Infection Control & Hospital Epidemiology (2020), **41**, 438–443
doi:10.1017/ice.2019.374

Original Article

Self-reported beta-lactam allergy and the risk of surgical site infection: A retrospective cohort study

Philip W. Lam MD[1,2], Payam Tarighi MD[3], Marion Elligsen BScPhm[4], Keith Gunaratne MD[1], Avery B. Nathens MD[3], Jordan Tarshis MD[5] and Jerome A. Leis MD[1,2,6]

[1]Department of Medicine, University of Toronto, Toronto, Ontario, Canada, [2]Division of Infectious Diseases, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada, [3]Department of Surgery, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada, [4]Department of Pharmacy, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada, [5]Department of Anesthesia, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada and [6]Centre for Quality Improvement and Patient Safety, University of Toronto, Toronto, Ontario, Canada

Abstract

Objective: To assess whether a self-reported β-lactam allergy is associated with an increased risk of surgical site infection (SSI) across a broad range of procedures and to determine whether this association is mediated by the receipt of an alternate antibiotic to cefazolin.

Design: Retrospective cohort study.

Participants: Surgical procedures sampled by an institutional National Surgical Quality Improvement Program database over an 18-month period (January 2017 to June 2018) from 7 surgical specialties.

Setting: Tertiary-care academic hospital.

Results: Of the 3,589 surgical procedures included in the study, 369 (10.3%) were performed in patients with a reported β-lactam allergy. Those with a reported β-lactam allergy were significantly less likely to receive cefazolin (38.8% vs 95.5%) or metronidazole (20.3% vs 26.1%) and were more likely to receive clindamycin (52.0% vs 0.2%), gentamicin (3.5% vs 0%), or vancomycin (2.2% vs 0.1%) than those without allergy. An SSI occurred in 154 of 3,220 procedures (4.8%) in patients without reported allergy and 27 of 369 (7.3%) with reported allergy. In the multivariable regression model, a reported β-lactam allergy was associated with a statistically significant increase in SSI risk (adjusted odds ratio [aOR], 1.61; 95% confidence interval [CI], 1.04–2.51; $P = .03$). This effect was completely mediated by receipt of an alternate antibiotic to cefazolin (indirect effect aOR, 1.68; 95% CI, 1.17–2.34; $P = .005$).

Conclusions: Self-reported β-lactam allergy was associated with an increased SSI risk mediated through receipt of alternate antibiotic prophylaxis. Safely increasing use of cefazolin prophylaxis in patients with reported β-lactam allergy can potentially lower the risk of SSIs.

(Received 6 October 2019; accepted 14 December 2019; electronically published 23 January 2020)

Beta-lactams comprise a family of antibiotics that share a common β-lactam ring structure; they include penicillins, cephalosporins and carbapenems. In the perioperative setting, cefazolin (a first-generation cephalosporin) is the preferred agent for antimicrobial prophylaxis in most surgical procedures.[1] However, due to misperceptions regarding allergy cross-reactivity, cefazolin is often avoided by prescribers in patients who report a penicillin allergy.[2]

The impact of avoiding the preferred β-lactam antibiotic for the treatment of bacterial infection has been well documented and includes an increased risk of adverse events,[3] infection with an antibiotic-resistant organism,[4] and mortality.[5] To date, only 1 study has identified an association between penicillin allergy and surgical site infection (SSI).[6] However, this cohort was limited to only 5 surgical procedure types and included only patients with reported penicillin allergy.[6] It is also unclear whether the association exists at other institutions where the alternate antibiotic agent used may differ.

We hypothesized that patients with a reported β-lactam allergy have an increased risk of SSIs across a broad range of surgeries and that this risk is mediated by avoidance of cefazolin. The following retrospective cohort study was conducted to assess this association and the potential mediators of this effect.

