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MAJOR ARTICLE

Antibiotic Use in Patients With β-Lactam Allergies and Pneumonia: Impact of an Antibiotic Side Chain–Based Cross-Reactivity Chart Combined With Enhanced Allergy Assessment

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Background. β-lactam antibiotics with dissimilar R-group side chains are associated with low cross-reactivity. Despite this, patients with β-lactam allergies are often treated with non-β-lactam alternative antibiotics. An institutional β-lactam side chain–based cross-reactivity chart was developed and implemented to guide in antibiotic selection for patients with β-lactam allergies.

Methods. This single-center, retrospective cohort study analyzed the impact of the implementation of the cross-reactivity chart for patients with pneumonia. Study time periods were defined as January 2013 to October 2014 prior to implementation of the chart (historical cohort) and January 2017 to October 2018 (intervention cohort) following implementation. The primary outcome was the incidence of β-lactam utilization between time periods. Propensity-weighted scoring and interrupted time-series analyses compared outcomes.

Results. A total of 341 and 623 patient encounters were included in the historical and intervention cohorts, respectively. There was a significantly greater use of β-lactams in the intervention cohort (70.4% vs 89.3%; $P < .001$) and decreased use of alternative therapy (58.1% vs 36%; $P < .001$). There was no difference in overall allergic reactions between cohorts (2.4% vs 1.6%; $P = .738$) or in reactions caused by β-lactams (1.3% vs 0.9%; $P = .703$). Inpatient mortality increased (0% vs 6.4%; $P < .001$); however, no deaths were due to allergic reactions. Healthcare facility–onset *Clostridioides* difficile infections decreased between cohorts (1.2% vs 0.2%; $P = .032$).

Conclusions. Implementation of a β-lactam side chain–based cross-reactivity chart and enhanced allergy assessment was associated with increased use of β-lactams in patients with pneumonia without increasing allergic reactions.

Keywords: allergy; antimicrobial stewardship; β-lactam side chain; pneumonia.

Clinically significant immunologically mediated cross-reactivity among β-lactams is associated with R-group side chain homology, and β-lactam antibiotics with dissimilar side chains are thought to be associated with lower rates of cross-reactivity [1–13]. Expert-recommended comprehensive allergy assessments typically incorporate the administration of structurally dissimilar β-lactam antibiotics [2, 7, 8]. Despite this, many patients with any β-lactam allergies are treated with non-β-lactam alternative therapies (eg, fluoroquinolones) that are associated with known risks including clinical failures and increased adverse events (eg, *Clostridioides difficile* infection [CDI]) [2, 10, 14–18].

Recommendations for antibiotic treatment of pneumonias include regimens containing either β-lactam or non-β-lactam alternative therapy [19, 20]. Preference is not specified; however, antimicrobial stewardship programs (ASPs) often utilize first-line β-lactam use to avoid risks of alternative therapy [2, 10, 14–18]. The presence of a β-lactam allergy has been associated with 21% lower use of β-lactams and increased use of non-β-lactam alternative antibiotics for the treatment of pneumonia [21].

Strategies to increase β-lactam use in patients with β-lactam allergies include pathways that incorporate patient assessment through historical review, direct oral challenges, penicillin skin testing (PST), and specialist evaluation [2, 22, 23]. Several strategies may present challenges for institutions limited by resources, legal authority, or the time-limiting nature of the intervention in relation to the volume of patients with pneumonia [2, 24]. For example, the availability of an allergist for inpatient consultations and inpatient PST in the United States

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in community hospitals has been reported as 14% and 18%, respectively [25]. In addition, the reliability of cephalosporin skin testing is debated, and a positive PST does not rule out use of all β-lactams [10, 26]. These challenges underscore the necessity for strategies able to optimize prescribing on a wide scale and in settings with limited resources.

A previous analysis at our institution showed significant improvements in β-lactam prescribing for surgical prophylaxis with no increase in incidence of allergic reactions following introduction of an antibiotic side chain–based cross-reactivity chart and enhanced allergy assessment processes [27]. We describe the impact of our approach for the management of patients with β-lactam allergies on antibiotic use in patients with pneumonia.

