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Adherence and outcomes of a surgical prophylaxis guideline promoting cephalosporin use among patients with penicillin allergy

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ABSTRACT

Background: The study purpose was to assess adherence to a local surgical prophylaxis guideline in patients with reported penicillin allergies, which recommends cephalosporins as first-line prophylaxis. **Methods:** Adult patients with penicillin allergies admitted for a surgical procedure from July 2020 to June 2021 were retrospectively screened, and the first surgery per admission was included. The primary outcome was the proportion of surgeries using β -lactam prophylaxis. Additional outcomes included prophylaxis timing, hypersensitivity reactions, acute kidney injury, infectious complications, duration of stay, and 30-day mortality or readmission.

Results: Among 597 procedures, 504 patients (84.4%) received a β -lactam for surgical prophylaxis, including 494 (82.3%) who received a cephalosporin. Patients in the non- β -lactam group were more likely to have a type I IgE-mediated penicillin allergy (48.4% vs 31.7%, $P = .002$); however, the majority with type I reactions still received β -lactams (78.0%), including in the setting of anaphylaxis or angioedema to penicillin (67.7%). Zero allergic reactions to prophylaxis antibiotics were reported in either group, and there were no significant differences in the proportion of patients receiving drugs associated with the management of allergic reactions. Receipt of non- β -lactams was associated with inappropriate prophylaxis timing (9.7% vs 3.2%, $P = .005$) and postprocedural acute kidney injury (7.5% vs 0.6%, $P < .001$). All other outcomes were nonsignificant between the groups.

Conclusion: Among surgical patients with a documented penicillin allergy, most received cephalosporin prophylaxis as recommended by institutional guidelines, with zero allergic reactions. Receipt of non- β -lactam prophylaxis was associated with worsened outcomes. Cephalosporin prophylaxis should be preferred for surgical patients, including in the setting of true penicillin allergy.

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Introduction

Surgical prophylaxis represents a major source of antibiotic consumption within hospitals.^{1,2} Although the most recent clinical practice guidelines addressing antimicrobial selection recommend cephalosporins as the mainstay of surgical prophylaxis for most procedures, non- β -lactam antibiotics such as vancomycin, clindamycin, or fluoroquinolones are recommended in the setting of any β -lactam allergy.³ Furthermore, the guidelines state that cephalo-

sporins “should not be used [...] in patients with documented or presumed IgE-mediated penicillin allergy.”³ Accordingly, a sample of perioperative inpatients from 100 U.S. hospitals indicated that cefazolin was 9-fold less likely to be used for surgical prophylaxis in patients with reported β -lactam allergies compared to nonallergic patients (28% frequency vs 77%).⁴ Penicillin allergy is the most commonly reported drug allergy, encompassing approximately 10% of the U.S. population, although the percent with type I IgE-mediated allergies who are truly unable to tolerate penicillin therapy is estimated to be far lower at 1%.⁵ Patients with a penicillin allergy label are more likely to receive non-first-line, non- β -lactam antibiotics for infection prevention or treatment, which has been associated with numerous deleterious clinical outcomes, including an increased risk for methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridioides difficile* infection.⁶ Among surgical patients, use of non- β -lactam prophylaxis has been associated

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with increased surgical site infections,^{7,8} *C. difficile*,⁹ acute kidney injury,⁹ and increased 30-day readmissions.¹⁰ Therefore, avoidance of all β -lactams in penicillin allergy is undesirable and likely to result in suboptimal surgical outcomes.

