

Preoperative penicillin allergy testing in patients undergoing cardiac surgery

Jessica H. Plager, MD^{*}; Christian M. Mancini, BS^{†,‡,§}; Xiaoqing Fu, MS^{†,‡,§}; Serguei Melnitchouk, MD, MPH^{||,¶}; Erica S. Shenoy, MD, PhD^{¶,#,**}; Aleena Banerji, MD^{†,¶}; Laura Collier, MS, RN^{||}; Nivedita Chaudhary, BDS, MPH[†]; Sharmitha Yerneni, BS^{††}; Yuqing Zhang, DSc^{†,§,¶}; Kimberly G. Blumenthal, MD, MSc^{†,‡,§,¶}

^{*} Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

[†] Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

[‡] Medical Practice Evaluation Center, Massachusetts General Hospital, Boston, Massachusetts

[§] The Mongan Institute, Massachusetts General Hospital, Boston, Massachusetts

^{||} Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts

[¶] Harvard Medical School, Boston, Massachusetts

[#] Division of Infectious Diseases, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

^{**} Infection Control Unit, Massachusetts General Hospital, Boston, Massachusetts

^{††} Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital, Boston, Massachusetts

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Background: Cefazolin is a first-line prophylactic antibiotic used to prevent surgical site infections (SSIs) in cardiac surgery. Patients with a history of penicillin allergy often receive less effective second-line antibiotics, which is associated with an increased SSI risk.

Objective: To describe the impact of preoperative penicillin allergy evaluation on perioperative cefazolin use in patients undergoing cardiac surgery.

Methods: We performed a retrospective cohort study of patients with a documented penicillin allergy who underwent cardiac surgery at the Massachusetts General Hospital from September 2015 to December 2018. We describe penicillin allergy evaluation assessment and outcomes. We evaluated the association between preoperative penicillin allergy evaluation and first-line perioperative antibiotic use using a multivariable logistic regression model.

Results: Of 3802 cardiac surgical patients, 510 (13%) had a documented penicillin allergy; 165 (33%) were referred to allergy and immunology practitioners. Of 160 patients (31%) who underwent penicillin allergy evaluation (ie, penicillin skin testing and, if results were negative, an amoxicillin challenge), 154 (97%) were found not to have a penicillin allergy. Patients who underwent preoperative penicillin allergy evaluation were more likely to receive the first-line perioperative antibiotic (92% vs 38%, $P < .001$). After adjusting for potential confounders, patients who underwent preoperative penicillin allergy evaluation had higher odds of first-line perioperative antibiotic use (adjusted odds ratio, 26.6; 95% CI, 12.8–55.2).

Conclusion: Integrating penicillin allergy evaluation into routine preoperative care ensured that almost all evaluated patients undergoing cardiac surgery received first-line antibiotic prophylaxis, a critical component of SSI risk reduction. Further efforts are needed to increase access to preoperative allergy evaluation.

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Reprints: Kimberly G. Blumenthal, MD, MSc, Division of Rheumatology, Allergy, and Immunology, The Mongan Institute, Massachusetts General Hospital, 100 Cambridge St, 16th Floor, Boston, MA 02114; E-mail: kblumenthal@mgm.harvard.edu.

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Introduction

Every year in the United States, there are approximately 110,800 cases of surgical site infections (SSIs).¹ These infections not only carry a mortality of 3% but also prolong hospitalization by a mean of 11 days per patient and cost the US health care system more than \$3.3 billion dollars annually.^{1–6} Because approximately half of SSIs are considered preventable, evidence-based strategies to decrease SSIs should be investigated and implemented.⁷

