Improving cefazolin administration for surgical prophylaxis in reported penicillin allergy: A retrospective study of a health system intervention

Ami P. Belmont, MD,[a] Moeun Son, MD, MSCI,[b,c] Jaime B. Hyman, MD,[d] Lucia You, MD,[a] Chang Su, MD,[a] Nitu Kashyap, MD,[e] Jeffrey E. Topal, MD,[f,g] Dayna McManus, PharmD,[g] Richard A. Martinello, MD,[f,h,i] and Jason Kwah, MD, MSCI[a] *New Haven, Conn; and New York, NY*

Background: Cefazolin is the most common first-line antibiotic to prevent surgical-site infections. Patients with penicillin allergy labels often receive alternative antibiotics, which is associated with increased rates of surgical-site infections, multi–drug-resistant infections, and cost.
Objective: We sought to determine whether a hospital-wide guideline recommending first-line surgical prophylaxis in patients with penicillin allergy labels can increase the use of cefazolin without compromising safety.
Methods: We conducted a retrospective cohort study of adult surgical patients with penicillin allergy labels. The main intervention was updated hospital-wide surgical guidelines recommending first-line prophylaxis in most patients with penicillin allergy labels. We compared the preintervention and postintervention groups. The primary outcome was cefazolin use. Secondary perioperative outcomes included alternative antibiotic use and severe allergic episodes (anaphylaxis).
Results: The total sample comprised 7187 patients with penicillin allergy labels who underwent 8945 surgical encounters (median age [interquartile range], 61 [46-71] years); 4891 [68%] female). Cefazolin was used in 2256 (73%) patients in the preintervention group and 3390 (83%) patients in the postintervention group ($P < .001$), with an adjusted odds ratio of 1.87 (95% CI, 1.67-2.10). There was a decrease in the use of clindamycin from 14% to 8% ($P < .001$) and gentamicin from 16% to 8% ($P < .001$). There were no episodes of severe allergic reactions among patients who received guideline-directed therapy.
Conclusions: A hospital-wide guideline can improve use of cefazolin in surgical patients with penicillin allergy labels without increasing the risk for severe allergic reactions. National and international guidance should be considered to enhance administration of cefazolin in surgical patients with penicillin allergy labels. (J Allergy Clin Immunol Global 2025;4:100377.)

Key words: *Surgical-site infection, penicillin allergy, β-lactam allergy, antibiotic stewardship, antimicrobial stewardship, drug allergy, surgical prophylaxis*

Reported penicillin allergies affect 10% to 15% of patients and are a threat to appropriate administration of first-line surgical-site infection (SSI) antimicrobial prophylaxis.[1-3] The scope of this impact is enormous: SSIs are the most common and costly health care–associated infections, affecting 2% to 5% of surgeries in the United States.[4-6] The aims of administering first-line surgical antibiotic prophylaxis are to prevent SSI, lower the risk of multi–drug-resistant organisms, and reduce morbidity, mortality, and health care costs.[7-13] Cefazolin is the medication of choice for most procedures because of its desirable spectrum of activity, favorable safety profile, and low cost.[12,14-18] The presence of a penicillin allergy label alone is associated with a 50% increased risk of SSI, likely mediated by reduction in use of first-line antibiotics (most often cefazolin).[14-17,19-21] When alternative antibiotics are used for surgical prophylaxis, there are demonstrably higher rates of SSIs, prosthetic joint infections, surgical revisions, and multi–drug-resistant infections across a broad range of surgical specialties and procedures.[14-18,20,22,23]

Although reported penicillin allergies commonly affect prescribing decisions, there is good evidence that most are inaccurate: more than 95% of these patients can tolerate penicillin safely and even more can tolerate cephalosporins.[3] Patients are often inaccurately labeled because either a patient was mislabeled at the time of the inciting event or because, in cases of true allergy, most cases will be outgrown within 10 years.[24] For this reason, such patients are referred to as having penicillin allergy labels, termed to connote the common mislabel. Moreover, a plethora of research now suggests that even in true IgE-mediated penicillin allergies, there is limited cross-reactivity between penicillins and cephalosporins, especially cephalosporins with dissimilar R1 side chains.[3,25-31] In congruence with this understanding, the Joint Task Force of the American Academy of Allergy, Asthma &

From [a]the Section of Rheumatology, Allergy, and Immunology, Department of Internal Medicine, and [b]the Section of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale School of Medicine, New Haven; [c]the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Weill Cornell Medical College, New York; and [d]the Department of Anesthesiology, [e]Yale New Haven Health, Yale School of Medicine, [f]the Section of Infectious Disease, Department of Internal Medicine, Yale School of Medicine, the Departments of [g]Pharmacy Services and [h]Infection Prevention, Yale New Haven Hospital, and [i]the Division of Infectious Diseases, Department of Pediatrics, Yale School of Medicine, New Haven.