Methods

A retrospective cohort study of patients undergoing a surgical procedure between January 1, 2017, and June 30, 2018, was conducted using the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database at our acute-care

Author for correspondence: Philip Lam, E-mail: philip.lam@sunnybrook.ca
Cite this article: Lam PW, *et al.* (2020). Self-reported beta-lactam allergy and the risk of surgical site infection: A retrospective cohort study. *Infection Control & Hospital Epidemiology*, 41: 438–443, https://doi.org/10.1017/ice.2019.374

hospital. Sunnybrook Health Sciences Centre (SHSC) is a 627-bed, academic, tertiary-care hospital located in Toronto, Ontario, Canada. Using a systematic 8-day sampling cycle, NSQIP extracts 135 variables relating to preoperative, intraoperative, and postoperative care. Approximately 15,000 surgical procedures are performed at SHSC annually, and nearly 2,500 of these are sampled by NSQIP.

During the study period, the following surgical specialties were sampled for NSQIP: general surgery, vascular surgery, gynecology-oncology, neurosurgery, urology, orthopedic surgery, and plastic surgery. A complete list of the specific procedures and sampling techniques is included in the Supplementary Material (online). Cases that were excluded from NSQIP sampling included brain-death organ donors, cases involving hyperthermic intraperitoneal chemotherapy, trauma cases, transplant cases, any surgical procedure related to an occurrence or complication of a prior procedure, and multiple surgical cases from the same patient within 30 days.[7] Due to a markedly different pathogenesis of postoperative infections in transurethral procedures, these procedures were excluded from the study. This study received approval from our institutional research ethics board.

β-lactam allergy exposure

The exposure of interest was a self-reported β-lactam allergy, defined by any allergy to an antibiotic containing a β-lactam ring molecular structure. To obtain β-lactam allergy data, patients identified from the NSQIP database were cross-referenced with the Stewardship Program Integrating Resource Information Technology (SPIRIT) database, which aggregates microbiology, laboratory, and pharmacy information for patients admitted to the hospital.[8] Since the current literature describing the association between penicillin and SSI is thought to be mediated by receipt of an alternate antibiotic (rather than a direct immune mechanism),[6] any type of patient-perceived allergic reaction was included, regardless of whether it constituted a true drug-hypersensitivity reaction.

Study outcome

The primary outcome was 30-day SSI (superficial incisional, deep incisional, or organ-space infection), as defined by ACS NSQIP,[7] which are based on the National Healthcare Safety Network (NHSN) definitions for SSI.[9] This variable was collected as part of NSQIP surveillance through retrospective chart review. When postoperative follow-up notes were unavailable, the patient was contacted to inquire about SSI occurrence.

Based on the known risk factors associated with reported β-lactam allergy and SSI,[10,11] the following variables were selected a priori for inclusion in the multivariable logistic regression model: age, gender, current smoker, diabetes mellitus, steroid or immunosuppressant use, American Society of Anesthesiologists (ASA) physical status classification, and wound classification. Definitions for diabetes mellitus, smoking status, and steroid or immunosuppressant use were those established by ACS NSQIP.[7]

Data synthesis and analysis

As part of NSQIP chart extraction, patient demographic information, comorbidities, and 30-day SSI outcome data were available for each surgical procedure. A manual review of the anesthetic record was performed for each surgical procedure to extract the type, dose, and time of preoperative antibiotic administration. This review also served to identify additional cases of reported β-lactam allergy, which were not documented electronically or detected by the cross-referencing process.

The association between a reported β-lactam allergy and SSI was evaluated using a multivariable logistic regression (generalized linear model). Because a single patient could have been sampled more than once during the study period, a generalized estimating equation was applied to estimate the model parameters. To avoid model overspecification, the ASA physical status classification covariate was reclassified as a dichotomous variable (<3, ≥ 3).

To understand the causal mechanisms that link a reported β-lactam allergy with SSI, mediation analysis was performed to determine whether the effect was mediated by receipt of an alternate antibiotic to cefazolin. The analysis used a natural effects model, which is an extension of marginal structural models for mean nested counterfactuals.[12] This method allows for direct parameterization of each mediated pathway while producing estimates that correspond to the natural scale of the outcome model (an adjusted odds ratio).[12] The same multivariable logistic regression (generalized linear model) using the same covariates was used as the outcome model for the mediation analysis. To minimize the risk of mediator-outcome confounding, surgical procedures where no preoperative antibiotic was administered was excluded from mediation analysis. All statistical analyses were performed using R version 3.4.3 statistical software (Foundation for Statistical Computing, Vienna, Austria).

