

Impact of an Antibiotic Side-Chain–Based Cross-reactivity Chart Combined With Enhanced Allergy Assessment Processes for Surgical Prophylaxis Antimicrobials in Patients With β -Lactam Allergies

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Background. β -Lactam antibiotics are first-line therapy for perioperative prophylaxis; however, patient-reported allergies often lead to increased prescribing of alternative antibiotics that may increase the incidence of surgical site infections. The R-group side chain of the β -lactam ring is responsible for allergic cross-reactivity and experts recommend the use of β -lactams that are structurally dissimilar.

Methods. An internally developed, antibiotic side-chain–based cross-reactivity chart was developed and implemented alongside enhanced allergy assessment processes. This single-center, quasi-experimental study analyzed antibiotic prescribing in all adult patients with a documented β -lactam allergy undergoing an inpatient surgical procedure between quartile (Q) 1 (2012)–Q3 (2014) (historical group) and Q3 (2016)–Q3 (2018) (intervention group). Propensity-weighted scoring analyses compared categorical and continuous outcomes. Interrupted time-series analysis further analyzed key outcomes.

Results. A total of 1119 and 1089 patients were included in the historical and intervention cohorts, respectively. There was a significant difference in patients receiving a β -lactam alternative antibiotic between cohorts (84.9% vs 15.1%; $P < .001$). There was a decrease in 30-day readmissions in the intervention cohort (7.9% vs 6.3%; $P = .035$); however, there was no difference in the incidence of SSIs in patients readmitted (14.8% vs 13%; $P = .765$). No significant differences were observed in allergic reactions (0.5% vs 0.3%; $P = .323$), surgical site infections, in-hospital and 30-day mortality, healthcare facility–onset *Clostridioides difficile* infection, acute kidney injury, or hospital costs.

Conclusions. Implementation of an antibiotic cross-reactivity chart combined with enhanced allergy assessment processes significantly improved the prescribing of β -lactam antibiotics for surgical prophylaxis.

Keywords. allergy; beta-lactam side chain; antimicrobial stewardship; surgical prophylaxis.

Approximately 7–16% and 1–2% of people in the United States report a penicillin and cephalosporin allergy, respectively [1–3]. True immunoglobulin E (IgE)–mediated penicillin allergies are rare, and 85% to 99% of patients reporting penicillin allergies are able to tolerate penicillins [4–6]. Furthermore, the cross-reactivity rates with cephalosporins are approximately 1% in patients reporting a penicillin allergy and 2.6% in those with a confirmed penicillin allergy [7]. The myths surrounding the incidence and reporting of β -lactam allergies, as well as the

cross-reactivity between β -lactam antibiotics, leads to prescribing of alternative antibiotics that may possess less efficacy and/or an increased risk of adverse events [8].

β -lactam antibiotics, usually cefazolin, are recommended as first-line agents for surgical prophylaxis in a majority of procedures due to desirable duration of action, spectrum of activity, reasonable safety, and low cost [9]. In addition, recent evidence supports efficacy benefits with β -lactams for surgical prophylaxis. Blumenthal and colleagues [10] outlined that patients reporting a penicillin allergy were 8–16 times more likely to receive an alternative to a β -lactam antibiotic. This subsequent use was associated with a 50% increased odds of developing a surgical site infection (SSI).

Several strategies are suggested for the management of patients with reported β -lactam allergies. Among these include careful assessment including allergy de-labeling and penicillin skin testing (PST), when appropriate [11–13]. Penicillin skin

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testing, particularly in the preoperative population, provides its own challenges. The time required to perform PST, infrastructure and resources needed, clinician knowledge, and legal authority of the performing parties must all be considered [8, 14]. Furthermore, skin testing is unreliable in predicting allergic response to cephalosporins in penicillin-allergic patients and, while effectively used in a variety of populations, may not always lead to a reduction in the prescribing of preoperative alternative antibiotics [7,15]. Given the therapeutic and safety advantages of β -lactam antibiotics, alternative strategies and the ability to implement them on a large scale are critically needed.

The R-group side chain of the β -lactam ring is primarily responsible for allergic cross-reactivity [7, 16–21]. Experts recommend strategies for comprehensive allergy assessment to incorporate administration of β -lactam antibiotics that are structurally dissimilar to that of the allergic agent [16–24]. Cefazolin is unique in that it does not share a similar R-group side chain with other β -lactams, thereby allowing for its expanded use, including in patients with other cephalosporin allergies [8, 17, 23].

We describe the impact of an internally developed, antibiotic side-chain-based, cross-reactivity chart in combination with enhanced antimicrobial stewardship and institutional processes for allergy assessment to optimize surgical prophylaxis in patients with documented β -lactam allergies.

METHODS

Cross-reactivity Chart Development and Implementation

In 2013, a multidisciplinary team at our 537-bed community-teaching hospital, including representatives from the institution's antimicrobial stewardship program, pharmacy, infectious diseases, surgery, and allergy and immunology departments, collaborated on the development of an antibiotic cross-reactivity chart and enhanced allergy-assessment processes to guide antibiotic prescribing in patients with documented β -lactam allergies. The team utilized existing literature recommendations to develop antibiotic side-chain-based recommendations for each of our institution's formulary β -lactam antibiotics (Supplementary Figure 1) [16–21]. The chart assesses similarities between β -lactam side chains and incorporates literature reports to recommend strategies for prescribers and pharmacist assessment at the time of order verification. While the chart continues to evolve, guidance indicating that cefazolin does not share side chains with other β -lactams has not changed. Accompanying guidance documents include recommendations for taking a patient allergy history.