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Corresponding author: Ami P. Belmont, MD, Department of Internal Medicine, Yale University School of Medicine, 333 Cedar St, PO Box 208013, New Haven, CT 06520. E-mail: ami.belmont@yale.edu.

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Abbreviations used
EMR: Electronic medical record
SSI: Surgical-site infection

Immunology and the American College of Allergy, Asthma, and Immunology released updated drug allergy practice parameters in 2022, suggesting that patients with a history of anaphylaxis to penicillin can be given cephalosporins with structurally dissimilar R1 side chains, such as cefazolin.[3] However, other national infectious disease, anesthesiology, and surgical guidelines have not been updated to this effect, and this has not yet been implemented in many surgical centers.[12,19-21,32-36]

To date, 1 single-site retrospective study demonstrated that an institutional algorithm to promote cefazolin use in surgical patients with penicillin allergy labels could be effective.[37] However, larger studies have not yet replicated these findings. More data are needed to demonstrate effective interventions to improve cefazolin use in surgical patients with penicillin allergy labels, establish safety, and support additional institutions and national guidelines to adopt recommendations to use cefazolin in patients with penicillin allergy labels. The purpose of this large retrospective cohort study was to evaluate the effectiveness and safety of a hospital-wide intervention to increase use of cefazolin for surgical patients with penicillin allergy labels at a large academic tertiary care center. We hypothesized that implementation of a hospital-wide guideline to use cefazolin in surgical patients with penicillin allergy labels would increase use of first-line surgical prophylaxis (cefazolin) without compromising safety.

METHODS

Setting

We conducted a retrospective cohort study of surgical patients with penicillin allergy labels at Yale New Haven Hospital, a large tertiary care center in New Haven, Connecticut. This study was approved by the institutional review board at Yale School of Medicine. Informed consent was waived for this retrospective analysis.

Intervention

This retrospective study was conducted to evaluate the results of a health system–wide intervention implemented in 2022 to expand use of cefazolin for surgical prophylaxis in patients with penicillin allergy labels. This initiative was led by a team of leaders from the fields of infectious disease, antimicrobial stewardship pharmacy, infection prevention, anesthesiology, surgery, and allergy and immunology. It was part of a greater antibiotic stewardship effort within the Yale New Haven Health System for surgical patients. The main intervention was updating the Yale New Haven Health System Surgical Prophylaxis Guideline, which was formally released hospital-wide on February 13, 2022. The updated guideline recommended the use of first-line antibiotics (most often cefazolin) for most patients with penicillin allergy labels, including those with a history of anaphylaxis and IgE-mediated reactions to penicillins (Fig 1). The guideline was designed to exclude the following patients with penicillin allergy labels from receiving cephalosporins: patients with histories of severe cutaneous adverse reactions (eg, drug reaction with eosinophilia and systemic symptoms as well as Stevens-Johnson syndrome), serum sickness, hemolytic anemia, other severe delayed reactions, and patients with a concurrent cephalosporin allergy. The steps in the guideline were modified from a smaller retrospective study performed at another institution.[37] The guideline change (and algorithm to support it [Fig 1]) was considered the main intervention. To support implementation of the updated guideline, before guideline implementation the team also conducted a series of talks to educate perioperative clinicians, including Grand Rounds for the Departments of Anesthesiology and Surgery and virtual perioperative staff educational sessions. There was also a best practice advisory alert in the electronic medical record (EMR) as part of the outpatient presurgical assessment to notify perioperative staff that cefazolin use was a guideline-recommended option for surgical prophylaxis. There were no changes made to the standard Yale New Haven Health system–wide alerts that notify providers of a penicillin allergy label when a cephalosporin is ordered (if the patient is not already denoted as tolerating cephalosporins).

