use of cefazolin monotherapy in patients with a reported nonsevere penicillin allergy without MRSA risk factors, the use of cefazolin plus vancomycin in patients with a nonsevere penicillin allergy with MRSA risk factors, and the use of vancomycin monotherapy for patients with a severe penicillin allergy (regardless of MRSA risk factors). Appropriate weight-based dosing for cefazolin was defined as 2 g IV for patients less than 120 kg and 3 g IV for patients at least 120 kg; dosing for vancomycin was defined as 1 g IV for patients less than 80 kg and 1.5 g IV for patients at least 80 kg; previous dosing recommendations for clindamycin were 900 mg IV regardless of weight. Infection data included documented *Clostridioides difficile* or surgical site infection (SSI) within 90 days of the procedure. Allergy data included any documented signs of an allergic reaction within 72 hours of the procedure in patients who received cefazolin, type of allergic reaction documented, medications used to treat allergic reactions, and whether an allergy to cefazolin was added to the patient's chart. Allergy testing data included patients who had an appointment with or were seen by allergy, immunology, and rheumatology (AIR) within 60 days before their scheduled procedure, patients who underwent penicillin skin testing or direct oral challenge, and whether penicillin allergies were removed or added back to the chart before or within 90 days after the procedure. The data collected were used to compare differences in outcomes between the preintervention and postintervention groups.

Study Patients

Adult patients undergoing an elective primary THA or TKA were identified through an electronic data query. Patients who had a documented allergy to penicillins (for example, penicillin, amoxicillin, ampicillin, nafcillin, amoxicillin/clavulanate, piperacillin/tazobactam, or dicloxacillin) within 60 days before the procedure and received at least one dose of a preoperative antibiotic were included. Patient charts were manually

reviewed for eligibility based on their documented allergy. SSIs and *C. difficile* infections were identified through data collected and provided by the infection prevention committee at our institution. Patients were excluded if they had an active prosthetic joint infection or a cephalosporin allergy (that is, exhibiting rash, hives, or anaphylaxis). Patients with a cephalosporin intolerance only (for example, experiencing nausea, vomiting, or diarrhea) were included. Patients were also excluded if they were receiving broad-spectrum antibiotics for another indication at the time of surgery for which additional perioperative prophylaxis was not indicated.

Stewardship Interventions

Five distinct changes constituted the stewardship interventions in this study (Table 1). Our institution has guidelines regarding antibiotics for surgical prophylaxis in adult patients and for alternative prophylaxis in patients with a history of penicillin reactions. The stewardship program, which includes an infectious diseases physician and a pharmacist, updated the institutional guidelines between March 2018 and April 2019 (Table 2). The first update redefined severe allergy by removing reactions such as hives and local swelling and reclassifying these reactions as a nonsevere allergy. With this update, cefazolin was the preferred perioperative antibiotic for orthopaedic procedures in patients with nonsevere penicillin allergies (for example, skin rash, pruritus, urticaria/hives, local swelling, other reactions not consistent with an immunologic reaction), penicillin intolerance (such as, nausea, vomiting, diarrhea, headache), or a remote history (> 10 years) of penicillin exposure with an unknown reaction. Additionally, clindamycin was removed as an alternative prophylaxis recommendation for patients with beta-lactam allergies due to high local rates of *Staphylococcus* resistance. The guideline also clarified that vancomycin monotherapy should be reserved for patients with a history of a severe penicillin allergy (such as, anaphylaxis, laryngeal edema, hypotension, Stevens-Johnson syndrome, toxic epidermal necrolysis, hemolytic anemia, vasculitis, neutropenia, or thrombocytopenia) and that vancomycin and cefazolin combined is preferred for patients with MRSA risk factors such as a history of MRSA infection, a positive MRSA nasal screen, being on hemodialysis, or residing in a chronic care facility. The infectious diseases and orthopaedic groups agreed upon MRSA risk factors that necessitated the addition of vancomycin guided by ICM recommendations. Guideline changes were approved through several institutional committees including a multidisciplinary committee with representatives from infectious diseases, orthopaedics, AIR, and pharmacy.