The institutional approach for the management of patients with β -lactam allergies was approved by health-system oversight committees in 2014 and implemented alongside updated surgical prophylaxis guidance [9]. A subsequent educational campaign targeting prescribers and pharmacy staff reviewed

changes in procedure-specific recommendations and institutional allergy guidance. Following an initial assessment of adoption, processes evolved to standardize active engagement by pharmacy personnel. Emphasized tasks included historical profile review to assess for previous tolerance of β -lactam agents and defined communication procedures to ensure allergy clarification and discuss antibiotic selection prior to surgical procedures. These processes were formalized in early 2016.

Study Design

This was a single-center, retrospective, quasi-experimental study conducted between January 2012–September 2014 (historical cohort) and July 2016–September 2018 (intervention cohort). A washout period (October 2014–June 2016) allowed for implementation, evolution, and adoption of the cross-reactivity chart and institutional processes. The primary objective of this study was to determine the impact of the initiative on perioperative antibiotic prescribing for surgical prophylaxis. Secondary objectives were to compare the incidence of allergic reactions attributed to the administration of antibiotic prophylaxis, SSIs, acute kidney injury (AKI), incidence of healthcare facility-onset *Clostridioides difficile* infection (HO-CDI), length of stay, 30-day all-cause and infection-related readmission rates, all-cause mortality at discharge and 30 days postdischarge, and total hospital costs between the historical and intervention cohorts. Compliance with international recommendations for antibiotic timing, selection, and duration was also assessed between cohorts [9, 25]. A subset analysis was performed on patients who achieved a composite outcome defined as meeting all components of recommended antibiotic timing and selection.

All adult surgical patients aged 18 and over receiving procedures reported to the Centers for Disease Control and Prevention's National Healthcare Safety Network (NHSN) during the study time period were included if they received an antibiotic for surgical prophylaxis, had an inpatient stay associated with their procedure, had a reported β -lactam allergy documented prior to the procedure, and had not received antibiotics during the inpatient stay prior to surgery. The NHSN procedural categories were further grouped into specialty area (orthopedic, neurology/spine/head, thoracic/cardiac/vascular, gastrointestinal, gynecology, breast, and nephrology/prostate). Primary and secondary outcomes were also analyzed by procedure grouping between cohorts (Supplementary Table 1) [26]. Only the first surgical procedure was included if a patient had multiple procedures per hospital encounter. Our Institutional Review Board approved the study.

Supplemental patient and procedural data were obtained from NHSN reporting, our hospital's administrative database, and manual chart review. American Society of Anesthesiologists (ASA) Classification of Physical Status score, wound class, procedure duration, emergency, and trauma variables were obtained from institutional NHSN reporting. Medical

comorbidities were identified by a combination of Agency for Healthcare Research and Quality Clinical Classifications Software scoring and *International Classification of Diseases, 9th and 10th Revision, Clinical Modification* (ICD-9-CM and ICD-10-CM) coding [27]. Patient-reported allergies were grouped for statistical analysis according to previously reported categorizations: Gell and Coombs type I IgE-mediated hypersensitivity reactions (HSRs) (anaphylaxis, angioedema, wheezing, bronchospasm, hypotension, hives/urticaria); type II–IV HSRs (serum sickness, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute interstitial nephritis, drug rash eosinophilia, hemolytic anemia, and drug fever); mild reactions (eg, itching, morbilliform/maculopapular eruption without hives); unknown allergies (eg, when a β -lactam was documented as an allergy, but the reaction experienced was not recorded or reported); and drug intolerance (eg, nausea, vomiting) [21, 22, 28].

Outcomes

Alternative antibiotic therapy was defined as any prophylactic regimen not incorporating a β -lactam antibiotic. SSIs and HO-CDI following surgical procedures were identified according to NSHN definitions as determined and reported by trained infection preventionists [26, 29]. The only change in diagnostic testing for CDI during the study time period was a change in multistep testing in November 2012 from glutamine dehydrogenase plus enzyme immunoassay then cytotoxicity assay for discrepant results, to the use of polymerase chain reaction confirmation for discrepant results. Acute kidney injury was defined as a postoperative increase in serum creatinine of 0.3 mg/dL within 24–48 hours postoperatively in patients not receiving hemodialysis [30]. Intravenous vancomycin or aminoglycosides with or without β -lactam therapy were classified as nephrotoxic agents [31].

The presence of an allergic reaction to surgical prophylaxis was determined by a query of previously reported ICD-9/10-CM coding (Supplementary Table 2) [32–34]. This was supplemented by manual chart review in patients who received diphenhydramine; who received a combination of 2 or more of epinephrine, albuterol, or corticosteroids within 48 hours of surgery; who specifically received antibiotics listed as a direct allergy (eg, cefazolin prescribed with any documented cefazolin or nonspecific cephalosporin allergy); who received a β -lactam and had an unknown penicillin reaction or any documented type I–IV HSR; and those with a new antibiotic allergy added to their profile within 6 months following their surgical procedure [35]. Board-certified allergy and immunology physicians analyzed all potential reactions and determined whether the attributable cause was likely the surgical prophylaxis antibiotic based on timing of medication administration and likelihood of reactions from antibiotics and concomitant medications.

The correct antibiotic timing (ie, initiated within 1 hour prior to surgical incision (2 if receiving vancomycin or fluoroquinolone), antibiotic selection (ie, any choice consistent with current guidelines), and duration (ie, prophylactic antibiotics discontinued within 24 hours after surgery end time [48 hours for cardiac surgery]) were defined according to international recommendations [9, 25]. Hospital cost data included all inpatient costs and were unavailable for patients admitted after May 2018 due to changes in our institutional data warehouse. These patients were excluded from cost analyses.