Data collection

Initial data abstraction from the EMR was performed by the Yale School of Medicine Joint Data Analytics Team in August of 2023. We identified all adults (≥18 years) with penicillin allergy labels who underwent surgery at Yale New Haven Hospital between April 2, 2021 and July 5, 2023. Data were collected from April 2021 onward to have at least 9 months of data preintervention. Patients were excluded from the analysis if no perioperative antibiotics were administered or if they had a contaminated wound (in which case they would receive treatment rather than prophylactic antibiotics). The following data were abstracted for the study cohort: demographic characteristics, surgical encounter (eg, outpatient/inpatient, surgical service, and wound class), antibiotics administered perioperatively, previous cephalosporin prescriptions, penicillin allergy history, and *International Classification of Diseases, Tenth Revision* (*ICD*) code for anaphylaxis (T78.2 or T88.6, consistent with previous literature).[29] The allergy section of the EMR was used to identify patients with penicillin allergy labels, as well as the reaction history. We also recorded when patients' allergy histories were listed as "penicillin tolerates cephalosporins," reflecting a previous antibiotic stewardship initiative in our health system to flag patients who had previously tolerated cephalosporins to improve cephalosporin administration. Patient charts were manually reviewed for intraoperative reactions by an allergist if they had an *ICD* code for anaphylaxis in their medical record, including but not limited to codes associated with the surgical encounter. In addition, the Yale School of Medicine Department of Anesthesiology has a robust adverse events database, in which all major perioperative adverse events are noted. This was manually reviewed for allergic reactions among patients during the study period.

Outcomes

The primary outcome was cefazolin use. Secondary outcomes included the total number of perioperative antibiotics received, alternative antibiotic use (eg, clindamycin, gentamicin, and vancomycin), and perioperative anaphylaxis episodes as per the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria.[38]

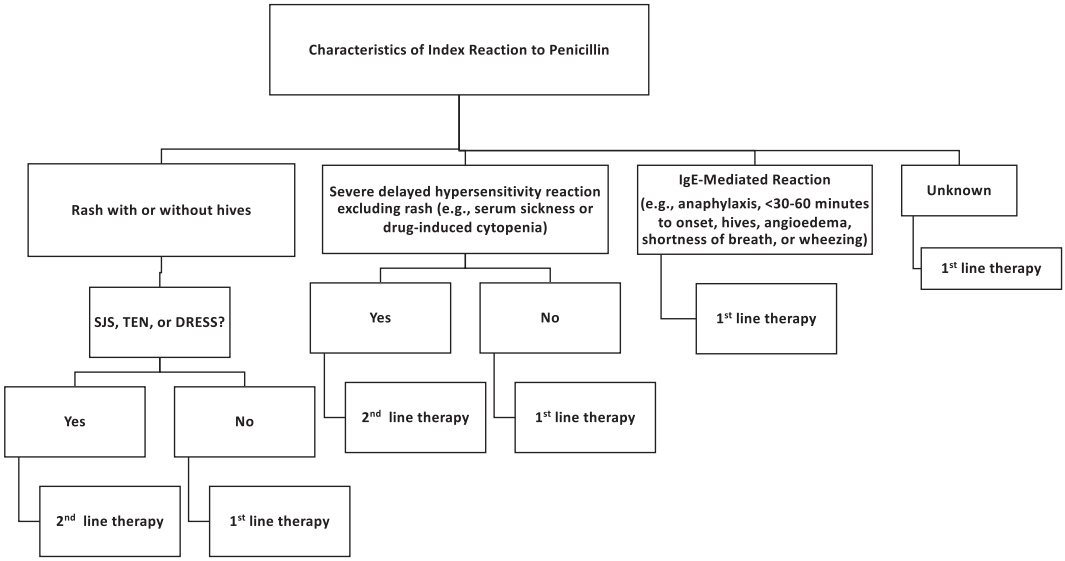

FIG 1. Yale New Haven Hospital's surgical prophylaxis algorithm for patients with penicillin allergy labels. *DRESS*, Drug reaction with eosinophilia and systemic symptoms; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

Statistical analysis

Individuals who underwent surgery during the time period before the rollout of the new hospital guidelines on February 13, 2022 ("preintervention" group) were compared with those who underwent surgery during the time period after the rollout date of the guidelines ("postintervention" group). If a patient had more than 1 surgery during the study period, the first surgical encounter was used for the analysis. Continuous variables are described using median (interquartile range), given the nonnormal distribution of the data. Categorical variables are described as counts and proportions. Bivariate analyses were performed using chi-square test and the Fisher exact test, as appropriate, for categorical variables and the Mann-Whitney *U* test for continuous variables. Multivariable analysis was performed for the outcome variable of cefazolin administration and its association with the exposure of time period (on the basis of the date of health system–wide guideline rollout), adjusting for covariates with a *P* value less than .1 in the bivariate analyses. A sensitivity analysis was performed using all surgical encounters during the study period as the unit of analysis, rather than each individual patient. Statistical tests were 2-tailed, and *P* values less than .05 were considered statistically significant. There was no adjustment made for multiple comparisons. There were no missing data for all the variables of interest. All statistical analyses were performed using STATA version 14.2 (StataCorp LLC, College Station, Tex).