Historically, rates of allergic reaction to cephalosporins among penicillin-allergic patients were rumored to be as high as 10%; however, this inflated rate was never supported by population-based challenge data.¹¹ During more recent decades, it has been increasingly recognized that despite their similar chemical configurations, cephalosporin allergy cross-reactivity in the setting of true penicillin allergy is rare and not mediated by the shared β -lactam ring.^{11–13} These differences in antigenic sites have been supported with studies of monoclonal antibodies that recognize structures unique to cephalosporins with little or no recognition of penicillins.^{14,15} Notably, a large health system reported increased cephalosporin utilization among patients with a penicillin allergy with no significant increase in anaphylaxis or new allergies after the removal of a default electronic medical record (EMR) alert warning against cephalosporin use in patients with penicillin allergies.¹⁶ A minority of cephalosporins (eg, cephalexin, cefaclor) share a similar 7-position (R1) side chain with select penicillins and have been proposed to pose a risk for immunologically mediated cross-reactivity in the setting of penicillin allergy, although recent literature has challenged whether side chain-mediated cross-reactivity, if present, is truly clinically significant.^{11,17} Regardless, cefazolin, cefuroxime, and ceftriaxone represent examples of cephalosporins commonly used for surgical prophylaxis that do not have side chain similarity with any penicillin and therefore would not be anticipated to produce allergic reactions at a higher rate among penicillin-allergic patients compared to non-allergic patients. Similarly, despite historical rates of reported cross-reactivity as high as 47% for carbapenems in the setting of penicillin allergy, more modern prospective studies of carbapenems suggest that true cross-reactivity is very unlikely or nonexistent.^{13,18}

In light of the prior evidence, internal surgical prophylaxis guidelines were updated at the study center to recommend cephalosporin administration for all patients with penicillin allergy, including type I IgE-mediated reactions, with the exception of known type IV severe cutaneous adverse reactions (SCAR). The primary objective of this study was to assess how often a β -lactam was administered for surgical prophylaxis among inpatients with reported penicillin allergies. Secondarily, surgical and clinical outcome measures (including the occurrence of hypersensitivity reactions to prophylaxis antibiotic) were compared between patients receiving β -lactam and non- β -lactam surgical prophylaxis.

Methods

Study setting and guideline development

This study was approved by the institutional review board of St. Joseph's Hospital and Medical Center (SJHMC), a 600-bed tertiary care hospital in Phoenix, Arizona. Internal clinical practice guidelines at SJHMC were updated in late November 2017 to recommend use of formulary cephalosporins cefazolin, cefuroxime, ceftriaxone, ceftazidime, and cefepime, for the treatment of patients with any IgE-mediated penicillin allergy (ie, anaphylaxis, urticaria, laryngeal edema, bronchospasm, hypotension, or pruritic rash). Avoidance of β -lactams was recommended in the setting of documented SCAR (ie, Stevens-Johnson syndrome, toxic epidermal necrosis, drug reactions with eosinophilia, and systemic symptoms) or immunologically mediated interstitial nephritis given the limited data on the potential risks and mechanisms of cross-reactivity in this situation. The guideline document included background information on the relationship between side-chain similarity and β -lactam

cross-reactivity and the association of penicillin allergy with worsened clinical outcomes likely attributed to the use of second line agents with either less efficacy or more adverse effects. In February 2018, SJHMC surgical prophylaxis guidelines were similarly updated to recommend a cephalosporin as the preferred preoperative antibiotic prophylaxis for all surgical procedures (predominantly cefazolin or cefuroxime with the addition of metronidazole for anaerobic coverage when appropriate; ceftriaxone was recommended in the setting of type III open fracture and optionally over cefazolin for high-risk biliary tract procedures), including for patients with type I penicillin allergy. Education was provided to surgical, anesthesia, and pharmacy groups by the antimicrobial stewardship subcommittee at the time of initial rollout.