Although the use of perioperative prophylactic antibiotics decreases SSI risk, the choice of antibiotic and the time it is administered are also important factors in determining prophylactic antibiotic efficacy.⁸ Cefazolin, a first-generation cephalosporin, is the preferred first-line perioperative antibiotic in most procedures because of its ability to rapidly reach bactericidal concentrations against common skin flora, including methicillin-sensitive *Staphylococcus aureus* and *Streptococcus* species.^{9–12} This is especially pertinent in patients undergoing cardiac surgery because staphylococci are the primary pathogens in both sternal and vein donor site infections.¹³ However, in the approximately 10% of surgical patients who report a penicillin allergy, cefazolin is routinely avoided because of fear of cross-reactivity, and instead second-line antibiotics, including vancomycin, fluoroquinolones, and clindamycin, are used in most cases.¹⁴ Not only are these antibiotics associated with higher odds of SSIs, they also have been associated with multidrug-resistant organisms, increased rates of *Clostridioides difficile* infection, and other adverse events.^{9,15} This suboptimal choice in perioperative antibiotic occurs despite cefazolin having very low likelihood of cross-reactivity with penicillins (1%–2%) and clinically significant penicillin hypersensitivity being rare in patients reporting penicillin allergy histories (<5%).¹⁶

Previous studies have found that patients with a documented penicillin allergy have a 50% to 65% increased odds of SSI, entirely attributable to the receipt of second-line perioperative antibiotics.^{9,17} The objective of our study was to describe the impact of preoperative penicillin allergy evaluation on first-line perioperative antibiotic use in patients undergoing cardiac surgery.

Methods

Data Source

We performed a retrospective cohort study of patients with reported penicillin allergy who underwent cardiac surgery at a large Boston-based academic medical center from September 2015 to December 2018. During this time, as part of hospital quality improvement initiatives, the cardiac surgery division began to routinely refer patients scheduled for surgery with a penicillin allergy history for testing on a case-by-case basis. We identified patients who underwent coronary artery bypass grafting (CABG), aortic valve replacement (AVR), mitral valve (MV) replacement, MV repair, CABG and AVR, CABG and MV replacement, and other cardiac operations at our academic medical center using the Society of Thoracic Surgeons database, the national clinical registry for cardiac surgery.¹⁸ We subsequently identified patients with a documented penicillin allergy history before their surgery date using allergy module data from the electronic health record (EHR) database. Documented penicillin allergy and the associated penicillin reaction(s) were manually verified by one of us (J.H.P.).

Exposure

The exposure of interest was a preoperative penicillin allergy evaluation, defined as outpatient or inpatient penicillin allergy assessment. All penicillin allergy assessments were performed by an allergy and immunology professional. Although this academic medical center uses a standardized risk stratification tool to evaluate patients with penicillin allergy histories,¹⁹ all patients undergoing cardiac surgery were considered high-risk hosts given that they have compromised cardiac anatomy that requires pending surgical intervention; therefore, their evaluation began with history-appropriate penicillin skin testing.

Penicillin skin testing was performed with epicutaneous (prick-puncture) and intradermal steps with penicilloyl-polylysine (Pre-Pen), penicillin G, histamine (positive control), and saline (negative control). Patients with negative penicillin skin test results received