RESULTS

In total, 64,170 patients were identified as having surgery requiring antibiotics during the study period. Of these patients, 7,187 (11.1%) had penicillin allergy labels. There were no missing data for outcomes of interest. The preintervention group included 3,085 surgical patients with penicillin allergy labels who had 3,514 surgical encounters, and the postintervention group included 4,102 surgical patients with penicillin allergy labels who had 5,431 surgical encounters (Table I). The median age at time of surgery and female-to-male ratio between the 2 groups were similar. There were significant differences in ethnicity and race between the groups. Surgical encounters were conducted in similar settings in both groups, with no significant differences in the proportion of outpatient/inpatient surgeries, surgical services, or wound class. The preintervention group had significantly more patients with EMR penicillin allergy labels denoting "penicillin tolerates cephalosporins" as well as more patients with previous cephalosporin prescriptions documented in the EMR (Table I). Documented EMR penicillin reaction histories were similar (Table II).

Before the implementation of the updated surgical prophylaxis guideline, cefazolin was used in 2256 (73.0%) surgical patients with penicillin allergy labels. After implementation, cefazolin use increased to 3390 (82.6%) surgical patients with penicillin allergy labels ($P < .001$) (Table III). This corresponds to an adjusted odds ratio of 1.87 (95% CI, 1.67-2.10) (Table IV). There was a decrease in use of clindamycin (from 14.4% to 8.5%; $P < .001$) and gentamicin (from 15.6% to 7.6%; $P < .001$; Table III) comparing the pre- and postintervention groups (Table III). The use of vancomycin decreased from 8.9% to 8.0%, but it was used relatively infrequently and the change was not statistically significant ($P = .223$; Table III). Of note, 1261 patients had multiple surgeries during the study period (n = 3018 surgeries, ranging from 2 to 6 surgical encounters per patient). A sensitivity analysis looking at all surgical encounters rather than individual patients found that cefazolin use increased from 73.0% in the preintervention group (n = 3514 total surgical encounters) to 82.8% (n = 5431) in the postintervention group ($P < .001$), with a concomitant decrease in use of clindamycin (from 13.7% to 8.1%; $P < .001$), gentamicin (from 15.4% to 7.3%; $P < .001$), and vancomycin (from 9.4% to 8.1%; $P = .03$).

In terms of safety, no patients with *ICD* codes for anaphylaxis had perioperative anaphylaxis on chart review. During the study period, there were 3 cases of possible perioperative anaphylaxis related to medications reported in the Department of Anesthesiology database in more than 64,000 surgical patients. Of these 3 cases, 1 occurred in a patient with a penicillin allergy label along with a concurrently listed cephalosporin allergy ("cephaloglycin-bradycardia"). This patient received cefazolin intraoperatively outside of guideline recommendations; however, she had tolerated cefazolin 3 times before in our hospital system. During

TABLE I. Characteristics of patients with penicillin allergy labels undergoing surgery before and after the implementation of the hospital-wide updated surgical guideline on February 13, 2022

Patient characteristics	Before guideline release (n = 3085)	After guideline release (n = 4102)	*P* value
Sex: female	2069 (67.1)	2822 (68.8)	.120
Age (y)	61 (46-71)	61 (46-71)	.945
Ethnicity			<.001
Hispanic/Latino	291 (9.4)	442 (10.8)	
Non-Hispanic	2758 (89.4)	3539 (86.3)	
Declined to answer or unknown	36 (1.2)	121 (3.0)	
Patient-reported race			
White	2446 (79.3)	3187 (77.7)	<.001
Black or African American	385 (12.5)	484 (11.8)	
Asian	41 (1.3)	39 (1.0)	
Other or unknown	213 (6.9)	391 (9.6)	
Surgical setting			
Inpatient	1538 (49.1)	2094 (51.1)	.316
Outpatient	1547 (50.1)	2008 (48.9)	
Wound class			
Clean	1736 (56.3)	2301 (56.1)	.881
Contaminated	1349 (43.7)	1801 (43.9)	
Surgical service			
Orthopedics	672 (21.8)	870 (21.2)	.015
Genitourinary*	884 (28.7)	1184 (28.9)	
Cardiovascular and thoracic†	319 (10.3)	469 (11.4)	
General surgery, pediatrics, endocrine, transplant, trauma, gastroenterology, and oncology	447 (14.5)	577 (14.1)	
Breast and plastic surgery	237 (7.7)	261 (6.4)	
Neurosurgery	184 (6.0)	257 (6.3)	
Ophthalmology; ear, nose, and throat; and oral surgery	213 (6.9)	329 (8.0)	
Interventional radiology, medical and anesthetic procedures, podiatry	129 (4.2)	155 (3.8)	
Documented "penicillin tolerates cephalosporin" label in the EMR			.051
Yes	634 (20.6)	752 (18.3)	
No	2115 (68.6)	2910 (70.9)	
Not specified or unknown	336 (10.9)	440 (10.7)	
Previous cephalosporin prescription in the EMR	1346 (43.6)	1443 (35)	<.001