Data collection and outcome measures

All patients who underwent a surgical procedure reported to the Centers for Disease Control and Prevention's National Healthcare Safety Network during a 1-year period (July 2020 through June 2021) were retrospectively screened for study inclusion. Included patients were 18 years of age or older, had an inpatient stay associated with their procedure, had a documented penicillin allergy at the time of the surgical procedure of any type, and received one or more antibiotics for surgical prophylaxis. If a patient underwent multiple surgeries during a single admission, only the first surgery was evaluated. Data extracted from the EMR included patient demographics, allergies, procedural details, antibiotic prophylaxis (including timing and duration), and outcome measures. Penicillin allergic reactions were categorized according to standard classifications^{10,19} as a Gell and Coombs type I IgE-mediated hypersensitivity reaction (anaphylaxis, angioedema, wheezing, shortness of breath, bronchospasm, hypotension, hives, urticarial rash), mild reaction (maculopapular or non-specified rash, itching, redness), drug intolerance (nausea/vomiting or other adverse drug event not associated with an allergy), type II to IV hypersensitivity reaction (blistering rash, SCAR, acute interstitial nephritis, drug rash eosinophilia, hemolytic anemia, serum sickness, drug fever), or an unknown or not documented reaction. In the event that multiple reactions were listed (for example, shortness of breath and redness), patients were classified according to the most severe reaction (in this case, as a type I reaction).

The primary outcome was the proportion of patients with penicillin allergy receiving a β -lactam for surgical prophylaxis with or without adjunctive non- β -lactam antibiotics. A key secondary outcome was assessing for any resultant adverse reaction to prophylaxis antibiotic among patients who received a β -lactam and among those who received alternative non- β -lactam prophylaxis. Potential reactions were evaluated by reviewing operative notes, physician progress notes, nursing notes, and discharge notes for any documented adverse reaction, in addition to reviewing patient allergy lists for any new allergy reports to a prophylaxis antibiotic added within 6 months after the surgical procedure. As a sensitivity analysis, the proportion of patients receiving any drugs (epinephrine, diphenhydramine, albuterol, or systemic corticosteroids) used to treat acute-onset hypersensitivity within 6 hours of exposure or delayed-onset hypersensitivity within 48 hours of the operation was also compared between the groups. Additional outcomes included prophylaxis timing (with appropriate timing defined as administration within 1 hour before first incision, or within 2 hours for vancomycin or fluoroquinolones²⁰), acute kidney injury (≥ 0.3 mg/dL increase in serum creatinine from presurgical baseline within 48 hours of prophylaxis among patients not receiving hemodialysis), postoperative surgical site infection, *C. difficile*

Table 1Baseline characteristics of penicillin allergic patients receiving and not receiving a β -lactam for surgical prophylaxis

Characteristic	β -lactam prophylaxis (n = 504)	Non- β -lactam prophylaxis (n = 93)	P value
Age at surgery, y, median (IQR)	61 (45–71)	62 (52–69)	.97
Age ≥ 75 y, no. (%)	72 (14.3)	11 (11.8)	.53
Female sex, no. (%)	315 (62.5)	60 (64.6)	.71
Race, no. (%)			
White	445 (88.3)	80 (86.0)	.54
Black or African-American	28 (5.6)	6 (6.5)	.73
American Indian or Alaska Native	3 (0.6)	3 (3.2)	.05
Other/unknown	28 (5.6)	4 (4.3)	.62
Hispanic ethnicity, no. (%)	69 (13.7)	11 (11.8)	.63
BMI, median (IQR)	27.6 (24.0–32.6)	28.2 (24.0–32.2)	.94
BMI ≥ 30 , no. (%)	188 (37.3)	32 (34.4)	.60
Comorbidities, no. (%)			
Malignancy/cancer	132 (26.2)	23 (24.7)	.77
Diabetes mellitus	93 (18.5)	21 (22.6)	.35
Asthma	57 (11.3)	17 (18.3)	.06
Chronic renal impairment	45 (8.9)	8 (8.6)	1.0
COPD	32 (6.3)	4 (4.3)	.64
Congestive heart failure	12 (2.4)	2 (2.2)	1.0
Procedure type, no. (%)			
Neurosurgical/spine	328 (65.1)	48 (51.6)	.013
Orthopedic	60 (11.9)	17 (18.3)	.092
Gastrointestinal	57 (11.3)	8 (8.6)	.44
Breast/plastics	20 (4.0)	2 (2.2)	.55
Urological/nephrology/ prostate	13 (2.6)	6 (6.5)	.051
Thoracic/cardiac/vascular	12 (2.4)	3 (3.2)	.72
Gynecological	9 (1.8)	7 (7.5)	.002
Head and neck	5 (1.0)	2 (2.2)	.30
Emergency surgery, no. (%)	35 (6.9)	5 (5.4)	.58
Trauma, no. (%)	51 (10.1)	8 (8.6)	.65
Preprocedural infection, no. (%)	39 (7.7)	15 (16.1)	.010
Total allergies, median (IQR)	2 (1–3)	3 (1–5)	<.001
Cephalosporin allergy, no. (%)	21 (4.2)	28 (30.1)	<.001
Non- β -lactam antibiotic allergy, no. (%)	119 (23.6)	32 (34.4)	.028
Penicillin allergy categorization, no. (%)			
Type I IgE HSR	160 (31.7)	45 (48.4)	.002
Anaphylaxis	18 (3.6)	13 (14.0)	<.001
Angioedema	45 (8.9)	13 (14.0)	.13
Mild reaction allergy	138 (27.4)	19 (20.4)	.16
Drug intolerance	44 (8.7)	2 (2.2)	.03
Unknown allergy	159 (31.5)	26 (28.0)	.49
Type II-IV HSR	3 (0.6)	1 (1.1)	.49