In addition to the institutional guideline changes, the presurgical screening procedures were standardized; advanced practice providers (physician's assistants and nurse practitioners) and the perioperative medicine (anesthesia)

Table 1. Stewardship interventions

Intervention	Description
Guideline changes	
Redefined severe penicillin allergy	Hives and local swelling redefined as a nonsevere allergy
Updated second-line alternatives	Removed clindamycin as alternative prophylaxis based on high rates of local <i>Staphylococcal</i> resistance
Defined MRSA risk factors	History of MRSA infection, a positive MRSA nasal screen, on hemodialysis, or residing in chronic care facility
Multidisciplinary committee approval	Guideline changes were approved by a multidisciplinary committee including infectious diseases, orthopaedics, AIR, and pharmacy
Presurgical screening orders	Advanced practice providers ordered antibiotics based on updated guidelines
Orthopaedic physician champion	Provided education to peers, specifically surgeons for increased compliance
Preoperative referral to AIR	Orthopaedic surgeons were encouraged to identify patients reporting a severe penicillin allergy at their outpatient preoperative appointment and refer them to AIR for allergy evaluation before their scheduled procedure in the hopes of delabeling erroneous penicillin allergies

MRSA = methicillin-resistant *Staphylococcus aureus*; AIR = allergy, immunology, and rheumatology.

team ordered antibiotics based on updated guidelines. An orthopaedic physician served as a champion to educate peers, specifically surgeons, on increased compliance. Orthopaedic surgeons were encouraged to identify patients reporting a severe penicillin or “questionable” cephalosporin allergy at their outpatient preoperative appointment and refer them to AIR for allergy evaluation before their scheduled procedure in the hopes of delabeling erroneous penicillin allergies. These decisions ensured adherence to guidelines and consistency between surgeons.

A total of 396 patients with a history of a documented penicillin allergy underwent a THA or TKA at Highland Hospital from March 1, 2017 to August 30, 2017 (preintervention) and from March 1, 2019 to August 30, 2019 (postintervention). Based on the screening method previously described, 59% (106 of 180) of patients were evaluated in the preintervention group and 55% (119 of 216) of patients were evaluated in the postintervention group until 90 patients met eligibility criteria in each group (Fig. 1). Eight percent (9 of 106) of patients in the preintervention group did not meet inclusion criteria, and 7% (7 of 97) of patients had a documented cephalosporin allergy and were excluded. Seventeen percent (20 of 119) of patients in the postintervention group did not meet inclusion criteria, and 9% (9 of 99) of patients had a documented cephalosporin allergy and were excluded. There were no differences in demographic characteristics between the pre- and postintervention groups except that there were more females in the postintervention group (70% [63 of 90] versus 83% [75 of 90]; $p = 0.03$) (Table 3). Most patients were white with a median age of 68 years (Table 3). TKA was the most frequently performed procedure in each group (Table 4). At the time of the procedure, 76 patients in each group had a non-severe penicillin allergy. Rash was the most reported allergy in both groups (49% [37 of 76] versus 37% [29 of 79]; $p = 0.13$)

(Table 5). Several patients reported multiple nonsevere reactions to penicillin, including 13 patients in the preintervention group and seven patients in the postintervention group. Four patients in the postintervention group were referred to allergy before their procedure for evaluation of their penicillin allergy. Of the referred patients, two underwent skin testing, and all four patients underwent a direct oral challenge with amoxicillin. Three patients had their allergy removed from the medical chart, and all four patients received cefazolin for their procedures. One patient who did not have their allergy removed had reported an intolerance of nausea and vomiting to amoxicillin-clavulanate. Fourteen patients in the preintervention group reported severe penicillin allergies, as did 11 patients in the postintervention group ($p = 0.58$). Anaphylaxis was the most reported severe reaction in both groups (100% (14 of 14) versus 91% (10 of 11); $p = 0.38$) (Table 5). There was no difference in MRSA risk factors between groups (Table 3).

Primary and Secondary Study Outcomes

Our primary study goal was to evaluate whether antibiotic stewardship interventions improve adherence to appropriate prophylactic antibiotics in patients with a documented penicillin allergy undergoing primary TJA. To achieve this, we implemented several antibiotic stewardship interventions, including institution guidelines and standardization of antibiotic ordering across various orthopaedic surgeons as well as assessed appropriateness of SSI prophylaxis, including drug selection and dosing. We then evaluated the incidence of appropriate antibiotic selection pre- and postimplementation of the stewardship interventions. Our secondary study goal was to assess the risk of allergic or adverse reactions secondary to cefazolin use in patients with a documented penicillin allergy.