Statistical Analysis

To determine the overall effect of the intervention, primary and secondary outcomes were assessed using a *t* test for continuous variables and the chi-square test or Fisher's exact test for discrete variables. Demographic variables and clinical characteristics were used to determine propensity scores, defined as the probability of being in either intervention group. Propensity score analysis was used to minimize overfitting the outcomes and to improve inference about the average treatment effects on the outcome. The propensity scores were calculated using Gradient Boosting Machine regression with the intervention cohort as the outcome and the baseline characteristics as covariates. The propensity scores were converted to weights (inverse probability of treatment weights), and the weights were used to adjust the sample to account for pretreatment confounders. The outcomes were then compared using weighted versions of the chi-square test or *t* test. If not all baseline variables were balanced after weighting, propensity score-weighted logistic regression models were used to further adjust for the unbalanced variables when examining the outcomes.

Interrupted time series (ITS) analysis was used to assess the extent to which implementation was associated with changes in the primary outcome and SSIs, and to distinguish a program effect from a secular trend. Segmented least-squares regression models were fit to the quarterly series for each outcome, with parameters for intercept, preintervention trend, and changes in level and trend in the intervention group, assuming linearity of the trend lines within each segment. Durbin-Watson tests were used to determine autocorrelation before fitting each model. If there was evidence of autocorrelation within the series, an first order autoregressive correlation structure was specified when fitting the model. Statistical analysis was performed using R Version 3.6.0 (R Foundation). All *P* values $\leq .05$ were considered statistically significant.

RESULTS

A total of 2208 adult surgical patients met the inclusion criteria, 1119 and 1089 in the historical and intervention cohorts, respectively. The historical and intervention cohorts were mostly similar when comparing demographic and clinical characteristics

Table 1. Demographic and Clinical Characteristics by Cohort

Variable ^a and Label	Historical (n = 1119)	Intervention (n = 1089)	P value	PS-Weighted P Value
Categorical variables				
Gender			.353	.528
Female	793 (70.9)	751 (69)		
Male	326 (29.1)	338 (31)		
Race			.415	.494
White	1035 (92.5)	996 (91.5)		
Other	84 (7.5)	93 (8.5)		
Procedure type			.001	.917
Orthopedic	428 (38.3)	384 (35.3)		
Neurology/spine/head	225 (20.1)	191 (17.5)		
Thoracic/cardiac/vascular	185 (16.5)	166 (15.2)		
Gastrointestinal	148 (13.2)	192 (17.6)		
Gynecology	82 (7.3)	119 (10.9)		
Breast	32 (2.9)	17 (1.6)		
Nephrology/prostate	19 (1.7)	20 (1.8)		
ASA class description			.523	.617
1—A normal healthy patient	17 (1.5)	24 (2.2)		
2—A patient with mild systemic disease	434 (38.8)	419 (38.5)		
3—A patient with severe systemic disease	535 (47.8)	522 (47.9)		
4—A patient with severe systemic disease that is a constant threat to life	133 (11.9)	122 (11.2)		
5—A moribund patient who is not expected to survive without the operation	0 (0)	2 (0.2)		
Wound class			<.001	.127
Clean	862 (77)	743 (68.2)		
Clean—contaminated	214 (19.1)	299 (27.5)		
Contaminated	17 (1.5)	36 (3.3)		
Dirty	26 (2.3)	11 (1)		
Emergency procedure	33 (2.9)	49 (4.5)	.07	.265
Trauma	0 (0)	8 (0.7)	.003	.005
Surgery within previous 180 days	174 (15.6)	199 (18.3)	.099	.428
Diabetes mellitus	251 (22.4)	254 (23.3)	.653	.817
Congestive heart failure	278 (224.8)	283 (26)	.57	.989
Malignancy	282 (25.2)	347 (31.9)	<.001	.293
Asthma	105 (9.4)	120 (11)	.23	.454
COPD	102 (9.1)	118 (10.8)	.201	.623
Cystic fibrosis	0 (0)	0 (0)		
Chronic renal impairment	145 (13)	142 (13)	>.999	.921
Hemodialysis	12 (1.1)	13 (1.2)	.946	.842
Proton pump inhibitor use in previous 10 days	83 (7.4)	85 (7.8)	.792	.995
Postoperative normothermia (>96.8°F)	938 (83.8)	928 (85.2)	.398	.699
Allergy type				
Drug intolerance	86 (7.7)	106 (9.7)	.103	.442
Mild reaction allergy	357 (31.9)	328 (30.1)	.39	.943
Type I IgE-mediated HSRs	539 (48.2)	496 (45.6)	.233	.417
Unknown allergy	130 (11.6)	148 (13.6)	.183	.625
Type II–IV HSRs	7 (0.6)	11 (1)	.443	.456
Continuous variables^b				
Age, y	64.2 (14)	63.7 (14)	.445	.836
BMI, kg/m ²	30.8 (7.4)	30.7 (7.1)	.862	.983
Charlson score	0.12 (0.5)	0.24 (0.7)	<.001	.041
Internal mortality index [36]	4.2 (0.8)	4.1 (0.9)	.031	.608
Duration of surgery, minutes	31.3 (17.4)	30.4 (17.3)	.218	.831

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HSR, hypersensitivity reaction; IgE, immunoglobulin E; PS, propensity score; SD, standard deviation.

^aData are no. (%) unless otherwise specified.

^bData are summarized as means (SD) unless otherwise specified.