METHODS

Development and Integration

A multidisciplinary team at our hospital implemented an institutional approach for antibiotic stewardship of patients with β-lactam allergies in October 2014. Strategies included enhanced allergy assessment and the use of an internally developed, literature-based, antibiotic side chain–based cross-reactivity chart to guide prescribing (Figure 1). The chart provides guidance based on a patient's allergy type and severity and the likelihood of reaction based on antibiotic side chains. No allergy-related changes were made in the electronic medical record for allergy documentation or to guide antibiotic ordering at the time of prescribing. Pharmacists actively intervened to assess for previous tolerance of β-lactams, ensure compliance with chart recommendations, and communicate with prescribers when warranted. Consultation with allergy/immunology specialists was available for assessment and interventions including PST, oral challenges, and desensitization when requested. In general, consultations were used sparingly and typically in cases with limited treatment options when the resistance profile of an organism and/or the patient allergy profiles made prescribing structurally dissimilar antibiotics challenging.

Patient Consent Statement

The design of the work and waiver of patient consent has been approved by the St Joseph Mercy Health System Institutional Review Board.

Study Design

This single-center, retrospective, cohort study at a 548-bed community teaching hospital analyzed the impact of the implementation of allergy assessment processes with a cross-reactivity chart in adult patients with documented β-lactam allergies and pneumonia. Study time periods were defined as January 2013 to October 2014 prior to implementation (historical cohort) and January 2017 to October 2018 following implementation (intervention cohort). Patients ≥18 years of age

Antibiotic ordered \ Antibiotic allergy	"Penicillin"	"Cephalosporin"	Amoxicillin/Amox/clav	Ampicillin/Amp/sulb	Aztreonam	Cefactor	Cefazolin	Cefepime	Cefotaxime	Cefoxitin	Cefdinir	Ceftaroline	Ceftriaxone	Cefuroxime	Cephalexin	Ceftazidime/avibactam	Ceftolozane/tazobactam	Nafcillin	Penicillin G	Piperacillin/tazobactam
Amoxicillin/Amox/clav	N	CP[a, b]		N[b]	Y[b]	N[a, b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	N[b]	Y[b]	Y[b]	CP[b]	N[b]	CP[b]
Ampicillin/Amp/sulb	N	CP[a, b]	N[b]		Y[b]	N[a, b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	N[b]	Y[b]	Y[b]	CP[b]	N[b]	CP[b]
Aztreonam	Y[b]	Y[b]	Y[b]	Y[b]		Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	N[b]	CP[b]	Y[b]	Y[b]	Y[b]
Cefactor	N	N	N[a, b]	N[a, b]	Y[b]		Y[b]	Y[a, b]	Y[b]	Y[b]	Y[b]	Y[b]	UA[a]	UA[a]	N[a, b]	Y[b]	Y[b]	Y[b]	UA[b]	CP[b]
Cefazolin	Y[a, b]	N	Y[b]	Y[b]	Y[b]	Y[b]		Y[b]	Y[b]	Y[a, b]	Y[b]	Y[b]	Y[a, b]	Y[a, b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]
Cefepime	Y[a, b]	N	Y[b]	Y[b]	Y[b]	Y[a, b]	Y[b]		N[b]	Y[b]	UA[b]	UA[b]	N[a, b]	N[a, b]	Y[b]	CP b	CP[b]	Y[b]	Y[b]	Y[b]
Cefotaxime	Y[a, b]	N	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	N[b]		UA[b]	UA[b]	UA[b]	N[a, b]	N[a, b]	Y[a, b]	N[a, b]	CP[b]	Y[b]	Y[b]	Y[b]
Cefoxitin	UA[b]	N	Y[b]	Y[b]	Y[b]	Y[b]	Y[a, b]	Y[b]	UA[b]		Y[b]	Y[b]	UA[b]	N[b]	Y[a, b]	Y[b]	Y[b]	Y[b]	N[b]	Y[b]
Cefdinir	Y[b]	N	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	UA[b]	UA[b]	Y[b]		UA[b]	UA[b]	Y[b]	Y[b]	UA[b]	UA[b]	Y[b]	Y[b]	Y[b]
Ceftaroline	Y[b]	N	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	UA[b]	UA[b]	Y[b]	UA[b]		UA[b]	UA[b]	Y[b]	UA[b]	UA[b]	Y[b]	Y[b]	Y[b]
Ceftriaxone	Y[a, b]	N	Y[b]	Y[b]	Y[b]	UA[a]	Y[a, b]	N[a, b]	N[a, b]	UA[b]	UA[b]	UA[b]		N[a, b]	UA[a, b]	N[a, b]	UA[b]	Y[b]	Y[b]	Y[b]
Cefuroxime	Y[a, b]	N	Y[b]	Y[b]	Y[b]	UA[a]	Y[a, b]	N[a, b]	N[a, b]	N[b]	Y[b]	UA[b]	N[a, b]		Y[a, b]	UA[a, b]	UA[b]	Y[b]	Y[b]	Y[b]
Cephalexin	N[a, b]	N	N[b]	N[b]	Y[b]	N[a, b]	Y[b]	Y[b]	Y[a, b]	Y[a, b]	Y[b]	Y[b]	UA[a, b]	Y[a, b]		UA[a]	Y[b]	Y[b]	N[b]	CP[b]
Ceftazidime/avibactam	Y[a, b]	N	Y[b]	Y[b]	N[b]	Y[b]	Y[b]	CP[b]	N[a, b]	Y[b]	UA[b]	UA[b]	N[a, b]	UA[a, b]	UA[a]		N[b]	Y[b]	Y[b]	Y[b]
Ceftolozane/tazobactam	Y[b]	N	Y[b]	Y[b]	CP[b]	Y[b]	Y[b]	CP[b]	CP[b]	Y[b]	UA[b]	UA[b]	UA[b]	UA[b]	Y[b]	N[b]		Y[b]	Y[b]	N[c]
Ertapenem	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]
Meropenem	Y[a, b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]
Nafeillin	CP[b]	Y[b]	CP[b]	CP[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]		CP[b]	CP[b]
Penicillin G	N	CP[b]	N[b]	N[b]	Y[b]	UA[b]	Y[b]	Y[b]	Y[b]	N[b]	Y[b]	Y[b]	Y[b]	Y[b]	N[b]	Y[b]	Y[b]	CP[b]		CP[b]
Piperacillin/tazobactam	N	UA	CP[b]	CP[b]	Y[b]	CP[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	CP[b]	Y[b]	N[c]	CP[b]	CP[b]	