Table 2. Institutional guidelines for total joint arthroplasty antibiotic prophylaxis pre- and poststewardship intervention

Preintervention	What type of reaction did the patient previously experience when receiving a penicillin product?	
	Nonsevere allergy	Severe allergy
	Rash	Urticaria/hives
	Pruritus	Local swelling
	N/V	Anaphylaxis
	Headache	Laryngeal edema
	GI intolerance	Stevens-Johnson syndrome
	Other reaction not consistent with an immunologic reaction	Toxic epidermal necrolysis
	Remote history of penicillin exposure and unsure of reaction	Interstitial nephritis
		Hemolytic anemia
		Vasculitis
		Neutropenia
		Thrombocytopenia
	Recommendation if any of the above:	
	Cefazolin	Vancomycin or clindamycin
	If high risk ^a , add vancomycin	
Postintervention	What type of reaction did the patient previously experience when receiving a penicillin product?	
	Nonsevere allergy	Severe allergy
	Urticaria/hives	Anaphylaxis
	Local swelling	Laryngeal edema
	Rash	Stevens-Johnson syndrome
	Pruritus	Toxic epidermal necrolysis
	N/V	Interstitial nephritis
	Headache	Hemolytic anemia
	GI intolerance	Vasculitis
	Other reaction not consistent with an immunologic reaction	Neutropenia
	Remote history of penicillin exposure and unsure of reaction	Thrombocytopenia
	Recommendation if any of the above:	
	Cefazolin	Vancomycin
	If MRSA risk factors present ^b , add vancomycin	

^aPatients colonized with MRSA and undergoing a procedure involving placement of implants or foreign material.

^bHistory of MRSA infection, MRSA-screen positive, hemodialysis, patient resides in chronic care facility; N/V = nausea/vomiting; MRSA = methicillin-resistant *Staphylococcus aureus*.

We reviewed tolerability of cefazolin, including signs of allergic reactions; actions taken in response to penicillin allergy, including referral to allergy for consult and potential removal of the allergy in patient chart.

Ethical Approval

Ethical approval for this study was waived by the University of Rochester Research Subjects Review Board. Approval was waived based on a secondary research use of identifiable private information or identifiable biospecimens exemption.

Statistical Analysis

We anticipated that approximately 2000 records would be identified from the electronic data query. Based on data showing that 10% of the US population reports a penicillin allergy, we anticipated that 200 patients would have a documented penicillin allergy [11]. Previous reports have shown that patients with reported penicillin allergies receive cefazolin as a perioperative antibiotic about 12% to 27% of the time [1, 11]. In these studies, 10% to 18% of patients reported hives and 6% reported swelling. Using these numbers, we estimated that we would need