Table 2. Outcomes by Cohort (Unadjusted and Propensity Score-Weighted)

Variable ^a	Historical (n = 1119)	Intervention (n = 1089)	P value	PS-Weighted P Value
Categorical outcomes				
Received β -lactam alternative	950 (84.9)	164 (15.1)	<.001	<.001
SSI	24 (2.1)	15 (1.4)	.227	.093
Any allergic reaction to surgical prophylaxis	6 (0.5)	3 (0.3)	.507	.323
Readmission	88 (7.9)	69 (6.3)	.189	.035
Readmission with SSI ^b	13 (14.8)	9 (13)	.938	.765
In-hospital mortality	4 (0.4)	8 (0.7)	.36	.269
30-Day mortality	12 (1.1)	14 (1.3)	.789	.957
Infection-related 30-day mortality	2 (0.2)	4 (0.4)	.446	.665
Nephrotoxic prophylaxis	414 (37)	96 (8.8)	<.001	<.001
Acute kidney injury	37 (3.3)	32 (3)	.712	.622
Nephrotoxic prophylaxis ^c	16 (43.2)	5 (15.6)	.026	.011
HO-CDI	2 (0.2)	1 (0.1)	>.999	.557
Continuous outcomes^d				
Inpatient costs, \$	16 063 (12 725)	16 922 (12 873)	.125	.367
LOS, days	3.6 (3.4)	3.6 (3.6)	.977	.317

Abbreviations: HO-CDI, healthcare facility-onset *Clostridioides difficile* infection; LOS, length of stay; PS, propensity score; SD, standard deviation; SSI, surgical site infection.

^aData are no. (%) unless otherwise specified.

^bAnalysis performed on the subset of patients who were positive for readmission (historical cohort, n = 88; intervention cohort, n = 69).

^cAnalysis performed on the subset of patients with acute kidney injury (historical cohort, n = 37; intervention cohort, n = 32).

^dData are summarized as means (SD) unless otherwise specified.

(Table 1). After adjusting using propensity score weights, only trauma surgeries and Charlson score differed significantly between cohorts.

There was a significant difference in the number of patients who received an alternative antibiotic between the historical and intervention cohorts (84.9% vs 15.1%; $P < .001$) (Table 2). This was an 82.3% decrease in the percentage of patients receiving β -lactam alternative prophylaxis; however, ITS analysis showed there was not a significant decrease in the trend by calendar quarter ($P = .336$) (Figure 1).

There was no change in the rate of allergic reactions between cohorts (0.5% vs 0.3%; $P = .323$). When combining cohorts, a total of 1114 received alternative prophylaxis and 1094

received β -lactam prophylaxis. Cefazolin was used 98.2% of the time when β -lactams were administered. We identified 9 patients (0.4%) with an antibiotic-related allergic reaction in combined cohorts, 6 after receiving alternative therapy and 3 following β -lactam prophylaxis (0.5% vs 0.3%; $P = .507$). The 3 patients who reacted to β -lactam prophylaxis, 1 in the historical cohort and 2 in the intervention cohort, were prescribed cefazolin with documented pre-existing severe ampicillin allergies. Of these patients, 1 experienced a type I IgE-mediated HSR and 2 experienced mild-type reactions, 1 of whom also had a concomitant mild cephalixin allergy and their reaction was thought to be due to either cefazolin or opioid therapy.

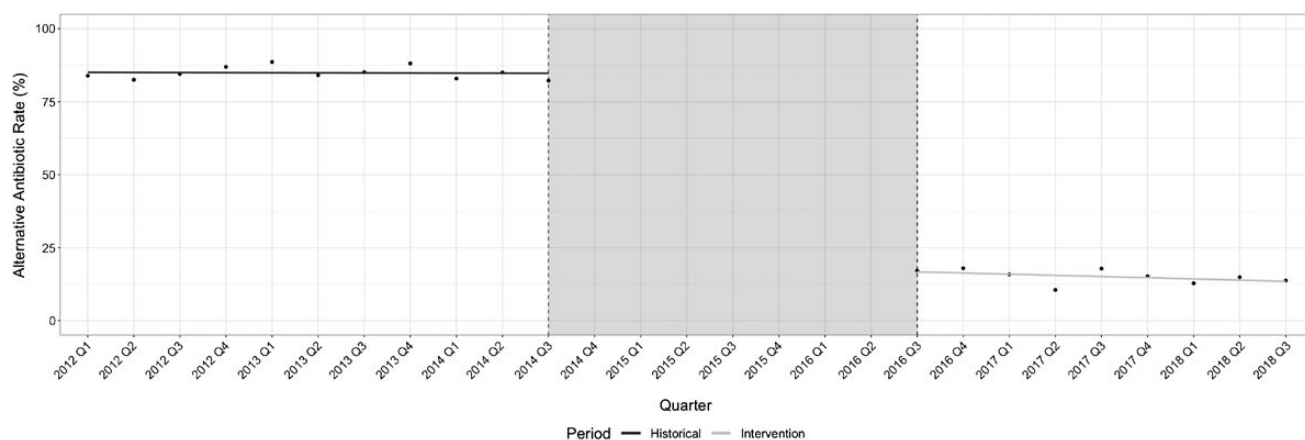


Figure 1. Interrupted time-series analysis of alternative antibiotic use for surgical prophylaxis. The percentage of alternative antibiotic use is shown by calendar quarter.