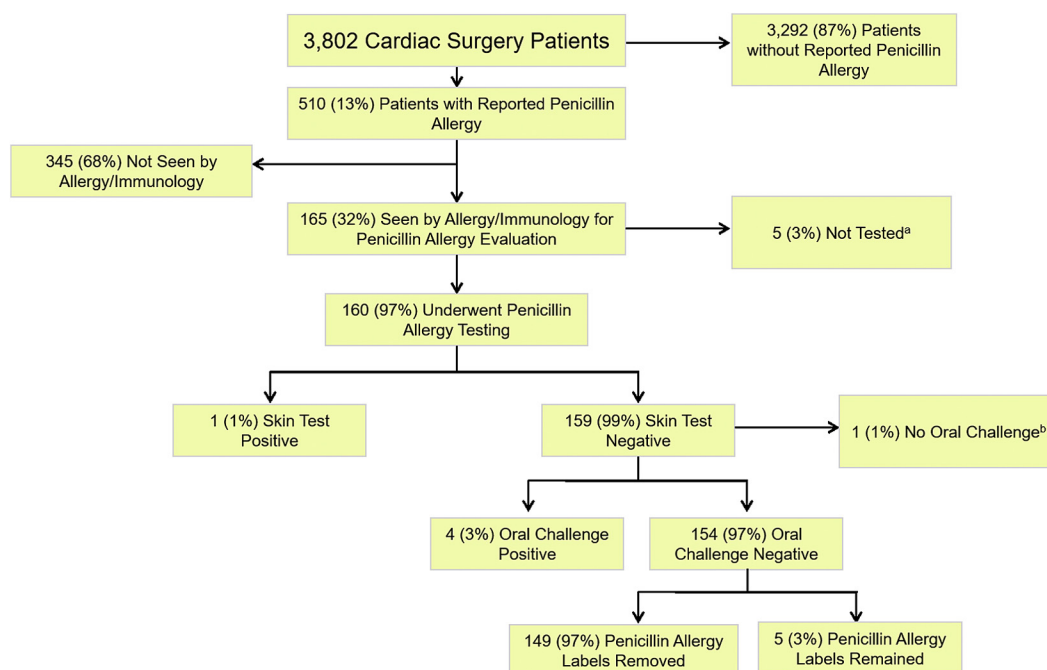


Figure 1. Flow diagram of patients with a documented penicillin allergy undergoing cardiac surgery. ^aAfter assessing the drug allergy history, allergy and immunology practitioners recommended that cefazolin be administered directly in 4 patients, and in 1 patient, testing was not recommended because of a recent penicillin reaction. ^bInpatient with negative penicillin skin test results had drug challenge deferred by the primary care team.

Table 1
Clinical Characteristics of Patients With Penicillin Allergy Undergoing Cardiac Surgery

Characteristic	Penicillin allergy evaluation (n = 165 [32%])	No penicillin allergy evaluation (n = 345 [68%])	P value
Demographics			
Age, mean (SD), y	63 (13)	65 (14)	.13
Sex			.23
Male	82 (50)	191 (55)	
Female	83 (50)	154 (45)	
Race			.79
White	149 (90)	311 (90)	
Black	4 (2)	7 (2)	
Hispanic	2 (1)	6 (2)	
Asian	4 (2)	4 (1)	
Other	6 (4)	17 (5)	
BMI, mean (SD)	29.4 (7)	29.2 (6)	.38
Surgical details			
ASA class			.06
II	7 (4)	7 (2)	
III	105 (64)	196 (57)	
IV	53 (32)	136 (39)	
V	0	6 (2)	
Type of operation			<.001
CABG	28 (17)	139 (40)	
AVR, MV replacement, or MV repair	63 (38)	47 (14)	
CABG and MV replacement or AVR	9 (5)	24 (7)	
Other	65 (39)	135 (39)	
Status of surgery			<.001
Elective	139 (84)	144 (42)	
Urgent	25 (15)	173 (50)	
Emergency	1 (1)	28 (8)	
MRSA colonization	6 (4)	10 (3)	.65
VRE colonization	5 (3)	17 (5)	.48
Allergy history			
Penicillin allergy			
Rash	63 (38)	104 (30)	.07
Urticaria	44 (27)	60 (17)	.015
Gastrointestinal symptoms	5 (3)	54 (16)	<.001
Angioedema or swelling	18 (11)	27 (8)	.25
Anaphylaxis or hypotension	7 (4)	18 (5)	.63
Itching or flushing	11 (7)	10 (3)	.04
Shortness of breath	4 (2)	6 (2)	.60
Acute interstitial nephritis	0 (0)	2 (<1)	.33
Other	8 (5)	35 (10)	.04
Unknown	27 (16)	72 (21)	.23
Cephalosporin allergy	15 (9)	30 (9)	.88

Abbreviations: ASA, American Society of Anesthesiologists; AVR, aortic valve replacement; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CABG, coronary artery bypass graft; MRSA, methicillin-resistant *Staphylococcus aureus*; MV, mitral valve; VRE, vancomycin-resistant *Enterococcus*.