Data are presented as n (%) and median (interquartile range), unless otherwise specified.
*Genitourinary represents combined obstetrics, gynecology, gynecology oncology, and urology surgical services.
†Cardiovascular and thoracic surgery represents combined cardiac, vascular, and thoracic surgical services.

this surgical encounter, she developed brief hypotension, which was responsive to routine therapy and the case was completed without issue. After the surgery, she was noted to have another episode of hypotension along with a newly discovered rash, which prompted treatment with epinephrine. She then recovered without issue. No episodes occurred in patients with penicillin allergy labels who received guideline-appropriate therapy.

DISCUSSION

To our knowledge, this is the largest cohort study to date that examines the effectiveness and safety of a hospital-wide intervention to increase use of first-line surgical prophylaxis in patients with penicillin allergy labels. We demonstrate the safety and effectiveness of our main intervention, an updated surgical prophylaxis guideline for surgical patients with penicillin allergy labels. Of note, we used a multidisciplinary and multifaceted approach to support these guidelines, including targeted education for perioperative clinicians. We found that our intervention was associated with a clinically significant increased rate of cefazolin use in surgical patients with penicillin allergy labels. We also found that using cefazolin in a large cohort of more than 7000 surgical patients with penicillin allergy labels was safe, with no significant increase in severe allergic reactions.

Our results significantly strengthen findings from other smaller studies, demonstrating that updating surgical prophylaxis algorithms for surgical patients with penicillin allergy labels can safely increase cefazolin use. This includes a smaller study in which an institutional algorithm increased cephalosporin use in surgical encounters in patients with penicillin allergy labels from 22% to 80% without increasing adverse events. However, notably this study included only 688 surgical encounters after algorithm introduction (with 551 cephalosporin administrations), as compared with 5431 postintervention surgical encounters in our cohort, in which cefazolin was administered more than 4452 instances without issue.[37] Likewise, another small study of approximately 200 surgical patients with penicillin allergy labels with reported anaphylactic histories found no differences in adverse events attributable to cefazolin compared with adverse events attributed to alternative antibiotics.[39] To our knowledge, there are no conflicting studies that raise concern for increased cefazolin reaction rates in patients with penicillin allergies.

Historically, there has been concern about penicillin and cephalosporin cross-reactivity, but we now know this has been largely overstated. Cephalosporin allergy is mediated by a different mechanism than penicillin allergy: penicillin allergy is typically mediated by breakdown products of the β-lactam ring,

TABLE II. Penicillin reaction types as listed in the EMR

Reaction histories	Before guideline release (n = 3085)	After guideline release (4102)	*P* value
Reaction type			
Rash (unspecified type)	785 (25.5)	1062 (25.9)	.257
Unknown	589 (19.1)	834 (20.3)	
Hives	550 (17.8)	754 (18.4)	
Swelling/angioedema	225 (7.3)	240 (5.9)	
Gastrointestinal symptoms	179 (5.8)	188 (4.6)	
Anaphylaxis	150 (4.9)	195 (4.8)	
Itching (isolated)	74 (2.4)	101 (2.5)	
Diarrhea (isolated)	62 (2.0)	85 (2.1)	
Other*	58 (1.9)	80 (2.0)	
Dyspnea or wheezing	50 (1.6)	78 (1.9)	
Intolerance	20 (0.7)	30 (0.7)	
Fever	3 (0.1)	9 (0.2)	
Blisters	4 (0.1)	4 (0.1)	
Concern for SCAR†	0 (0)	2 (0.1)	
No data/missing	336 (10.9)	440 (10.7)	

Data are presented as n (%).
*"Other" includes the following as listed in the chart: seizures, tingling, family history, *Clostridium difficile*, yeast infection, internal bleeding, change in mental status, tinnitus, vaginal itching, muscle pain, shaking, sore gums, insomnia, psoriasis flare, blood poisoning, transient paralysis, headache, cracked tongue, fatigue, delirium, pancreatitis, black tongue, nightmares, lockjaw, and acne.
†SCAR represents severe cutaneous adverse reaction such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug rash with eosinophilia and systemic symptoms.