BMI, body mass index; COPD, chronic obstructive pulmonary disease; HSR, hypersensitivity reaction; IQR, interquartile range.

infection, postprocedural length of stay, 30-day mortality, and 30-day readmission.

Statistical analysis

Data were reported using medians and interquartile ranges for nonnormally distributed continuous data and percentages for event rates and nominal data. Mann-Whitney *U* was used to compare continuous data. χ^2 and Fisher exact test were used to compare proportions. All statistical analyses were performed with Excel.

Results

At total of 8,044 surgeries occurred over the study time period, of which 797 involved a patient with a listed penicillin allergy (9.9% of all procedures). After applying all study criteria, a total of 597 initial inpatient surgeries representing 544 unique patients were included. More than one third (205, 34.3%) of the documented reactions to penicillin were suggestive of type I IgE-mediated hypersensitivity reactions, including 89 listed reactions of anaphylaxis (5.2%) or angioedema (9.7%) among 79 unique patients. Another 157 (26.3%) of the allergies consisted of minor reactions, including unspecified rash, while 185 (31.0%) of the reactions were unknown. Drug side effects (adverse effects not

suggestive of an immunologically mediated hypersensitivity) were uncommonly documented as allergies (46, 7.7%) and potential type II to IV reactions were rare (4, 0.7%).

Patients with a listed penicillin allergy received a β -lactam for surgical prophylaxis in 504 (84.4%) of the surgical encounters (β -lactam group). Ninety-eight percent received a cephalosporin, predominantly cefazolin (280, 55.6%) or cefuroxime (195, 38.7%). Other β -lactams administered included ertapenem (7, 1.4%) and penicillins (3, 0.6%). A small minority (13, 2.6%) additionally received a non- β -lactam antibiotic, most commonly metronidazole for expanded anaerobic activity. Ninety-three patients (15.8%) did not receive any β -lactam for surgical prophylaxis and comprised the non- β -lactam group. Approximately 30% of these patients had a listed allergy to one or more cephalosporins. The most commonly administered antibiotics in this group were clindamycin (51, 54.8%) and vancomycin (38, 37.6%). Less than 5% received either a fluoroquinolone or an aminoglycoside. Among the 35 patients in the non- β -lactam group who received vancomycin, only 5 (14.3%) had a documented history of MRSA colonization or infection.