NOTE. Data are presented as number (percentage) of patients unless otherwise indicated.

500 mg of amoxicillin and were monitored for an hour. If no penicillin allergy was identified, the penicillin allergy diagnosis in the EHR was deleted, and the allergist's note indicated that (1) there was no penicillin allergy, and (2) cefazolin could be used preoperatively. The allergist's note was communicated electronically to the referring health care professional when signed.

Outcomes

The primary outcome was first-line perioperative antibiotic prophylaxis; for all cardiac operations considered, this prophylaxis was defined as cefazolin administered from 1 hour before surgery until the end of surgery.¹⁰ Of note, even for patients with methicillin-resistant *Staphylococcus aureus* (MRSA) colonization, cefazolin is recommended (along with vancomycin).¹⁰

We considered hospital length of stay, defined as the total number of hospital days for the patient encounter that included the cardiac surgery, as a secondary outcome. The hospital length of stay was calculated as an integer value by subtracting the admission date from the discharge date. In addition, SSIs were also considered as a secondary outcome and were defined according to the Centers for Disease Control and Prevention's National Healthcare Safety

Network definitions and included all types: superficial, deep, and organ space.¹

Covariates and Confounders

Age, sex, and race were identified from the EHR demographic section. Body mass index (BMI) was calculated from height and weight assessments at the time of surgery. American Society of Anesthesiologists (ASA) class was identified from the preoperative anesthesiology visit and documented according to established guidelines.²⁰ Resistant organism colonization was identified using EHR flags for patients with MRSA and vancomycin-resistant *Enterococcus* (VRE) at the time of surgery, which were maintained by the facility's infection control staff. Documented cephalosporin allergy was identified from the allergy module, considering the allergy history before the surgery date. Surgery type and status were identified from the Society of Thoracic Surgeons database according to standard definitions.¹⁸

Statistical Analysis

Continuous variables were presented as means (SDs) or medians (interquartile ranges), as appropriate. Categorical variables were presented as number (percentage). We compared patient and

Table 2
Univariable Assessment of Preoperative Penicillin Allergy Evaluation on Clinical Outcomes

Outcome	Total patients with penicillin allergy history (N = 510)	Penicillin allergy evaluation (n = 165)	No penicillin allergy evaluation (n = 345)	P value
First-line perioperative antibiotic used, n (%)	284 (56)	152 (92)	132 (38)	<.001
Hospital length of stay, median (IQR), d	9 (6–14)	8 (5–11)	10 (7–16)	<.001
Surgical site infection, n (%)	13 (2.6)	3 (1.8)	10 (2.9)	.47

Abbreviation: IQR, interquartile range.

procedure characteristics in patients with a penicillin allergy history who did and did not undergo preoperative allergy evaluation using the *t* test for continuous variables and the χ^2 test for binary or categorical variables. A multivariable logistic regression model was used to evaluate the association between penicillin allergy evaluation and first-line perioperative antibiotic use. The Wilcoxon rank sum test was used to compare median length of stay between patients with a penicillin allergy who underwent preoperative allergy evaluation and those who did not. We reported odds ratios with 95% CIs for first-line perioperative antibiotic use. All *P* values were 2-sided with *P* < .05 considered statistically significant. Statistical analyses were performed in SAS software, version 9.4 (SAS Institute Inc, Cary, North Carolina).

Results

Cohort Description

A total of 3802 patients underwent cardiac surgery from September 2015 to December 2018 (Fig 1). Of those, 510 (13%) had a documented penicillin allergy, of whom 165 patients (33%) were evaluated by allergy and immunology practitioners before their surgery. Of these 165 patients, 160 (97% of those evaluated and 31% of eligible) underwent penicillin allergy evaluation with skin testing. There were 159 patients (99%) with negative skin test results, 158 of whom received an oral amoxicillin challenge (direct oral challenge in 1 patient was deferred per the primary inpatient team and not completed). A total of 154 patients (97%) with negative skin test results tolerated the oral amoxicillin challenge, with 149 (97%) having their penicillin allergy diagnosis appropriately removed before surgery.