TABLE III. Outcomes of patients with penicillin allergy labels undergoing surgery before and after the updated surgical guideline implementation

Outcomes	Before guideline release (n = 3085)	After guideline release (n = 4102)	*P* value
No. of antibiotics received, mean ± SD	1.5 ± 0.9	1.5 ± 1.0	.294
Medication administration, n (%)			
Cefazolin	2256 (73.2)	3390 (82.6)	<.001
Vancomycin	273 (8.9)	330 (8.0)	.223
Clindamycin	444 (14.4)	350 (8.5)	<.001
Gentamicin	482 (15.6)	313 (7.6)	<.001
Safety outcomes, n (%)			
Anaphylaxis	0 (0)	1 (0.02)	1.000

TABLE IV. Cefazolin administration before and after guideline implementation

Primary outcome	Before guideline release (n = 3085)	After guideline release (n = 4102)	Crude OR (95% CI)	Adjusted OR (95% CI)*
Cefazolin administration	2256 (73.2)	3390 (82.6)	1.75 (1.56-1.96)	1.87 (1.67-2.10)

OR, Odds ratio.
*Adjusted for patient race, ethnicity, previous cephalosporin use, and surgical setting.

whereas cephalosporin allergy is primarily mediated by the R1 side chain, and so cephalosporins with dissimilar R1 side chains are likely to be safe, even in patients with IgE-mediated penicillin allergies.[27-31] Cefazolin has a completely unique R1 side chain and for this reason it may be the safest of all cephalosporins in patients with penicillin allergy. Safety of cephalosporins in patients with penicillin allergy labels has been demonstrated on a large scale by a very large health system (Kaiser Permanente Southern California), which removed the EMR automatic warning against cephalosporin use in patients with penicillin allergy labels and found an increase in cephalosporin use without adverse safety signals.[29] Furthermore, a recent small study of US patients with allergist-verified penicillin allergies demonstrated that the overwhelming majority tolerated cephalosporins.[27]

We identified only 1 patient with a penicillin allergy label who had a severe allergic reaction in the perioperative window. However, this patient had a concomitant listed cephalosporin allergy, and thus an alternative antibiotic would have been recommended as per our hospital guidelines. The patient had received cefazolin on numerous occasions before this event. We surmise that this patient likely developed sensitization to cefazolin given the previous administrations. Otherwise, there were no episodes of anaphylaxis attributable to antibiotic administration in our cohort. This is not surprising because perioperative anaphylaxis is rare, with reported frequencies of 1 in 1,250 operations to 1 in 20,000 operations.[40] Our low reaction rate to cefazolin is consistent with those in other studies that have demonstrated that surgical patients with penicillin allergy labels have rates of reaction to cefazolin similar to the general population rate.[26,40] Our results suggest on a larger scale that patients with penicillin allergy labels do not seem to have high reaction rates to cefazolin, and cefazolin use can be implemented safely

and effectively in the perioperative population, after excluding patients with severe delayed reactions.

Lastly, it is noteworthy that the preintervention rate of cephalosporin use at our institution was much higher than previously published rates.[14,15,20,37] We believe this high baseline rate of cephalosporin use reflects previous institutional antibiotic stewardship efforts including an initiative by the hospital Antimicrobial Stewardship Team to update patients' allergy histories after tolerating cephalosporins to "penicillin tolerates cephalosporins." Patients in our preintervention group also had a higher rate of a listed "penicillin tolerates cephalosporins" label and a higher rate of previous cephalosporin prescriptions in the EMR, both of which would bias our findings toward the null hypothesis. Despite this and strong institutional practices in general promoting cephalosporin use in patients with penicillin allergy labels, our intervention still showed a meaningful increase in cefazolin use in surgical patients, which lends further strength to the power of this initiative.

Taken as a whole, our results hold great significance for antibiotic stewardship in surgical patients with penicillin allergy labels. SSIs are devastating for patients and the health care system. They are the leading cause of health care–associated infections and associated with increased morbidity, mortality, and cost. Furthermore, using alternative second-line antibiotics increases the risk of adverse outcomes.[4,5,8-17] Our findings demonstrate that a first-line antibiotic (ie, cefazolin) is safe for most patients with penicillin allergy labels. On the basis of these findings, we advocate for similar interventions, when appropriate, for surgical patients with penicillin allergy labels across the country and for consideration of national and international guidance to enhance administration of cefazolin in perioperative patients with penicillin allergy labels.