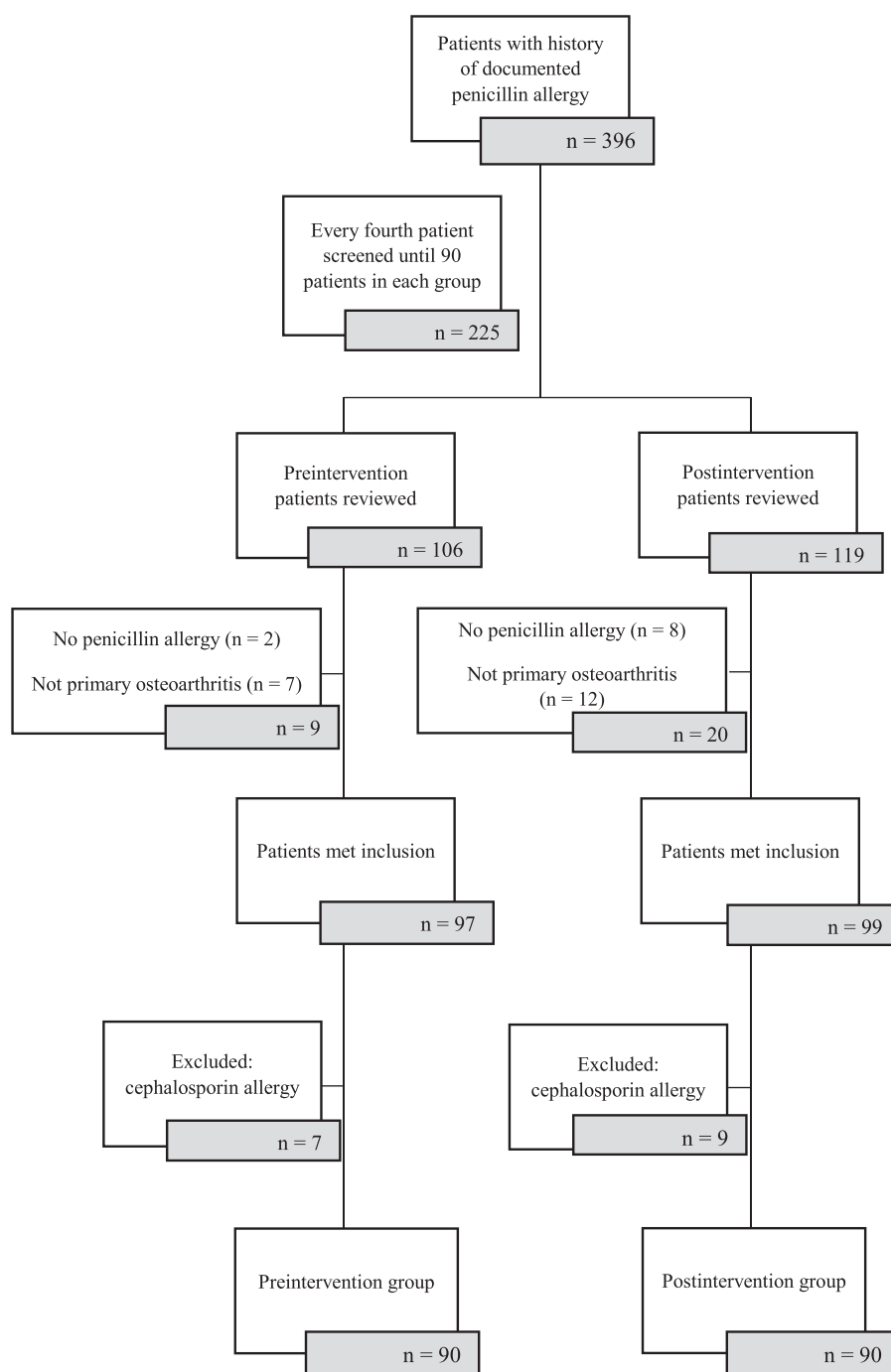


Fig. 1 Flow diagram detailing subjects enrolled in the study.

approximately 90 patients in each group to detect a 20% absolute difference with 80% power and an $\alpha < 0.05$. Of the approximately 200 records with a listed penicillin allergy, every fourth patient was screened until 90 patients in each intervention group was reached.

The primary outcome of adherence to appropriate prophylactic antibiotic usage in patients with a documented

penicillin allergy undergoing primary TJA was evaluated using the chi-square test. We analyzed the secondary endpoints using Fisher exact or chi-square tests for categorical variables or the Mann-Whitney U test for continuous variables. We analyzed normally distributed continuous variables with a two-group t test. A p value of ≤ 0.05 was considered statistically significant.

Table 3. Patient demographics

Characteristic	Preintervention (n = 90)	Postintervention (n = 90) ^a	p value ^{b,c}
Female sex	70 (63)	83 (75)	0.03
Age in years, median (IQR)	67 (61-74)	68 (62-73)	0.49
BMI in kg/m ² , median (IQR)	31 (27-34)	30 (27-36)	0.94
Race			
White	96 (86)	89 (80)	0.16
Black	4 (4)	10 (9)	0.24
Other	0 (0)	1 (1)	> 0.99
Smoking history	46 (41)	43 (39)	0.76
Diabetes mellitus	9 (8)	13 (12)	0.48
Controlled	6 (5)	12 (11)	0.26
Uncontrolled	3 (3)	1 (1)	
Immunosuppressed	12 (11)	4 (4)	0.10
MRSA risk factor ^d			
History of MRSA	1 (1)	3 (3)	0.62

All statistics are expressed as % (n) unless otherwise stated.