Patients who underwent penicillin allergy evaluation and patients who did not were of similar age, sex, race, BMI and ASA class (Table 1). Among patients who underwent various types of cardiac operations, patients who underwent a CABG were less likely to have preoperative allergy evaluation (17% vs 40%, *P* < .001), whereas patients who underwent valvular operations (AVR, MV replacement, and MV repair) were more likely to have preoperative allergy assessment (38% vs 14%, *P* < .001). Patients undergoing elective operations were more likely to undergo preoperative allergy assessment (84% vs 42%, *P* < .001), whereas those undergoing urgent operations (15% vs 50%, *P* < .001) and emergency operations

(1% vs 8%, *P* < .001) were less likely to have a preoperative allergy evaluation. There was no difference between VRE and MRSA colonization frequency by exposure groups. Patients undergoing cardiac surgery who underwent preoperative allergy assessment and patients who did not had similar penicillin reactions recorded; patients with gastrointestinal symptoms (3% vs 16%, *P* < .001) and other reactions (5% vs 10%, *P* = .04) were less likely to undergo preoperative allergy evaluation, whereas patients with urticaria (26.7% vs 17%, *P* = .02) and itching or flushing (7% vs 3%, *P* = .04) were more likely to have had preoperative allergy evaluation. There were similar frequencies of documented cephalosporin allergy histories between patients who underwent preoperative allergy assessment and patients who did not.

Outcomes

Patients who underwent preoperative penicillin allergy evaluation were more likely to receive the first-line perioperative antibiotic (92% vs 38%, *P* < .001, Table 2). Adjusting for age, sex, race, BMI, ASA class, surgery type, surgery status, MRSA, VRE, penicillin reaction, and cephalosporin allergy history, patients who underwent penicillin allergy evaluation had higher odds of receiving the first-line perioperative antibiotics than those who did not undergo penicillin allergy evaluation (adjusted odds ratio, 26.6; 95% CI, 12.8–55.2; Table 3).

Patients with penicillin allergy evaluation had shorter median (interquartile range) hospital lengths of stay (8 days [5–11 days] vs 10 days [7–16 days], *P* < .001, Fig 2 and Table 2). In addition, SSIs were rare in both groups (1.8% vs 2.9%, *P* = .47, Table 2).

Discussion

In this study, we identified that 13% of patients who underwent cardiac operations had a penicillin allergy history. Patients who underwent preoperative allergy evaluation were approximately 27 times more likely to receive first-line antibiotic prophylaxis with cefazolin. Our study demonstrates the importance and impact of incorporating preoperative penicillin allergy evaluation for patients who require operations for which the perioperative antibiotic of choice is cefazolin or another β -lactam to maximize SSI prevention strategies.

We found that 92% of patients evaluated for penicillin allergy received perioperative cefazolin, whereas just 38% of those not evaluated by allergy and immunology practitioners received cefazolin. Our prior study of more than 9000 operations performed from 2010 to 2014 identified that just 12% of patients with a penicillin allergy history received perioperative cefazolin.⁹ In this study, after controlling for baseline patient and procedure differences between groups, there was a large and significant 27 times increased odds of cefazolin use in the patients who received allergy and immunology assessment. This adjusted odds ratio is notably higher than that found in a recent meta-analysis of 4 studies in which penicillin allergy testing reduced non- β -lactam antibiotic use compared with usual care by an odds ratio of 3.64.¹⁵

Although cefazolin is the first-line antibiotic recommended to prevent SSIs in cardiac surgery, patients with a history of penicillin

Table 3
Multivariable Model of Preoperative Penicillin Allergy Evaluation Impact on Clinical Outcome^a

Outcome	Odds ratio (95% CI)	
	Penicillin allergy evaluation	No penicillin allergy evaluation
First-line perioperative antibiotic used	26.6 (12.8, 55.2)	1.0 [Reference]

Abbreviation: CI, confidence interval.