Limitations

We acknowledge several limitations of this study. This includes its retrospective nature, reliance on EMR data, and single site. It is also possible that mild allergic reactions were missed given reliance on EMR data and the safety database, although mild reactions likely would not have had a clinically significant impact on overall surgical outcomes. Of note, this project included all patients with penicillin allergy labels and, as such, included patients without true penicillin allergies. Future studies looking specifically at the safety of cefazolin in patients with recent severe reactions to penicillin verified by allergist evaluation may be of benefit, although we know that this population is very small and cross-reactivity appears to be low.[27-31]

In addition, some of the data were collected during the coronavirus disease 2019 pandemic, which may have changed prescribing patterns in unpredictable ways. Another limitation is the follow-up period limited to 18 months postintervention. An even longer follow-up period may help determine whether effects of the guideline change were sustained in the long-term, especially because education before guideline release may have also played a role initially in cefazolin use. It is possible that education would need to be repeated on a regular basis to maintain improvements in practice patterns, especially in academic health systems that have a natural turnover in trainees. Lastly, this study was conducted in a large academic tertiary care center where cephalosporin use was already quite high, likely attributable to existing antimicrobial stewardship, infectious disease, and infection prevention efforts. It is likely that a greater effect would be seen at other institutions where cephalosporins are not as commonly prescribed in patients with penicillin allergy labels. Future research evaluating long-term follow-up of SSIs, adverse effects of antibiotics (eg, *Clostridium difficile*), health care utilization, and cost would all assist in understanding the scope of impact of an intervention like ours.

Conclusions

The findings of this retrospective cohort study of surgical patients with penicillin allergy labels suggest that a hospital-wide guideline change (with targeted education and support) can meaningfully enhance cephalosporin use as prophylaxis for surgical patients with penicillin allergy labels. Furthermore, our study demonstrates that cefazolin was safely used in a large cohort of patients with penicillin allergy labels, without severe reactions. Surgical, anesthesiology, allergy, and infectious disease guidelines that support the use of cefazolin in surgical patients with penicillin allergy labels should be an important next step to improve rates of SSIs and would likely have an enormous public health impact.

DISCLOSURE STATEMENT

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Key messages

- **SSIs are common and costly. Penicillin allergy labels often compromise preferred SSI prophylaxis (eg, cefazolin). They are associated with increased rates of SSIs, surgical revisions, and multi–drug-resistant infections.**
- **This retrospective cohort study found that a hospital-wide intervention to increase the use of cefazolin in surgical patients with penicillin allergy labels was effective and safe. This is the largest study of its kind to date.**
- **On the basis of our study, we advocate for national and international multidisciplinary joint guidelines across surgical, anesthesiology, allergy, and infectious disease specialty societies to promote the use of cefazolin in appropriate surgical patients with penicillin allergy labels.**