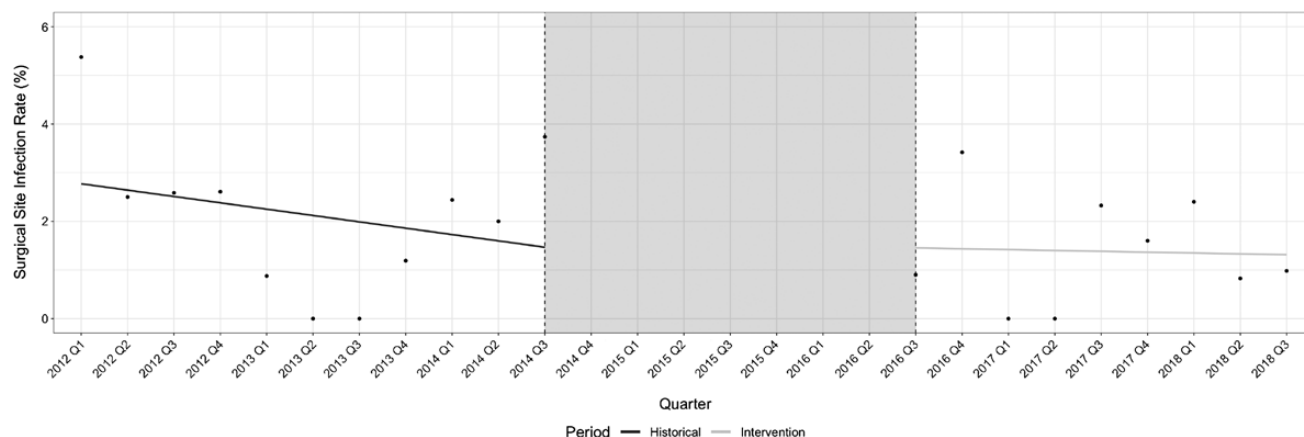


Figure 2. Surgical site infection rates by calendar quarter. The percentage of patients who developed surgical site infection by calendar quarter is shown for each study cohort.

There was a significant decrease in 30-day readmissions in the intervention cohort (7.9% vs 6.3%; $P = .035$); however, there was no difference in the incidence of SSIs in patients who were readmitted (14.8% vs 13%; $P = .765$). There were significant increases in the patients who received recommended preoperative antibiotic timing (93.7% vs 95.9%; $P = .003$), antibiotic selection (92.6% vs 96.2%; $P < .001$), and duration of antibiotic prophylaxis between cohorts (98.3% vs 99.2%; $P = .05$).

There was no difference in SSIs between cohorts after propensity score weighting (2.1% vs 1.4%; $P = .093$; ITS, $P = .637$) (Figure 2). There were no significant differences observed in any additional secondary outcomes including in-hospital and 30-day mortality, HO-CDI, and hospital costs. The use of nephrotoxic agents significantly decreased (37% vs 8.8%; $P < .001$); however, there was no difference in the incidence of AKI (3.3% vs 3%; $P = .557$). Significance was not changed for any outcome after fitting propensity score-weighted logistic regression models for each outcome with trauma surgery and Charlson score as covariates. This confirmed the unbalanced clinical variables after propensity score weighting did not influence results.

The use of β -lactam therapy significantly improved in all patient allergy types (Table 3) and across all procedure groupings (Table 4). When analyzed by individual surgical group, the incidence of SSIs significantly decreased in gastrointestinal surgeries (5.4% vs 1.6%; $P = .041$) but was unchanged in the subset of patients who received recommended preoperative timing and antibiotic selection (4.8% vs 1.3%; $P = .15$). Antibiotic timing significantly improved in orthopedic and neurology/spine/head procedures while antibiotic selection improved in gastrointestinal and gynecology procedures.

When bundled into a composite outcome variable, patients with the combined composite of recommended preoperative timing and antibiotic selection significantly increased from the

historical to the intervention cohort (88.1% vs 94%; $P < .001$). Additionally, the use of alternative antibiotic(s) significantly decreased in this composite subset (83.5% vs 12%; $P < .001$) (Supplementary Table 3). No other differences in outcomes were noted in this composite subset.

DISCUSSION

We describe outcomes associated with the comprehensive implementation of a β -lactam cross-reactivity chart in combination with enhanced allergy assessment processes to guide surgical prophylaxis in patients with a documented β -lactam allergy. Development and implementation significantly improved prescribing of β -lactam therapy. Prescribers increasingly administered β -lactam-based regimens in patients with both minor and more severe documented allergies. Only 2 patients in our intervention group (0.2%) and 3 patients in our combined cohorts (0.3%) developed an allergic reaction following β -lactam administration. Whether the 3 patients in our study who developed a reaction had a true cross-reactivity allergy or had an additional undocumented cefazolin allergy is unknown. This low reaction rate is similar to previous published reports. For example, Goodman and colleagues [23] reported a 0.3% reaction rate to cephalosporins in 300 penicillin-allergic patients undergoing orthopedic procedures. A recent study by Kuruvilla and colleagues [37] reported 1 of 551 (0.2%) documented penicillin allergic patients receiving a cephalosporin developed a rash with no immediate reactions requiring epinephrine. Results of our study further contribute to this body of literature and support increased administration of cefazolin in patients without documented β -lactam type II-IV HSRs, cefazolin, or nonspecific cephalosporin allergies.

Our results also demonstrate the impact of a multidisciplinary team-based approach to improving care in the perioperative setting. The additional, significant improvements

Table 3. Antibiotic Selection by Allergy Severity Type

Variable ^a and Label	Historical (n = 1119)	Intervention (n = 1089)	P value	PS- Weighted P Value
Drug intolerance, n	86	106	<.001	<.001
Alternative	52 (60.5)	12 (11.3)		
β-lactam	34 (39.5)	94 (88.7)		
Mild reaction allergy, n	357	328	<.001	<.001
Alternative	285 (79.8)	28 (8.5)		
β-lactam	72 (20.2)	300 (91.5)		
Type I IgE-mediated HSRs, n	539	496	<.001	<.001
Alternative	497 (92.2)	99 (20)		
β-lactam	42 (7.8)	397 (80)		
Unknown allergy, ^b n	130	148	<.001	<.001
Alternative	109 (83.9)	22 (14.9)		
β-lactam	21 (16.2)	126 (85.1)		
Type II–IV HSRs (combined), n	7	11	.004	<.001
Alternative	7 (100)	3 (27.3)		
β-lactam	0 (0)	8 (72.7)		
Type II HSRs, n	1	1	>.999	.079
Alternative	1 (100)	0 (0)		
β-Lactam	0 (0)	1 (100)		
Type III HSRs, n	0	2		
Alternative	0 (0)	1 (50)		
β-Lactam	0 (0)	1 (50)		
Type IV HSRs, n	6	8	.01	.001
Alternative	6 (100)	2 (25)		
β-Lactam	0 (0)	6 (75)		

Abbreviations: HSR, hypersensitivity reaction; IgE, immunoglobulin E; PS, propensity score.