^aAdjusted for age, sex, race, body mass index, American Society of Anesthesiologists class, surgery type, surgery status, resistant organisms, penicillin reaction, and cephalosporin allergy.

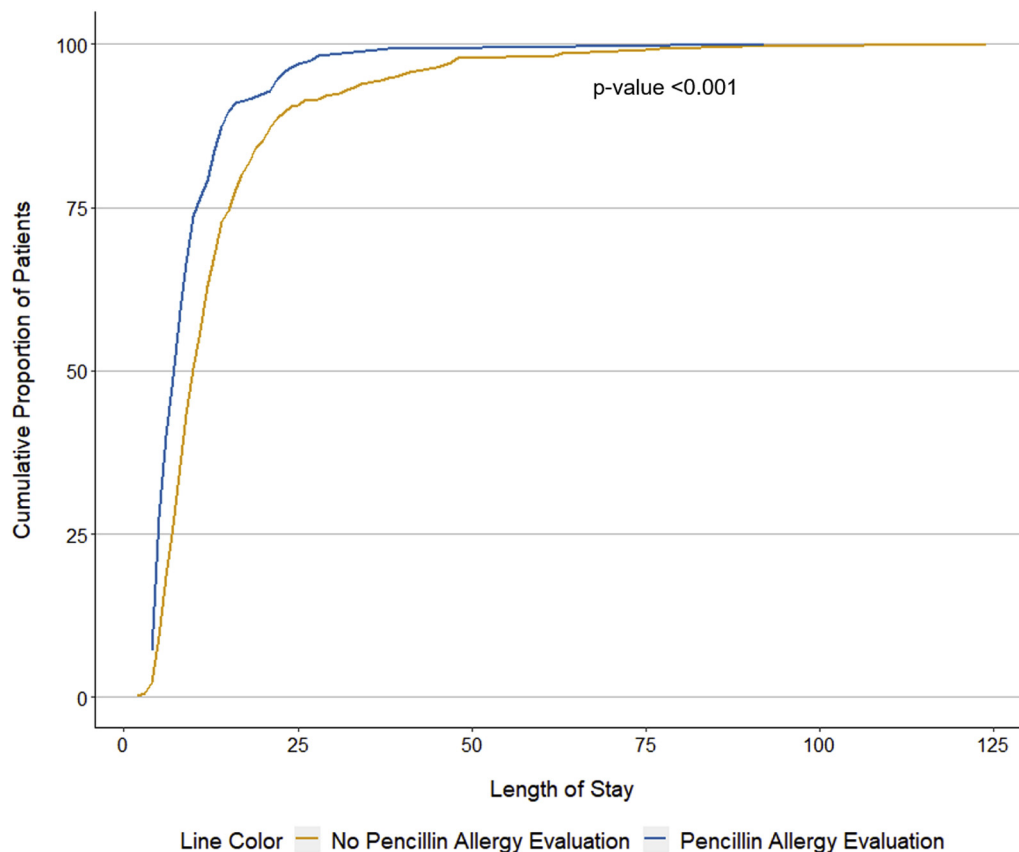


Figure 2. Length of hospital stay for patients with a documented penicillin allergy undergoing cardiac surgery.

allergy are less likely to receive cefazolin because of cross-reactivity concerns, given a shared β -lactam ring.^{9,21}

However, cefazolin has a unique side chain that results in low or potentially even negligible cross-reactivity.²² Few studies specifically address penicillin-cefazolin cross-reactivity; a meta-analysis of 3 observational studies estimated that the absolute risk of cross-reactivity to cefazolin in patients allergic to penicillin was 1.33% (95% CI, 0.19%–8.86%).¹⁶ Although the risk estimate is low, the CI is wide and the risk is not zero. Caution therefore is warranted given that cefazolin is the most commonly identified cause of perioperative allergic reactions in the United States,²³ and perioperative allergic reactions not only cause patient distress and disrupt hospital operations but also may necessitate postponing or rescheduling of the surgery.