The patient baseline characteristics of the β -lactam and non- β -lactam groups are shown in Table 1. Overall, both groups were demographically similar. The median age at surgery was 62 years, 87.9% of patients were white, and 13.4% of patients listed Hispanic as their ethnicity. The most common comorbidities were obesity,

Table IIComparison of outcome measures among penicillin allergic patients receiving and not receiving a β -lactam for surgical prophylaxis

Parameter	β -lactam prophylaxis ($n = 504$)	Non- β -lactam prophylaxis ($n = 93$)	P value
Inappropriate prophylaxis timing, no. (%) [*]	16 (3.2)	9 (9.7)	.005
Prophylaxis discontinued immediately postprocedure, no. (%)	362 (71.8)	69 (74.2)	.64
Prophylaxis discontinued within 48 h postprocedure, no. (%)	471 (93.5)	86 (92.4)	.73
Documented allergic reaction to surgical prophylaxis, no. (%)	0	0	1.0
Any receipt of select medications within 48 h postoperative, no. (%)			
Albuterol	17 (3.4)	1 (1.2)	.33
Corticosteroids	120 (23.8)	21 (22.6)	.80
Diphenhydramine	20 (4.0)	4 (4.3)	.78
Epinephrine	2 (0.4)	1 (1.0)	.40
Surgical site infection, no. (%)	11 (2.2)	2 (2.2)	1.0
<i>Clostridioides difficile</i> infection, no. (%)	1 (0.2)	0	1.0
Acute kidney injury, no. (%)	3 (0.6)	7 (7.5)	<.001
Postprocedure duration of stay, days, median (IQR)	2 (1–5)	2 (1–4)	.46
30-day mortality, no. (%)	9 (1.5)	1 (1.1)	1.0
30-day readmission, no. (%)	52 (8.7)	8 (8.6)	.97

IQR, interquartile range.

^{*} Analysis performed on the subset of patients who had adequate data to assess: β -lactam group, $n = 496$, non- β -lactam group, $n = 93$.

malignancy, and diabetes mellitus. Neurosurgical procedures comprised the majority of surgeries, followed by orthopedic procedures. Ten percent of surgeries represented traumas, and 9.0% of surgeries occurred in the setting of existing infection. Comparing the 2 groups, patients receiving a β -lactam were more likely to have undergone neurosurgical procedures (65.1% vs 51.6%, $P = .013$) and less likely to have received a gynecologic procedure (1.8% vs 7.5%, $P = .002$). Preprocedural infection was more common in the non- β -lactam group (16.1% vs 7.7%, $P = .010$). Patients in the non- β -lactam group were more likely to have a documented cephalosporin allergy (30.1% vs 4.2%, $P < .001$) as well as a higher median number of total allergies (3 vs 2, $P < .001$). A higher proportion of type I hypersensitivity reactions to penicillin was also observed for the non- β -lactam group (48.4% vs 31.7%, $P = .002$); however, severe reported reactions to penicillin were present in both groups. A β -lactam was administered in the setting of type I reaction to penicillin in the majority of cases (160/205, 78.0%), including 67.7% of the time (63/89 cases) with listed anaphylaxis or angioedema. Among patients with only drug intolerance to penicillin, a β -lactam was administered in 96.6% of cases.

Among all patients, there were zero documented allergic reactions to antibiotic prophylaxis (Table II). In the sensitivity analysis comparing the proportion of patients receiving epinephrine, diphenhydramine, albuterol, or corticosteroids within 48 hours postprocedure, no statistically significant differences were observed for any drug. With respect to other study outcomes, a statistically higher proportion of procedures in the non- β -lactam group had inappropriate timing of antibiotic prophylaxis outside of the recommended window (9.7% vs 3.2%, $P = .005$). A higher frequency of acute kidney injury was additionally observed in the non- β -lactam group (7.5% vs 0.6%, $P < .001$). Postprocedural duration of stay was generally short (median = 2 days) and did not differ between the groups. Only a single case of *C. difficile* infection was reported in a patient who received ertapenem for surgical prophylaxis and had an extended duration of hospitalization postsurgery. All other outcome measures including surgical site infection, readmissions, and mortality were nonsignificant.