^aData are no. (%) unless otherwise specified.

made across the spectrums of perioperative antibiotic management are noteworthy and generalizable. Enhanced allergy assessment processes and improved preoperative oversight, education, and communication among multidisciplinary team members may have led to improvements in preoperative antibiotic timing, selection, and duration. The increased utilization of β-lactam therapy may have alleviated confusion with respect to selection and/or timing of alternative agents with longer infusion times (eg, vancomycin). Accordingly, this change in prescribing may have mitigated delays to surgical incision and/or incorrect antibiotic administration times.

Limitations of our study include the single-center and retrospective nature of the analysis. The study was powered for historical and intervention cohort comparisons for β-lactam use and SSIs; therefore, comparisons of allergic reactions and additional analyses may be underpowered. The use of validated ICD-9/10-CM coding to identify patients experiencing allergic reactions to surgical prophylaxis is difficult in large-population datasets [32, 33]. The sensitivity of allergy-associated coding varies and is limited by a variety of factors, including provider and billing staff documentation, as well as recognition and attribution of antibiotic-induced reactions. We attempted to account for this by using a validated allergy-coding query

supplemented by a multicriteria chart review. We acknowledge all allergic reactions may not have been identified if not coded or documented properly.

Outside of our allergic reaction analysis, this study was not a direct comparison of β-lactam versus alternative therapy. Each cohort contained mixed populations and several results highlight the challenges of attributing outcomes to choice of antibiotic in such a diverse patient population. The significant decrease in readmissions in our intervention cohort was no longer significant when limited to patients readmitted with SSIs, or when antibiotic timing and selection were consistent with recommendations. Similarly, outside of gastrointestinal surgeries, where antibiotic selection also significantly improved, there was no difference in SSIs between time periods. These results suggest changes in outcomes may have been driven by factors including increased β-lactam selection [38]. While we attempted to account for many of these variables, significant changes in outcomes, or lack thereof, are likely multifactorial.

Initiatives to improve structurally dissimilar β-lactam prescribing may have implications beyond the surgical population. Our institutional approach for antibiotic use in patients with antibiotic allergies was intended for all patients, not solely for perioperative antibiotic use. While further real-world

Table 4. Outcomes by Cohort and Procedure Type (Unadjusted and Propensity Score-Weighted)

Outcome ^a and Procedure Type	Historical (n = 1119)	Intervention (n = 1089)	P value	PS-Weighted P Value
Received β -lactam alternative				
Orthopedic	384 (89.7)	25 (6.5)	<.001	<.001
Neurology/spine/head	219 (97.3)	32 (16.8)	<.001	<.001
Thoracic/cardiac/vascular	158 (85.4)	30 (18.1)	<.001	<.001
Gastrointestinal	111 (75)	38 (19.8)	<.001	<.001
Gynecology	41 (50)	32 (26.9)	.001	.005
Breast	28 (87.5)	5 (29.4)	<.001	<.001
Nephrology/prostate	9 (47.4)	2 (10)	.025	.008
SSI				
Orthopedic	3 (0.7)	1 (0.26)	.626	.272
Neurology/spine/head	4 (1.8)	3 (1.6)	>.999	.801
Thoracic/cardiac/vascular	4 (2.2)	7 (4.2)	.426	.467
Gastrointestinal	8 (5.4)	3 (1.6)	.063	.041
Gynecology	3 (3.7)	0 (0)	.066	.082
Breast	2 (6.3)	1 (5.9)	>.999	.894
Nephrology/prostate	0 (0)	0 (0)		
Recommended preoperative timing [9, 25]				
Orthopedic	418 (97.7)	383 (99.7)	.024	.011
Neurology/spine/head	207 (92)	187 (97.9)	.014	.002
Thoracic/cardiac/vascular	175 (94.6)	158 (95.2)	.995	.689
Gastrointestinal	126 (85.1)	168 (87.5)	.637	.416
Gynecology	72 (87.8)	111 (93.3)	.278	.395
Breast	32 (100)	17 (100)		
Nephrology/prostate	18 (94.7)	20 (100)	.487	.316
Recommended antibiotic selection [9, 25]				
Orthopedic	427 (99.8)	384 (100)	>.999	.317
Neurology/spine/head	222 (98.7)	189 (99)	>.999	.945
Thoracic/cardiac/vascular	183 (98.9)	166 (100)	.501	.157
Gastrointestinal	94 (63.5)	161 (83.9)	<.001	<.001
Gynecology	63 (76.8)	111 (93.3)	.002	.008
Breast	30 (93.8)	17 (100)	.537	.161
Nephrology/prostate	17 (89.5)	20 (100)	.231	.147
Recommended duration [9, 25]				
Orthopedic	420 (98.1)	382 (99.5)	.112	.088
Neurology/spine/head	218 (96.9)	188 (98.4)	.354	.228
Thoracic/cardiac/vascular	184 (99.5)	165 (99.4)	>.999	.985
Gastrointestinal	145 (98)	189 (98.4)	>.999	.653
Gynecology	82 (100)	119 (100)		
Breast	32 (100)	17 (100)		
Nephrology/prostate	19 (100)	20 (100)		
Composite outcome (recommended timing and selection)				
Orthopedic	417 (97.4)	383 (99.7)	.015	.007
Neurology/spine/head	205 (91.1)	185 (96.9)	.027	.007
Thoracic/cardiac/vascular	173 (93.5)	158 (95.2)	.658	.431
Gastrointestinal	84 (56.8)	152 (79.2)	<.001	<.001
Gynecology	60 (73.2)	109 (91.6)	<.001	.004
Breast	30 (93.8)	17 (100)	.537	.161
Nephrology/prostate	17 (89.5)	20 (100)	.231	.147

Abbreviations: PS, propensity score; SSI, surgical site infection.