Results

Over the 18-month study period, 3,708 surgical procedures were sampled by NSQIP. After excluding transurethral procedures, 3,589 procedures were performed among 3,499 patients. In total, 181 SSIs (5.0%) occurred in the study cohort. Of the 3,589 procedures, 369 (10.3%) occurred among patients who reported a β-lactam allergy.

Patient cohort

Patient demographic, comorbidities, and surgical data were available for all 3,589 procedures (Table 1). Patients with reported β-lactam allergy were older (68.4 vs 65.3 years; $P = .005$) and more likely to be female (67.8% vs 54.6%; $P < .001$) than those without allergy. Patient comorbidities, ASA physical status classification, surgical specialty, wound classification, and duration of surgery were similar between the 2 groups.

Preoperative antibiotic prophylaxis

Preoperative antibiotic use stratified by reported β-lactam allergy is summarized in Table 2. The most commonly prescribed antibiotics were cefazolin (89.6%), metronidazole (25.5%), and clindamycin (5.5%). Overall, 66 cases (1.8%) were balanced across groups where no preoperative antibiotic was given or documented.

Patients with reported β-lactam allergy were significantly less likely to receive cefazolin (38.8% vs 95.5%; $P < .001$) and more likely to receive clindamycin (52.0% vs 0.2%; $P < .001$) or vancomycin (2.2% vs 0.1%; $P < .001$) than those without allergy. Of the 226 patients with reported β-lactam allergy who did not receive cefazolin, the most common alternate antibiotics administered were clindamycin (85.0%), metronidazole (33.2%), and vancomycin (3.5%).

Of the 3,523 procedures where a preoperative antibiotic was administered, the antibiotic dose and administration time were documented in 3,496 (99.2%) and 3,485 (98.9%) of cases

https://doi.org/10.1017/ice.2019.374 Published online by Cambridge University Press

Table 1. Baseline Characteristics

Patient Factors	All (n = 3,589), No. (%)	No Reported β-Lactam Allergy (n = 3,220), No. (%)	Reported β-Lactam Allergy (n = 369), No. (%)
Age, median y (IQR)[a]	65.5 (54.4–74.5)	65.3 (54.3–74.1)	68.4 (57.2–76.6)
Gender, % male[a]	1,582 (44.1)	1,463 (45.4)	119 (32.2)
Comorbidities[b]			
Diabetes mellitus	559 (15.6)	499 (15.5)	60 (16.3)
Current smoker	507 (14.1)	453 (14.1)	54 (14.6)
History of Severe COPD	115 (3.2)	101 (3.1)	14 (3.8)
Ascites	42 (1.2)	40 (1.2)	2 (0.5)
Congestive Heart Failure	11 (0.3)	8 (0.2)	3 (0.8)
Hypertension	1,673 (46.6)	1,489 (46.2)	184 (49.9)
Dialysis	20 (0.6)	15 (0.5)	5 (1.4)
Disseminated Cancer	342 (9.5)	302 (9.4)	40 (10.8)
Steroid/Immunosuppressant Therapy	115 (3.2)	98 (3.0)	17 (4.6)
ASA classification (%)			
1	71 (2.0)	66 (2.0)	5 (1.4)
2	519 (14.5)	470 (14.6)	49 (13.3)
3	1,728 (48.1)	1,549 (48.1)	179 (48.5)
4	1,243 (34.6)	1,111 (34.5)	132 (35.8)
5	28 (0.8)	24 (0.7)	4 (1.1)
Operative factors			
Elective surgery	2,656 (74.0)	2,385 (74.1)	271 (73.4)
Surgical specialty			
General surgery	1,184 (33.0)	1,063 (33.0)	121 (32.8)
Gynecology	511 (14.2)	467 (14.5)	44 (11.9)
Neurosurgery	638 (17.8)	571 (17.7)	67 (18.2)
Orthopedic surgery	321 (8.9)	280 (8.7)	41 (11.1)
Plastic surgery	119 (3.3)	107 (3.3)	12 (3.3)
Urology	338 (9.4)	304 (9.4)	34 (9.2)
Vascular surgery	478 (133)	428 (13.3)	50 (13.6)
Wound classification			
Clean	1,683 (46.9)	1,504 (46.7)	179 (48.5)
Clean-contaminated	1,769 (49.3)	1,596 (49.6)	173 (46.9)
Contaminated	59 (1.6)	53 (1.6)	6 (1.6)
Dirty/Infected	78 (2.2)	67 (2.1)	11 (3.0)
Duration median min (IQR)	120.0 (84.0–191.0)	120.0 (84.0–190.0)	125.0 (87.0–209.0)
Length of stay, median d (IQR)[a]	3.0 (1.0–6.0)	3 (1.0–6.0)	4.0 (1.0–7.0)