^aAllergy was delabeled by allergy, immunology, and rheumatology in three patients in the postintervention group before the procedure.

^bp < 0.05 by Fisher exact or chi-square for categorical variables or Mann-Whitney U test for continuous variables, respectively.

^cNormally distributed continuous variables were analyzed using a two-group t test.

^dNo patient in either group had a positive MRSA nasal screen, were on hemodialysis, or resided in a chronic care facility; MRSA = methicillin-resistant *Staphylococcus aureus*.

Results

Improvement in Adherence After Intervention

Compared with the preintervention group, the postintervention group received more appropriate perioperative antibiotics based on updated guidelines. Patients were more likely to receive first-line perioperative prophylaxis after our stewardship interventions (preintervention: 54% [49 of 90], postintervention: 91% [82

of 90], risk ratio 1.67 [95% CI 1.37 to 2.04]; p < 0.01) (Table 6). This was largely due to an increase in appropriate antibiotics for patients with nonsevere allergies (47% [36 of 76] versus 96% [76 of 79]; p < 0.001) (Fig. 2). However, there was no difference in appropriate prophylaxis for patients with severe allergies in the postintervention group (64% [9 of 14] versus 55% [6 of 11]; p = 0.70). Most patients in each group received appropriate weight-based dosing (94% [85 of 90] versus 99% [89 of 90]; p = 0.21).

Table 4. Surgical data

Surgical data	Preintervention (n = 90)	Postintervention (n = 90)	p value ^{a,b}
Procedure			
TKA	49 (44)	42 (38)	0.37
THA	20 (18)	21 (19)	0.87
THA (anterior approach)	31 (28)	37 (33)	0.52
Tourniquet TKA	36 (16 of 44)	19 (13 of 68)	0.69
Length of surgery in minutes, median (IQR)	144 (110-142)	128 (110-142)	0.007
Estimated blood loss in mL, median (IQR)	150 (100-250)	200 (100-250)	0.10
Use of tranexamic acid	94 (85)	98 (88)	0.25
Need for transfusion	0	1 (1)	> 0.99

All statistics are expressed as % (n) unless otherwise stated.

^ap < 0.05 by Fisher exact or chi-square for categorical variables or Mann-Whitney U test for continuous variables, respectively.

^bNormally distributed continuous variables were analyzed using a two-group t test; IQR = interquartile range.

Table 5. Allergy data

Characteristic	Preintervention (n = 90)	Postintervention (n = 90)	p value ^{a,b}
Penicillin allergy removed before procedure	0	3 (3)	0.25
Nonsevere allergy ^c	84 (76 of 90)	88 (79 of 90) ^d	
Rash	49 (37 of 76)	37 (29 of 79)	0.13
Pruritus	5 (4 of 76)	5 (4 of 79)	> 0.99
Hives	36 (27 of 76)	37 (29 of 79)	> 0.99
Local swelling	9 (7 of 76)	4 (3 of 79)	0.33
Intolerance	16 (12 of 76)	20 (16 of 79)	0.54
Remote history and unknown	11 (8 of 76)	9 (7 of 79)	0.79
Severe allergy ^e	16 (14)	13 (11)	0.67
Anaphylaxis	100 (14)	91 (10)	0.51
Laryngeal edema	0	9 (1)	> 0.99

All statistics are expressed as % (n) unless otherwise stated.

^ap < 0.05 by Fisher exact or chi-square for categorical variables or Mann-Whitney U test for continuous variables, respectively.

^bNormally distributed continuous variables were analyzed using a two-group t test.

^cMultiple allergy types were reported by some patients with nonsevere allergies.

^dNonsevere allergy was delabeled by allergy, immunology, and rheumatology in three patients in the postintervention group before the procedure.

^eNo patient in either group had a documented allergic reaction of hypotension, Stevens-Johnson syndrome/toxic epidermal necrolysis, hemolytic anemia, vasculitis, neutropenia, or thrombocytopenia.

Risk of Allergic Reaction

Among the 180 patients with history of documented penicillin allergy, 130 patients tolerated treatment with cefazolin. Moreover, of the eight patients with documented severe penicillin allergy, although the numbers were small (four patients preintervention and four patients postintervention), no patients experienced an allergic reaction to cefazolin. Only 1% [2 of 130] of patients received diphenhydramine for itching, likely not related to cefazolin administration (Table 7).