^aData are no. (%) unless otherwise specified.

examples are urgently needed, there are opportunities for this strategy to promote β -lactam therapy in other infectious diseases. Use of this strategy may present a resource-friendly

and easily implemented alternative approach that can work in combination with the suite of existing allergy management strategies.

CONCLUSIONS

Implementation of an antibiotic side-chain-based cross-reactivity chart combined with enhanced allergy assessment processes significantly improved the prescribing of β -lactam antibiotic therapy for surgical prophylaxis.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Supplement Table 1. Surgical Procedures and Groupings

National Healthcare Safety Network Procedure Groupings [26]

Orthopedic

- open reduction of fracture (FX)
- hip prosthesis (HPRO)
- knee prosthesis (KPRO)

Neurology/Spine/Head

- craniotomy (CRAN)
- spinal fusion (FUSN)
- laminectomy (LAM)
- neck surgery (NECK)
- thyroid and/or parathyroid surgery (THYR)
- ventricular shunt (VHSN)

Thoracic/Cardiac/Vascular

- abdominal aortic aneurysm repair (AAA)
- limb amputation (AMP)
- shunt for dialysis (AVSD)
- cardiac surgery (CARD)
- coronary artery bypass graft with both chest and donor site incisions (CBGB)
- coronary artery bypass graft with chest incision only (CBGC)
- carotid endarterectomy (CEA)
- pacemaker surgery (PACE)
- peripheral vascular bypass surgery (PVBY)
- thoracic surgery (THOR)

Gastrointestinal

- appendix surgery (APPY)
- bile duct, liver or pancreatic surgery (BILI)
- gallbladder surgery (CHOL)
- colon surgery (COLO)
- gastric surgery (GAST)
- herniorrhaphy (HER)
- rectal surgery (REC)
- small bowel surgery (SB)
- spleen surgery (SPLE)
- exploratory laparotomy (XLAP)

Gynecology

- hysterectomy (HYST)
- ovarian surgery (OVRY)

vaginal hysterectomy (VHYS)

Breast

breast surgery (BRST)

Nephrology/Prostate

kidney surgery (NEPH)

prostate surgery (PRST)

Supplement Table 2. ICD-9/10-CM Coding Queries

Code Description [32-34]	ICD-9-CM	ICD-10-CM	E code
Eosinophilia	288.3	D72.1	
Dermatitis due to substances taken internally	693.0		
Generalized skin eruption due to drugs and medicaments taken internally		L27.0	
Localized skin eruption due to drugs and medicaments taken internally		L27.1	
Other pruritus	698.8	L29.8	
Unspecified pruritic disorder/Pruritus, unspecified	698.9	L29.9	
Allergic urticaria	708.0	L50.0	
Idiopathic urticaria	708.1	L50.1	
Dermatographic urticaria	708.3	L50.3	
Vibratory urticaria	708.4	L50.4	
Cholinergic urticaria		L50.5	
Other specified urticaria/Contact urticaria	708.8	L50.6	
Urticaria, unspecified	708.9	L50.9	
Rash and other nonspecific skin eruption	782.1	R21	
Poisoning by antibiotics	960	T36	
Poisoning by, adverse effect of and underdosing of other systemic anti-infectives and antiparasitics		T37	
Anaphylactic reaction due to food		T78.0	
Other adverse food reactions, not elsewhere classified		T78.1	
Other anaphylactic reaction	995.0	T78.2	
Angioneurotic edema, not elsewhere classified/Angioneurotic edema, initial encounter	995.1	T78.3	
Unspecified adverse effect of drug medicinal and biological substance not elsewhere classified/Adverse effect of unspecified drugs, medicaments and biological substances, initial encounter	995.2	T50.9	
Allergy, unspecified, not elsewhere classified/Allergy, unspecified, initial encounter	995.3	T78.4	
Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered		T88.6	
Unspecified adverse effect of drug or medicament		T88.7	
Allergy status to drugs, medicaments and biological substances		Z88	
Antibiotics causing adverse effects in therapeutic use			E930

Supplement Table 3. Composite Outcomes by Cohort – Appropriate Antibiotic Timing and Selection

Variable ^a	Historical (N=986)	Intervention (N=1024)	<i>P</i> value	PS weighted <i>P</i> value
Categorical Outcomes				
Received Beta-lactam Alternative	823 (83.5)	123 (12)	< 0.001	< 0.001
SSI	18 (1.8)	14 (1.4)	0.521	0.273
Any Allergic Reaction to Surgical Prophylaxis	5 (0.5)	3 (0.3)	0.499	0.398
Readmission	68 (6.9)	62 (6.1)	0.499	0.111
Readmission with SSI ^b	9 (13.2)	8 (12.9)	> 0.999	0.942
In-hospital Mortality	4 (0.4)	7 (0.7)	0.588	0.601
30-day Mortality	12 (1.2)	12 (1.2)	> 0.999	0.589
Infection Related 30-day Mortality	2 (0.2)	3 (0.3)	> 0.999	0.954
Nephrotoxic Prophylaxis	392 (39.8)	77 (7.5)	< 0.001	< 0.001
Acute kidney injury	33 (3.4)	30 (3)	0.681	0.686
Nephrotoxic prophylaxis ^c	15 (45.5)	4 (13.3)	0.012	0.007
HO-CDI	2 (0.2)	1 (0.1)	0.618	0.554
Continuous Outcomes ^d				
Inpatient Costs (\$)	16186 (12528)	17057 (13042)	0.138	0.265
LOS (days)	3.5 (3.3)	3.6 (3.6)	0.872	0.387

Abbreviations: PS, propensity score; SSI, surgical site infection; HO-CDI, healthcare facility-onset *Clostridioides difficile* infection; LOS, length of stay

^aData are no. (%) unless otherwise specified.