Discussion

Adherence rates to the institutional surgical prophylaxis guideline promoting cephalosporin use among patients with penicillin allergy were overall high (>80%) and in line with other academic medical centers that have implemented either similar or more intensive interventions to increase cephalosporin utilization

in this population.^{10,21} β -lactams were administered in the majority of surgeries across all penicillin allergy types, including severe type I hypersensitivity reactions. There was no evidence suggesting an increased risk for hypersensitivity reactions to cephalosporin prophylaxis compared to non- β -lactam prophylaxis in the setting of penicillin allergy, and increased rates of acute kidney injury were observed when non- β -lactam antibiotics were used. Furthermore, zero allergic reactions were observed among the 63 procedures among patients with anaphylaxis or angioedema receiving cephalosporin prophylaxis. Of note, the 5% observed rate of documented anaphylaxis to penicillin within the EMR is substantially higher than the anticipated population incident risk of 0.004% to 0.097%.^{22,23} This overcalling may be secondary to errors of documentation in the course of obtaining patient allergy history or facilitated by suboptimal EMR documentation systems (for example, selecting the first reaction from an alphabetically organized drop-down menu, which often would first list anaphylaxis). In the present study, procedures using non- β -lactam surgical prophylaxis were also nearly 3-times more likely to have inappropriate prophylaxis timing. This may be attributed to these nonpreferred antibiotics being stored outside of the surgical suite, creating potential logistical delays and resulting in a prolonged time to surgical incision. Fluoroquinolones and vancomycin also must be infused rather than given as a rapid intravenous push, which may increase the complexity of administration and lead to suboptimal timing. Although surgical site infections were rare in this study, precluding an adequately powered comparison, prophylaxis timing outside of the guideline-recommended window has previously been associated with an increased risk for surgical site infections given the lowered tissue concentrations at time of incision.²⁴

These results add to the growing literature supporting the safety of cephalosporins in penicillin allergy and use of β -lactam surgical prophylaxis over alternative antibiotics. In a before-and-after quasi-experimental study by Collins et al, the introduction of a cross-reactivity chart and allergy history guidance document increased the percentage of penicillin-allergic patients receiving β -lactam surgical prophylaxis from 15.1% to 84.9% with no increase in allergic reactions (0.5% versus 0.3%, $P = .323$). The educational campaign and subsequent increase in β -lactam utilization (98% cefazolin) also resulted in fewer 30-day readmissions (7.9% vs 6.3%, $P = .035$) and higher rates of appropriate prophylaxis timing (93.7% vs 95.9%, $P = .003$) and duration (98.3% vs 99.2%, $P = .05$).¹⁰ In a similar study by Kuruvilla et al, an institutional algorithm recommending cefazolin and cefuroxime surgical prophylaxis for all

penicillin-allergic surgical patients without SCAR reactions also increased the proportion of these patients receiving a first-line cephalosporin from 22.3% to 80.1% with no immediate allergic reactions and one delayed rash (0.2%) without antibiotic discontinuation.²¹

Additional studies have affirmed a low incidence of hypersensitivity reactions among penicillin-allergic patients after surgical prophylaxis, with comparable reaction frequencies among cephalosporins and β -lactam alternatives. In a study by Beltran et al, allergic reactions to cefazolin were rare among penicillin-allergic patients (0.7%), which was numerically lower than the proportion of patients with reactions following administration of clindamycin (2.1%) or ciprofloxacin (5.8%).²⁵ Similar findings were observed in a study by Fosnot et al, with immediate hypersensitivity reactions to cefazolin (1.7%) in line with rates after receipt of vancomycin (2.2%) or clindamycin (2.4%).²⁶ Thus, use of non- β -lactams in penicillin allergy does not appear to reduce the likelihood of hypersensitivity reactions and may increase the risk for adverse events.^{7–9} It should be acknowledged that patients with a true IgE-mediated penicillin allergy may be at increased risk for developing allergic reactions to other antibiotics, given the potential for multiple drug hypersensitivity syndrome.^{27,28} However, this increased sensitivity is inclusive of unrelated (non- β -lactam) antibiotic classes^{17,29} and therefore cannot be prevented by administering non- β -lactam alternative antibiotics in lieu of first-line cephalosporin therapy. Clinicians should recognize that unmatched comparisons of cephalosporin hypersensitivity reactions between penicillin-allergic and nonallergic patient populations may not be appropriate for assessing cross-reactivity risk given the increased propensity for allergy independent of drug selection in the former group.