Note. ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.
[a]Statistical significance ($P < .05$) on univariable analysis
[b]Definitions for comorbidities are based on *American College of Surgeons National Surgical Quality Improvement Program Operations Manual*.[7]

respectively. When cefazolin was used, selection of a 2-gram dose (97.2% vs 98.0%), and administration within 60 minutes before surgical incision (95.1% vs 94.2%) were similar between patients with and without a reported β-lactam allergy. When clindamycin was used, selection of a 600-mg dose (92.7% vs 100%) and administration within 60 minutes before surgical incision (90.1% vs 80.0%) were similar between patients with and without a reported β-lactam allergy.

β-lactam allergy characteristics

The 3 most commonly reported antibiotics were penicillin (85.4%), amoxicillin (4.0%) and cephalexin (3.7%); 7 patients (1.9%)

https://doi.org/10.1017/ice.2019.374 Published online by Cambridge University Press

Table 2. Preoperative Antibiotic Characteristics

Preoperative Antibiotic[a]	All (n = 3,589), No. (%)	No Reported β-Lactam Allergy (n = 3,220), No. (%)	Reported β-Lactam Allergy (n = 369), No. (%)
Cefazolin[b]	3,217 (89.6)	3,074 (95.5)	143 (38.8)
Ampicillin	10 (0.3)	10 (0.3)	0 (0.0)
Ceftriaxone	35 (1.0)	35 (1.1)	0 (0.0)
Ertapenem	1 (0.0)	0 (0.0)	1 (0.3)
Meropenem	2 (0.1)	1 (0.0)	1 (0.3)
Piperacillin-Tazobactam	50 (1.4)	47 (1.5)	3 (0.8)
Ciprofloxacin[b]	20 (0.6)	7 (0.2	13 (3.5)
Clindamycin[b]	197 (5.5)	5 (0.2)	192 (52.0)
Metronidazole[b]	915 (25.5)	840 (26.1)	75 (20.3)
Gentamicin[b]	13 (0.4)	0 (0.0)	13 (3.5)
Vancomycin[b]	12 (0.3)	4 (0.1)	8 (2.2)
None or not documented	66 (1.8)	62 (1.9)	4 (1.1)

[a]Cumulative antibiotic use exceeds cohort size as some patients received multiple antibiotics. For example, when metronidazole was used, it was coadministered with another antibiotic agent in 912 of 915 of cases (99.7%).
[b]Statistical significance ($P < .05$) on univariable analysis.

Table 3. Allergic Reactions to β-Lactam Antibiotics

Reaction	No. (%)[a]
Rash	139 (36.8)
Unknown to patient	94 (24.9)
Hives	50 (13.2)
Swelling or angioedema	39 (10.3)
Anaphylaxis	37 (9.8)
Dyspnea	6 (1.6)
Nausea, vomiting, or diarrhea	5 (1.3)
Pruritis	2 (0.5)
Seizure	2 (0.5)
Syncope	2 (0.5)
Dizziness	2 (0.5)
Cough	2 (0.5)
Acute interstitial nephritis	1 (0.3)
Headache	1 (0.3)
Blistering rash	1 (0.3)

[a]Cumulative total exceeds reported β-lactam allergy cohort size as some patients reported >1 type of reaction.

reported an allergy to 2 different β-lactam antibiotics. The 5 most commonly reported reactions were rash (36.8%), unknown to patient (24.9%), urticaria (13.2%), swelling or angioedema (10.3%), and anaphylaxis (9.8%) (Table 3).