^bAnalysis performed on the subset of patients who were positive for readmission (Historical Cohort N = 68, Intervention Cohort N = 62).

^cAnalysis performed on the subset of patients with acute kidney injury (Historical N = 33, Intervention N = 30).

^dData are summarized with mean (standard deviation) unless otherwise specified

Supplement Figure 1. Beta-lactam Cross-Reactivity Chart

	Antibiotic Allergy																			
	"Penicillin "	"Cephalosporin "	Amoxicillin/Amox/clav	Ampicillin/Amp/sulb	Aztreonam	Cefaclor	Cefazolin	Cefepime	Cefotaxime	Cefoxitin	Cefdinir	Ceftaroline	Ceftriaxone	Cefuroxime	Cephalexin	Ceftazidime/avibactam	Ceftolozane/tazobactam	Nafcillin	Penicillin G	Piperacillin/tazobactam
Antibiotic Ordered	Amoxicillin/Amox/clav [16-21]	N	CP a, b	Nb	Yb	Na, b	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Nb	Yb	Yb	CPb	Nb	CPb
	Ampicillin/Amp/sulb [16-21]	N	CP a, b	Nb	Yb	Na, b	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Nb	Yb	Yb	CPb	Nb	CPb
	Aztreonam [17, 19, 21]	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Nb	CPb	Yb	Yb	Yb
	Cefaclor [16-21]	N	N	Na, b	Na, b	Yb	Yb	Ya, b	Yb	Yb	Yb	Yb	UA a	UA a	Na, b	Yb	Yb	Yb	UA b	CPb
	Cefazolin [16-21]	Ya, b	N	Yb	Yb	Yb	Yb	Yb	Yb	Ya, b	Yb	Yb	Ya, b	Ya, b	Yb	Yb	Yb	Yb	Yb	Yb
	Cefepime [16-19, 21]	Ya, b	N	Yb	Yb	Ya, b	Yb	Yb	Nb	Yb	UA b	UA b	Na, b	Na, b	Yb	CPb	CPb	Yb	Yb	Yb
	Cefotaxime [16-21]	Ya, b	N	Yb	Yb	Yb	Yb	Nb	Yb	UA b	UA b	UA b	Na, b	Na, b	Ya, b	Na, b	CPb	Yb	Yb	Yb
	Cefoxitin [16-21]	UA b	N	Yb	Yb	Yb	Ya, b	Yb	UA b	Yb	Yb	Yb	UA b	Nb	Ya, b	Yb	Yb	Yb	Nb	Yb
	Cefdinir [16-19, 21]	Yb	N	Yb	Yb	Yb	Yb	UA b	UA b	Yb	Yb	UA b	UA b	Yb	Yb	UA b	UA b	Yb	Yb	Yb
	Ceftaroline [17-19, 21]	Yb	N	Yb	Yb	Yb	Yb	UA b	UA b	Yb	UA b	Yb	UA b	UA b	Yb	UA b	UA b	Yb	Yb	Yb
	Ceftriaxone [16-21]	Ya, b	N	Yb	Yb	Yb	UA a	Ya, b	Na, b	Na, b	UA b	UA b	UA b	Na, b	UA a, b	Na, b	UA b	Yb	Yb	Yb
	Cefuroxime [16-21]	Ya, b	N	Yb	Yb	Yb	UA a	Ya, b	Na, b	Na, b	Nb	Yb	UA b	Na, b	Yb	UA a, b	UA b	Yb	Yb	Yb
	Cephalexin [16-21]	Na, b	N	Nb	Nb	Yb	Na, b	Yb	Ya, b	Ya, b	Yb	Yb	UA a, b	Ya, b	Yb	UA a	Yb	CPa	Nb	CPb
	Ceftazidime/avibactam [16-21]	Ya, b	N	Yb	Yb	Nb	Yb	Yb	CPb	Na, b	Yb	UA b	UA b	Na, b	UA a, b	UA a	Nb	Yb	Yb	Yb
	Ceftolozane/tazobactam [17, 19, 21]	Yb	N	Yb	Yb	CPb	Yb	Yb	CPb	Yb	UA b	UA b	UA b	UA b	Yb	Nb	Yb	Yb	Nc	Yb
	Ertapenem [18]	Ya, b	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb
	Meropenem [18]	Ya, b	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb
	Nafcillin [17, 19]	CPb	Yb	CPb	CPb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	CPa	Yb	Yb	Yb	CPb	CPb
	Penicillin G [16-21]	N	CPb	Nb	Nb	Yb	UA b	Yb	Yb	Nb	Yb	Yb	Yb	Yb	Nb	Yb	Yb	CPb	Yb	CPb
	Piperacillin/tazobactam [17-19]	N	UA	CPb	CPb	Yb	CPb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	CPb	Yb	Nc	CPb	CPb	Yb

aComparison data in beta-lactam allergic patients; bSide chain extrapolation of beta-lactam antibiotic; cExtrapolation of beta-lactamase inhibitor

Y The order may be ordered/verified as long as any reaction other than type I-IV hypersensitivity reactions (HSRs). This includes general or non-specific allergy listings. For type I HSRs, a beta-lactam with a different side chain CAN be safely administered; however, prescribers should be notified to communicate this information and confirm the order. Avoid use in type II-IV HSRs.

UA "OK Unless Anaphylaxis" Agent may have limited or conflicting data or share a similar (not identical) side chain. Order/verify as long as the reaction is NOT listed as a type I-IV HSR.

N Should not be ordered/verified due to a higher likelihood of cross-reactivity. If ordered, the prescriber should be notified, and a different agent considered.

CP "Call Prescriber" The agent may have limited or conflicting data or share a similar (not identical) side chain. Risk/benefit should be evaluated.