REFERENCES

1. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. Lancet 2019;393:183-98.
2. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. JAMA 2019;321:188-99.
3. Khan DA, Banerji A, Blumenthal KG, Phillips EJ, Solensky R, White AA, et al. Drug allergy: a 2022 practice parameter update. J Allergy Clin Immunol 2022; 150:1333-93.
4. Zimlichman E, Henderson D, Tamir O, Franz C, Song P, Yamin CK, et al. Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. JAMA Intern Med 2013;173:2039-46.
5. Lewis SS, Moehring RW, Chen LF, Sexton DJ, Anderson DJ. Assessing the relative burden of hospital-acquired infections in a network of community hospitals. Infect Control Hosp Epidemiol 2013;34:1229-30.
6. Graves E. *National Hospital Discharge Survey: annual summary.* 1989. DHHS Pub No. PHS89-1760.
7. Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. N Engl J Med 1992;326:281-6.
8. Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes for patients having surgery. Clin Infect Dis 2006;43:322-30.
9. Voit SB, Todd JK, Nelson B, Nyquist AC. Electronic surveillance system for monitoring surgical antimicrobial prophylaxis. Pediatrics 2005;116:1317-22.
10. Consensus paper on the surveillance of surgical wound infections. The Society for Hospital Epidemiology of America; The Association for Practitioners in Infection Control; The Centers for Disease Control; The Surgical Infection Society. Infect Control Hosp Epidemiol 1992;13:599-605.
11. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Am J Infect Control 1992;20:271-4.
12. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect (Larchmt) 2013;14:73-156.
13. Fields AC, Pradarelli JC, Itani KMF. Preventing surgical site infections: looking beyond the current guidelines. JAMA 2020;323:1087-8.
14. 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; 66:329-36.
15. Robertsson O, Thompson O, W-Dahl A, Sundberg M, Lidgren L, Stefansdottir A. Higher risk of revision for infection using systemic clindamycin prophylaxis than with cloxacillin. Acta Orthop 2017;88:562-7.
16. 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;475:1767-74.
17. Bull AL, Worth LJ, Richards MJ. Impact of vancomycin surgical antibiotic prophylaxis on the development of methicillin-sensitive *Staphylococcus aureus* surgical site infections: report from Australian Surveillance Data (VICNISS). Ann Surg 2012;256:1089-92.
18. Wyles CC, Hevesi M, Osmon DR, Park MA, Habermann EB, Lewallen DG, 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-B:9-15.
19. 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;27:854-60.
20. Lam PW, Tarighi P, Elligsen M, Gunaratne K, Nathens AB, Tarshis J, et al. Self-reported beta-lactam allergy and the risk of surgical site infection: a retrospective cohort study. Infect Control Hosp Epidemiol 2020;41:438-43.
21. Bertram CM, Postelnick M, Mancini CM, Fu X, Zhang Y, Schulz LT, et al. Association of beta-lactam allergy documentation and prophylactic antibiotic use in surgery: a national cross-sectional study of hospitalized patients. Clin Infect Dis 2021; 72:e872-5.
22. Garner BH, Anderson DJ. Surgical site infections: an update. Infect Dis Clin North Am 2016;30:909-29.
23. Kuriakose JP, Vu J, Karmakar M, Nagel J, Uppal S, Hendren S, et al. β-Lactam vs non-β-lactam antibiotics and surgical site infection in colectomy patients. J Am Coll Surg 2019;229:487-96.e2.
24. Khan DA, Solensky R. Drug allergy. J Allergy Clin Immunol 2010;125:126-37.e1.
25. Picard M, Begin P, Bouchard H, Cloutier J, Lacombe-Barrios J, Paradis J, et al. Treatment of patients with a history of penicillin allergy in a large tertiary-care academic hospital. J Allergy Clin Immunol Pract 2013;1:252-7.
26. Sousa-Pinto B, Blumenthal KG, Courtney L, Mancini CM, Jeffres MN. Assessment of the frequency of dual allergy to penicillins and cefazolin: a systematic review and meta-analysis. JAMA Surg 2021;156:e210021.
27. Belmont AP, Su C, Kwah J. Cephalosporins can be safely administered to patients with verified penicillin allergy. J Allergy Clin Immunol Pract 2023;11: 2933-5.e2.
28. 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;8:1989-93.e2.
29. Macy E, McCormick TA, Adams JL, Crawford WW, Nguyen MT, Hoang L, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. JAMA Netw Open 2021;4: e218367.
30. Chiron A, Gaouar H, Autegarden J-E, Amsler E, Barbaud A, Soria A. Allergy to third- and second-generation cephalosporins in confirmed penicillin-allergic patients. J Allergy Clin Immunol Pract 2020;8:2409-11.e3.
31. Picard M, Robitaille G, Karam F, Daigle JM, Bedard F, Biron E, et al. Cross-reactivity to cephalosporins and carbapenems in penicillin-allergic patients: two systematic reviews and meta-analyses. J Allergy Clin Immunol Pract 2019;7:2722-38.e5.
32. Savic LC, Khan DA, Kopac P, Clarke RC, Cooke PJ, Dewachter P, et al. Management of a surgical patient with a label of penicillin allergy: narrative review and consensus recommendations. Br J Anaesth 2019;123:e82-94.
33. Hermanides J, Lemkes BA, Prins JM, Hollmann MW, Terreehorst I. Presumed β-lactam allergy and cross-reactivity in the operating theater: a practical approach. Anesthesiology 2018;129:335-42.
34. Anderson DJ, Podgorny K, Berríos-Torres SI, Bratzler DW, Dellinger EP, Greene L, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014;35:S66-88.
35. Seidelman JL, Mantyh CR, Anderson DJ. Surgical site infection prevention: a review. JAMA 2023;329:244-52.
36. Ban KA, Minei JP, Laronga C, Harbrecht BG, Jensen EH, Fry DE, et al. American College of Surgeons and Surgical Infection Society: surgical site infection guidelines, 2016 update. J Am Coll Surg 2017;224:59-74.
37. 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;8:1316-22.
38. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/ Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391-7.
39. Grant JM, Song WH, Shajari S, Mak R, Meikle AT, Partovi N, et al. Safety of administering cefazolin versus other antibiotics in penicillin-allergic patients for surgical prophylaxis at a major Canadian teaching hospital. Surgery 2021;170:783-9.
40. Volcheck GW, Hepner DL. Identification and management of perioperative anaphylaxis. J Allergy Clin Immunol Pract 2019;7:2134-42.