Surgical site infection

In the univariable analysis, 30-day SSI occurred in 154 of 3,220 patients (4.8%) without reported β-lactam allergy and 27 of 369 patients (7.3%) with reported allergy. In the multivariable logistic regression model, smoking status, ASA physical status classification ≥3, and a wound classified as contaminated or dirty were significantly associated with an increased risk of SSI (Table 4). After accounting for these variables and other covariates, a reported β-lactam allergy was associated with a statistically significant increase in 30-day SSI risk (adjusted odds ratio [aOR], 1.61; 95% confidence interval [CI], 1.04–2.51; $P = .03$).

Table 4. Estimated Effects of Reported β-Lactam Allergy and Covariates on 30-Day Surgical Site Infection in the Multivariable Logistic Regression Model

Variable	aOR	95% CI
Age (per 10-y increase)	1.09	0.96–1.24
Gender (male)	1.32	0.97–1.81
Current smoker	1.55	1.03–2.32
Steroid/Immunosuppressant therapy	1.17	0.48–2.84
Diabetes mellitus	1.19	0.80–1.76
ASA classification ≥ 3	2.95	1.47–5.88
Wound classification (compared to clean)		
Clean–contaminated	5.78	3.80–8.81
Contaminated	1.39	0.19–9.97
Dirty/Infected	12.00	5.78–24.90
Reported β-lactam allergy	1.61	1.04–2.51

Note. aOR, adjusted odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists.

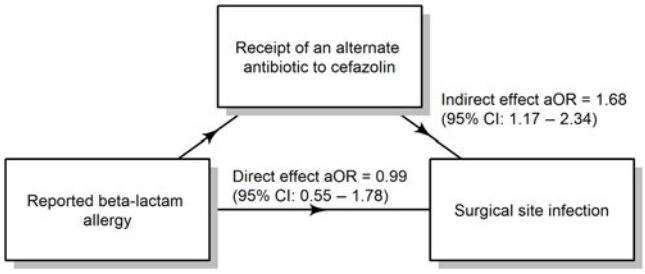

Fig. 1. Natural effects model estimates for receipt of an alternate antibiotic to cefazolin as the mediator. Although not shown in this figure, the following covariates were included in the natural effects model: age, gender, current smoker, diabetes mellitus, steroid/immunosuppressant use, American Society of Anesthesiologists physical status classification, and wound classification. Note. aOR, adjusted odds ratio; CI, confidence interval.

Mediation analysis

Following the exclusion of 66 procedures in which no preoperative antibiotics were administered, the effect of a reported β-lactam allergy on SSI was completely mediated by the receipt of an alternate antibiotic to cefazolin (indirect effect aOR, 1.68; 95% CI, 1.17–2.34; $P = .005$) (Fig. 1). When receipt of an alternate antibiotic to cefazolin was accounted for, the direct effect of a reported β-lactam allergy on the risk of SSI was not significant (direct effect aOR, 0.99; 95% CI, 0.55–1.78; $P = .96$).

Discussion

Using a NSQIP-sampled, surgically diverse cohort spanning an 18-month period, a reported β-lactam allergy was associated with an increased risk of SSI. This effect was completely mediated by receipt of an alternate antibiotic to cefazolin. Our findings add

https://doi.org/10.1017/ice.2019.374 Published online by Cambridge University Press

to the mounting evidence demonstrating the harms of avoiding preferred β-lactam antibiotic due to reported allergy. In the perioperative setting, it is imperative that surgeons and anesthesiologists carefully assess patient-reported β-lactam allergies because emerging literature indicates that most patients can tolerate cefazolin.[2]

One prior study assessed the relationship between reported penicillin allergy and the risk of SSI. Blumenthal et al[6] conducted a 5-year retrospective review of 9,004 surgical procedures and reported an adjusted odds ratio of 1.51 for developing a SSI in those with a reported penicillin allergy.[6] In their study, this association was completely mediated by receipt of a non–β-lactam antibiotic but was limited to 5 surgical procedures: coronary artery bypass, colon surgery, hip arthroplasty, hysterectomy, and knee arthroplasty.[6]