Discussion

Inaccurate penicillin allergy documentation and misconceptions regarding cross-reactivity between penicillin and cephalosporins results in patients with reported penicillin allergies being less likely to receive first-line perioperative antibiotics [7, 11]. Improving adherence to appropriate perioperative prophylaxis through antibiotic stewardship interventions and confirming the safety of cefazolin in penicillin allergic orthopaedic patients will expand evidence for recommending first-line prophylaxis across all TJA patients reporting penicillin allergies. We demonstrated that straightforward antibiotic stewardship interventions can quickly increase the use of appropriate perioperative prophylaxis. These interventions can be done safely in penicillin-allergic patients without evidence of allergic reactions.

Limitations

This retrospective study has several limitations. One limitation is the concern for loss of adherence to guidelines over time. This was minimized through streamlining ordering of prophylactic antibiotics to a limited number of providers on the perioperative care team, which minimized variation. Using perioperative antibiotic order sets makes selection of appropriate antibiotics quick and easy for providers and further reduces the risk of guideline deviations over time. The periods included in the study were consistent between groups, but we were unable to include all months of the year to account for variation in the seasonality of infections and other unseen variables. These variables had a limited effect on our primary outcome and were minimized by including the same time frames for both groups. Data also suggests warmer months may be associated with infection; these months were included in our study, and we did not report any infections [12]. Regardless, our study was underpowered to detect differences in infection rates, which is the main concern with seasonal variation. There was not an adequate washout period between the stewardship interventions period (March 2018 to April 2019) and the start of data collection in the postintervention group. Despite this limitation, we quickly noticed an increase in appropriate perioperative prophylaxis. Only a small number of patients had their allergy evaluated by AIR before their procedure, as education provided to the orthopaedic group about AIR referral was limited. We did not observe any unexpected, harmful consequences with the

Table 6. Antibiotic use

	Preintervention	Postintervention	Risk ratio (95% CI)	p value ^{a,b}
Appropriate use	54 (49 of 90)	91 (82 of 90)	1.67 (1.37 to 2.04)	< 0.01
Nonsevere allergy ^c	47 (36 of 76)	96 (76 of 79) ^d	2.03 (1.60 to 2.59)	< 0.01
Severe allergy ^e	64 (9 of 14)	55 (6 of 11)	0.85 (0.44 to 1.65)	0.70
Appropriate timing	62 (56 of 90)	91 (82 of 90)	1.46 (1.23 to 1.74)	< 0.01
With tourniquet	63 (10 of 16)	85 (11 of 13)	1.35 (0.87 to 2.11)	0.24
Appropriate dosing	95 (85 of 90)	99 (89 of 90)	1.05 (0.99 to 1.11)	0.21

All statistics are expressed as % (n) unless otherwise stated.

^ap < 0.05 by Fisher exact or chi-square for categorical variables or Mann-Whitney U test for continuous variables, respectively.

^bNormally distributed continuous variables were analyzed using a two-group t test.

^cNonsevere allergy defined as urticaria/hives, local swelling, rash, pruritus, nausea/vomiting, GI intolerance, headache, other reaction not consistent with an immunologic reaction, or remote history of penicillin exposure and unsure of reaction.

^dAllergy was delabeled by allergy, immunology, and rheumatology in three patients in the postintervention group before the procedure.

^eSevere allergy defined as anaphylaxis, laryngeal edema, Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, hemolytic anemia, vasculitis, neutropenia, or thrombocytopenia.

widespread use of cefazolin. Further study is warranted to assess the cost-effectiveness of AIR referral versus cefazolin challenge in patients with severe penicillin allergy. No patients in our study who received cefazolin in the setting of severe allergy experienced anaphylaxis. The small sample size precluded a robust analysis of the safety of cefazolin in the setting of severe penicillin allergy. Although establishing safety of cefazolin in severe penicillin allergies remains an area of importance, we demonstrated the safety of cefazolin in those patients who reported a nonsevere penicillin reaction, including rash, hives, and local swelling, which constitutes most reactions in patients with reported penicillin allergies. We demonstrated the safety of cefazolin in most patients reporting penicillin allergies through properly classifying hives and local swelling as nonsevere reactions. The inherent limitations present in any retrospective study design apply,

but specifically related to this study, they include the accurate documentation of allergic reactions, which cannot be assured.