Although preoperative allergy and immunology evaluation was tremendously effective in optimizing prophylactic antibiotics in those who were evaluated, only one-third of patients undergoing cardiac surgery with a history of penicillin allergy underwent a preoperative allergy assessment, and there was a notable diminishing frequency in penicillin allergy evaluation in urgent and emergency operations (15% and 1%, respectively). For preoperative penicillin allergy assessment programs to be maximally effective, increased testing access, particularly when patients are hospitalized and operations are not elective, is critical, especially because SSI risk is higher for urgent and emergent procedures.²⁴ Although feasible to implement penicillin skin testing for inpatients generally,²⁵ inpatients awaiting cardiac surgery have a crowded time-limited window during which required preoperative tests, such as dental radiography, vein mapping, and carotid ultrasonography, must be performed.²⁶ As an alternative, one could consider performing a test dose or drug challenge rather than skin testing;

however, the risks and benefits would need to be weighed given the potential consequences of precipitating a true allergic reaction in an unstable patient awaiting cardiac surgery. Improved uptake might be achieved by establishing dedicated drug allergy clinics.²⁷ Improved uptake might also be facilitated through EHR innovations; for example, McDanel et al²⁸ described an EHR alert that triggered allergy consultation when a patient with a documented β -lactam allergy checked into the surgical clinic.

A penicillin allergy label has implications for clinical decision making beyond patients' immediate perioperative antibiotic decision. Indeed, an unverified penicillin allergy diagnosis is associated with increased MRSA, *C difficile* infection, and overall mortality.^{29,30} As such, an upcoming surgery might be considered a good opportunity to address penicillin allergy histories that have never been questioned, and the testing provided (if results are negative and the patient's penicillin allergy label is removed) might improve individual and public health outcomes beyond the perioperative and postoperative period.³¹ In our study, 97% of patients with negative penicillin allergy test results had their penicillin allergy label removed. Although this is higher than that reported in other studies (72%–95%),^{19,32} allergy specialists erroneously left a penicillin allergy label for 6 patients who underwent cardiac surgery. To increase label removal to 100%, the EHR allergy module needs modification and potentially a testing section that can clearly communicate test results and recommendations.

Although we included only patients undergoing cardiac surgery in this study, our results are likely generalizable to the broader surgical population for whom cefazolin, or another β -lactam antibiotic, is the first-line perioperative antibiotic.^{10,21} We studied only 1 method of penicillin allergy evaluation in this study (ie, history-appropriate penicillin skin testing, followed by amoxicillin

challenge if the skin test result was negative). We are therefore unable to speak to the impact of alternative penicillin allergy evaluation models or methods, such as an allergy history tool or a direct amoxicillin challenge. However, a prior study³³ identified that a structured history tool alone increased perioperative β -lactam use in patients with a penicillin allergy from 18% to 57%. In addition, given that this specific population is a high-risk group awaiting cardiac surgery, a direct amoxicillin challenge strategy is not without risk.^{19,34} We captured only allergy and immunology evaluations that occurred within our health care system; however, if patients received a penicillin allergy assessment outside our health care system and were miscategorized in our study, this would have biased our study toward the null hypothesis, thus making our findings more conservative. Finally, although our study was powered to detect the large expected difference in first-line perioperative antibiotic use, we were underpowered to detect differences in hospital length of stay and SSIs. We will reassess these important outcomes as we continue our perioperative penicillin allergy evaluation programs.

In conclusion, SSIs have enormous clinical and economic consequences. Although studies have found that patients with a penicillin allergy have 50% higher odds of SSIs attributable to perioperative antibiotic choice, our study highlights that allergist-driven preoperative penicillin allergy assessment, which consumes only a few hours of patient time and carries only a modest cost,³⁵ can significantly and substantially increase the use of first-line perioperative antibiotics.

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