Our study strengthens the external validity of the association between reported allergy and SSI. In contrast to Blumenthal et al,[6] our study included 7 surgical specialties encompassing >20 different surgical procedures. Our findings suggest that improving the use of β-lactam prophylaxis among these patients could have a widespread impact on SSIs across surgical specialties. In addition, our study included patients who reported any β-lactam allergy rather than penicillin allergy alone. We hypothesize that the impact of a reported penicillin allergy is not drug specific but, rather, applies to all β-lactam antibiotics, since both result in the avoidance of cefazolin. Patient and physician misconceptions surrounding penicillin allergy and cross reactivity with cephalosporins are prevalent,[13] and interventions are urgently needed for clinicians to accurately assess a reported allergy and to determine whether they can safely receive cefazolin. Interventions such as β-lactam skin testing[14–19] and oral provocation challenges[18–20] have been used in the perioperative setting but have been limited in their scalability and sustainability due to resource requirements. It is now recognized that the cephalosporin cefazolin is non–cross-reactive with penicillin due to a structurally dissimilar side chain,[2] which suggests that the decision to administer cefazolin preoperatively could theoretically be achieved with a clinical history alone. Further studies are needed to determine whether such a strategy is sustainable and whether an increase in cefazolin use in the patients with reported β-lactam allergy results in a decline in SSIs.

Our study provides additional insight into preoperative antibiotic use and the mediators of SSI. In the study by Blumenthal et al, 34.7% of patients who reported penicillin allergy received vancomycin as an alternate antibiotic.[6] Preoperative administration of vancomycin is fraught with challenges, including the need for more stringent weight-based dosing, and unique to vancomycin, initiation of the antibiotic infusion ideally 60–120 minutes before surgical incision.[1] The challenges with antibiotic administration are reflected in the study by Blumenthal et al, in which 97.5% of patients did not receive vancomycin in the recommended time frame.[6] Given that one-third of their patients with reported β-lactam allergy received this antibiotic, it was unclear whether inferior antibiotic efficacy or inappropriate timing of alternate antibiotics was the main contributor to the increased SSI risk. In contrast, vancomycin utilization as preoperative prophylaxis at our institution is significantly lower; only 2.2% of patients with reported β-lactam allergy received this antibiotic. By demonstrating a similar mediation effect, combined with negligible use of vancomycin, our study strongly suggests that inferior efficacy of alternate antibiotic agents is the main explanation for the increased SSI risk observed among patients with reported β-lactam allergy.

Our study has several limitations. First, the prevalence of reported β-lactam allergy (10.3%) is probably underestimated in our study because accessibility to inpatient and outpatient allergy testing services at our institution likely resulted in de-labeling of a significant proportion of patients.[21] Similarly, cefazolin use in patients with reported β-lactam allergy were 3× higher (38.8%) compared to the results reported by Blumenthal et al (12.2%).[6] Therefore, the impact of a reported allergy on SSI may be more pronounced at other institutions where preoperative cefazolin utilization is lower. Second, we used the NSQIP-defined 30-day SSI outcome variable; thus, our study may not have included late-onset SSIs. Whether these would be affected by reported β-lactam allergy in the same way is unknown. Third, we cannot exclude the possibility of residual confounding variables, which could not be included due to limitations in sample size and outcome frequency. Finally, the findings of this study cannot be applied to transurethral procedures because they were excluded from this study.

A self-reported β-lactam allergy is associated with increased odds of SSI across a broad range of surgical specialties, which appears to be mediated by the use of alternate agents to intravenous cefazolin. Given recent data suggesting that cefazolin is a non–cross-reactive cephalosporin, there is great opportunity to improve SSI rates through interventions that promote the safe use of cefazolin prophylaxis among patients reporting a β-lactam allergy.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2019.374

Acknowledgments.

Financial support. No financial support was provided relevant to this article.

Conflicts of interest. All authors report no conflicts of interest relevant to this article.