Improvement in Adherence After Intervention

Use of appropriate perioperative antibiotic prophylaxis improved after an antibiotic stewardship intervention. Donà et al. [5] assessed appropriate perioperative antibiotic prophylaxis for 24 months after the implementation of an antimicrobial stewardship program involving clinical pathways and education. The antimicrobial stewardship program was found to be an effective and sustainable tool for improving the correct use of perioperative antibiotic prophylaxis. Similarly, Frenette et al. [6] also found that antibiotic stewardship interventions improved overall

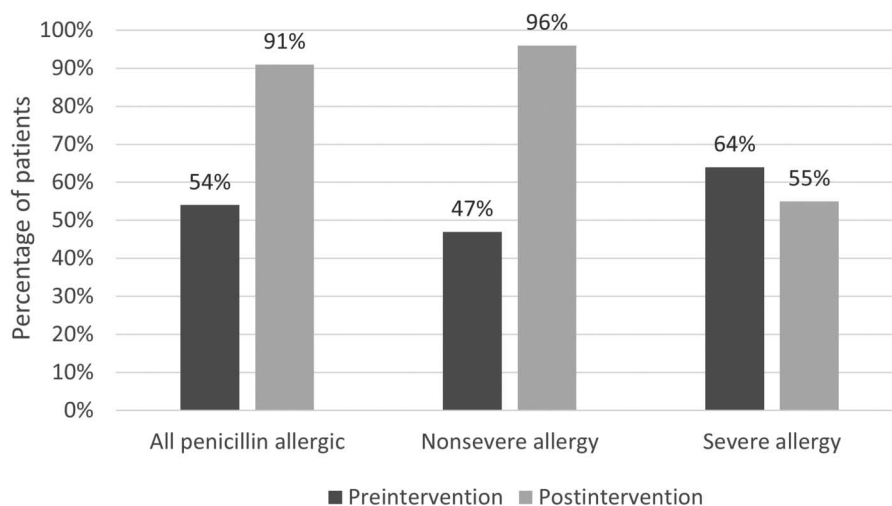


Fig. 2 Graph of appropriate antibiotic use pre- and postintervention.

Table 7. Adverse reactions in patients that received cefazolin

Reaction	% (n)
Itching	2 (2 of 130)
Received diphenhydramine	2 (2 of 130)
Tryptase level drawn	0
Anaphylaxis to cefazolin	0
Cefazolin added as allergy in chart	0

conformity to a cardiothoracic surgery prophylaxis protocol by 46.8% over a 5-year period. Therefore, the multifaceted stewardship intervention presented in this study with updated institutional guidelines, a limited number of providers ordering antibiotics, an updated perioperative antibiotic order set, and provider education helps to protect against deviations or decreased adherence across time. Adherence to appropriate perioperative antibiotic prophylaxis for TJA is an area of concern as cefazolin is less likely to be given to TJA patients with a reported penicillin allergy compared with patients without a reported penicillin allergy [7, 14]. Patients receiving cefazolin compared with alternative antibiotics have a reduced risk of prosthetic joint infections [15]. The dose and timing of antibiotic administration also influences SSI risk. By increasing cefazolin usage, appropriate timing is inherently influenced as cefazolin is given as an IV push while vancomycin is infused in a dose-dependent manner, typically over 60 to 90 minutes, which can be logistically challenging. Furthermore, Kheir et al. [8] found that vancomycin is frequently underdosed. We observed an increase in appropriate antibiotic timing in the postintervention group as a result of increased cefazolin use. In general, use of second-line antibiotics results in an increased risk of side effects including vancomycin-resistant *Enterococcus* (VRE) due to exposure to vancomycin and increased risk of *C. difficile* due to clindamycin exposure [4, 10]. The routine use of vancomycin in addition to cefazolin for all patients undergoing TJA has been associated with the development of acute kidney injury compared with cefazolin alone without reducing SSI rates [7]. We were unable to evaluate these effects because our study was not powered to detect any differences in SSIs or *C. difficile* rates due to the small sample size and overall low rates of these infections in the TJA surgery population.