Of note, 21 patients in the present study who additionally had a listed cephalosporin allergy also received β -lactam therapy, mostly other cephalosporins (81%). Although not included within SJHMC's internal guidelines, within-class cephalosporin allergy cross-reactivity is also believed to be side chain-mediated and true type I allergy to one cephalosporin does not represent a contraindication to all members of the cephalosporin class.³⁰ Cefazolin in particular has a unique structure that is not anticipated to cross-react with other cephalosporins.¹³ None of the patients with cephalosporin allergy received a cephalosporin that would be anticipated to pose a cross-reactivity risk; therefore, it was not surprising that no allergic reactions occurred among these patients. Owing to the relatively small number of patients with listed cephalosporin allergies compared to penicillin allergies and to avoid provider confusion, the SJHMC antimicrobial stewardship committee has not formally educated clinicians about intraclass cephalosporin allergy cross-reactivity or promoted the use of cephalosporins among patients with suspected IgE-mediated cephalosporin allergy. However, use of cefazolin as surgical prophylaxis with non-cefazolin cephalosporin allergy could be considered and has been implemented by some centers.¹⁰ We do recommend avoidance of cephalosporin prophylaxis among patients with a drug-unspecified cephalosporin allergy label when the reaction is unknown or suggestive of type I hypersensitivity unless the patient has previously received the cephalosporin being considered for prophylaxis safely. In the absence of cephalosporin allergy or documented SCAR to β -lactams, situations where non- β -lactam alternative antibiotics may be preferred for prophylaxis are likely to be patient-specific, for example, based on the resistance profile of a known colonizing organism before a genitourinary procedure.

Limitations of the present study include those inherent to single-center retrospective studies, with available information limited to what was charted in the EMR. It is possible that all allergic reactions may not have been identified if they were not adequately documented. We attempted to mitigate this limitation

by additionally comparing administration rates of drugs used in allergy management, which also did not reveal any concerning safety signals that would caution against β -lactam administration. The patient population, distribution of surgical procedures, and clinicians responsible for antibiotic prophylaxis selection at SJHMC may differ from other hospitals and could potentially influence rates of β -lactam use independent of the educational intervention. Of note, SJHMC is home to the Barrows Neurological Institute, a nationally recognized neurosurgical center for treatment of brain and spine disorders, and thus these procedures were anticipated to comprise a larger proportion of included procedures than may be present at other facilities. Additionally, comparisons of rare outcomes (eg, surgical site infection, *C. difficile*) were likely underpowered to detect potential true differences.

In conclusion, among surgical patients with a documented penicillin allergy, most received a cephalosporin as recommended by SJHMC surgical prophylaxis guidelines. Zero allergic reactions occurred, including among patients with documented type I IgE-mediated penicillin allergies. Receipt of non- β -lactam prophylaxis was associated with worsened outcomes, including inappropriate prophylaxis timing and acute kidney injury. The results of the study support the growing recognition that patients with penicillin allergy may be safely treated with other β -lactam classes, including cephalosporins that have side-chain determinants that are structurally dissimilar to penicillin compounds. Given the mounting real-world safety evidence and consistent linkage of second-line non- β -lactam antibiotics with deleterious surgical and clinical outcomes, national clinical practice guidelines should be updated to endorse the preferential administration of cephalosporins for surgical prophylaxis, including in the setting of true penicillin allergy.

Conflict of interest/Disclosure

Dr Nailor has served as a consultant for Shionogi, AbbVie, and Merck. All other authors declare no conflicts of interest.

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