References

1. Bratzler DW, Dellinger EP, Olsen KM, *et al.* Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm* 2013;70:195–283.
2. Zagursky RJ, Pichichero ME. Cross-reactivity in β-lactam allergy. *J Allergy Clin Immunol Pract* 2018;6:72–81.
3. MacFadden DR, LaDelfa A, Leen J, *et al.* Impact of reported beta-lactam allergy on inpatient outcomes: a multicenter prospective cohort study. *Clin Infect Dis* 2016;63:904–910.
4. Macy E, Contreras R. Healthcare use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. *J Allergy Clin Immunol* 2014;133:790–796.
5. Huang KG, Cluzet V, Hamilton K, Fadugba O. The impact of reported beta-lactam allergy in hospitalized patients with hematologic malignancies requiring antibiotics. *Clin Infect Dis* 2018;67:27–33.
6. Blumenthal KG, Ryan EE, Li Y, Lee H, Kuhlen JL, Shenoy ES. The impact of a reported penicillin allergy on surgical site infection risk. *Clin Infect Dis* 2018;66:329–336.
7. American College of Surgeons User Guide for the 2017. ACS NSQIP Participant use data file (PUF). American College of Surgeons website. https://www.facs.org/-/media/files/quality-programs/nsqip/nsqip_puf_userguide_2017.ashx?la=en. Published 2018. Accessed July 22, 2019.
8. Elligsen M. Prospective audit and feedback of antimicrobial stewardship in critical care: program implementation, experience, and challenges. *Can J Hosp Pharm* 2012;65:31–36.
9. Protocol for definition of surgical site infection. Centers for Disease Control (CDC)/National Healthcare Safety Network (NHSN). https://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf. Published 2019. Accessed June 24, 2019.
10. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. *Lancet* 2019;393:183–198.
11. Owens CD, Stoessel K. Surgical site infections: epidemiology, microbiology and prevention. *J Hosp Infect* 2008;70:3–10.

12. Steen J, Loeys T, Moerkerke B, Vansteelandt S. medflex: an R package for flexible mediation analysis using natural effect models. *J Stat Softw* 2017;76:1–46.
13. Vorobeichik L, Weber EA, Tarshis J. Misconceptions surrounding penicillin allergy: implications for anesthesiologists. *Anesth Analg* 2018;127:642–649.
14. Li JT, Markus PJ, Osmon DR, Estes L, Gosselin VA, Hanssen AD. Reduction of vancomycin use in orthopedic patients with a history of antibiotic allergy. *Mayo Clin Proc* 2000;75:902–906.
15. Park M, Marku P, Matesic D, Li JT. Safety and effectiveness of a preoperative allergy clinic in decreasing vancomycin use in patients with a history of penicillin allergy. *Ann Allergy Asthma Immunol* 2006;97:681–687.
16. Frigas E, Mark MA, Narr BJ. Preoperative evaluation of patients with history of allergy to penicillin: comparison of 2 models of practice. *Mayo Clin Proc* 2008; 83: 651–62.
17. Cook DJ, Barbara DW, Singh KE, Dearani JA. Penicillin skin testing in cardiac surgery. *J Thorac Cardiovasc Surg* 2014;147:1931–1935.
18. McDanel DL, Azar AE, Dowden AM. Screening for beta-lactam allergy in joint arthroplasty patients to improve surgical prophylaxis practice. *J Arthroplasty* 2017;32:S101–S108.
19. Moussa Y, Shuster J, Matte G, *et al.* Delabeling of β-lactam allergy reduces intraoperative time and optimizes choice in antibiotic prophylaxis. *Surgery* (in press). 2018. pii: S0039-6060(18)30127-2. doi: 10.1016/j.surg.2018.03.004.
20. Savic L, Gurr L, Kaura V, *et al.* Penicillin allergy de-labelling ahead of elective surgery: feasibility and barriers. *Br J Anaesth* 2019;123:e110–e116.
21. Leis JA, Palmay L, Ho G, *et al.* Point-of-care β-lactam allergy skin testing by antimicrobial stewardship programs: a pragmatic multicenter prospective evaluation. *Clin Infect Dis* 2017;65:1059–1065.

https://doi.org/10.1017/ice.2019.374 Published online by Cambridge University Press