Risk of Allergic Reaction

Previous authors have suggested cefazolin is safe for most patients with nonsevere penicillin allergies, such as hives and local swelling [3, 9, 13]. Our finding extends what is known because no patients had an allergic reaction to cefazolin in this study. Establishing documented

tolerability to cefazolin in patients with a documented penicillin allergy will expand antibiotic options for any future surgical prophylaxis or established infections (such as pneumonia or cellulitis). Patients with severe penicillin allergies could be referred for allergy consult to determine whether cefazolin is a safe option. Other authors have suggested that cephalosporins may be considered in the setting of severe penicillin allergy, as data exist to support the safety of this approach. One healthcare system removed the warning in the electronic medical record to avoid cephalosporins in patients with any type of penicillin allergy. Following this change, there were no incidences of anaphylaxis noted [11]. The safety of challenging severe penicillin allergies using test doses of cefazolin in monitored settings such as operating rooms is an area where further data are needed.

Conclusion

Implementation of antibiotic stewardship interventions, including updating institution guidelines, appropriately classifying allergy reactions, and standardizing antibiotic ordering across various orthopaedic surgeons, increased appropriate perioperative prophylaxis in patients with penicillin allergies. Patients with nonsevere penicillin allergies, even those reporting hives or local swelling, can tolerate cefazolin. Antibiotic stewardship interventions can be implemented across institutions to expand cephalosporin use in patients with a reported penicillin allergy within orthopaedic TJA patients. Future prospective studies should address ongoing questions of appropriate antibiotic timing and infection rates. Additionally, further data regarding the safety of cefazolin in patients with severe penicillin allergies would be helpful in guiding practice.

Acknowledgments We thank Joy Uzoma PharmD, for her help with data collection.

References

1. Aboltins CA, Berdal JE, Casas F, et al. Hip and knee section, prevention, antimicrobials (systemic): Proceedings of International Consensus on Orthopedic Infections. *J Arthroplasty*. 2019;34:S279-s288.
2. 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.
3. Chaudhry SB, Veve MP, Wagner JL. Cephalosporins: a focus on side chains and β -lactam cross-reactivity. *Pharmacy (Basel)*. 2019;7:103.
4. Courtney PM, Melnic CM, Zimmer Z, Anari J, Lee GC. Addition of vancomycin to cefazolin prophylaxis is associated with acute kidney injury after primary joint arthroplasty. *Clin Orthop Relat Res*. 2015;473:2197-2203.

5. Donà D, Luise D, Barbieri E, et al. Effectiveness and sustainability of an antimicrobial stewardship program for perioperative prophylaxis in pediatric surgery. *Pathogens*. 2020;9:490.
6. Frenette C, Sperlea D, Tesolin J, Patterson C, Thirion D. Influence of a 5-year serial infection control and antibiotic stewardship intervention on cardiac surgical site infections. *Am J Infect Control*. 2016;44:977-982.
7. 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.
8. Kheir MM, Tan TL, Azboy I, Tan DD, Parvizi J. Vancomycin prophylaxis for total joint arthroplasty: incorrectly dosed and has a higher rate of periprosthetic infection than cefazolin. *Clin Orthop Relat Res*. 2017;475:1767-1774.
9. 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.
10. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. *J Allergy Clin Immunol*. 2014;133:790-796.
11. Macy E, Crawford W, Nguyen M, et al. Removing the warning not to use cephalosporins in individuals with a penicillin allergy: the effect on cephalosporin allergy and anaphylaxis incidence. *J Allergy Clin Immunol*. 2020;145:AB174.
12. Parkinson B, Armit D, McEwen P, Lorimer M, Harris IA. Is climate associated with revision for prosthetic joint infection after primary TKA? *Clin Orthop Relat Res*. 2018;476:1200-1204.
13. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. *JAMA*. 2019;321:188-199.
14. Stone AH, Kelmer G, MacDonald JH, Clance MR, King PJ. The impact of patient-reported penicillin allergy on risk for surgical site infection in total joint arthroplasty. *J Am Acad Orthop Surg*. 2019;27:854-860.
15. Wyles CC, Hevesi M, Osmon DR, et al. 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. *Bone Joint J*. 2019;101(6 suppl B):9-15.