Y The order may be ordered/verified if any reaction other than type I–IV hypersensitivity reaction (HSR). This includes general or non-specific allergy listings. For type I HSRs, a β-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.

Figure 1. Institutional β-lactam cross-reactivity chart.

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who received an antibiotic during their inpatient stay with discharge coding indicating pneumonia were identified through our institution's data warehouse. Pneumonia and concomitant disease states were identified by the Agency for Healthcare Research and Quality's Clinical Classifications Software coding (Supplementary Table 1) [28]. Patients were excluded if they did not have a documented β-lactam allergy at their time of encounter. Patients with multiple admissions meeting inclusion criteria were counted as distinct encounters.

The primary outcome was the incidence of β-lactam use per patient encounter between time periods. Study outcomes also included the incidence of allergic reactions, 30-day readmission, all-cause mortality at discharge and 30-days postdischarge, healthcare facility–onset CDI (HO-CDI), hospital and antibiotic costs, antimicrobial utilization and duration of therapy, and incidence of β-lactam use per encounter by documented allergy severity between time periods. Additional analyses investigated β-lactam use by first and subsequent pneumonia encounters, and aggregate antibiotic days of therapy (DOTs) per 1000 patient-days by antibiotic and antibiotic class between time periods.

Preexisting allergies were grouped for analysis as drug intolerance, mild reactions, type I hypersensitivity reactions (HSRs), unknown allergies, and type II–IV HSRs (Supplementary Table 2) [29]. Patients with multiple β-lactam allergies of varying severity and antibiotic type were categorized according to the most severe reaction listed.

Use per patient encounter of β-lactam and other antibiotics was defined as any receipt of any dose during an encounter. Classification of antibiotic groupings is further defined in Supplementary Table 3 [30]. Patient-specific antibiotic DOTs and receipt of diphenhydramine, epinephrine, and hydrocortisone were obtained from institutional data warehouse reporting. Antibiotic duration per encounter was defined as the sum of unique calendar day DOTs during an encounter. The daily wholesale acquisition cost of antibiotics received was adjusted to 2021 dollars and multiplied by the respective antibiotic DOTs to determine antibiotic cost [31]. Antibiotic DOTs per 1000 patient-days were also analyzed in the aggregate by calendar quarter between time periods. Patient-days unique to the study population were calculated from encounter-specific LOS determined from admission dates in the respective admission calendar quarter. DOTs avoided was determined by multiplying difference in DOTs per patient day between cohorts by the patient-days in the intervention cohort.

Allergic reactions were confirmed through manual chart review and allergy-related *International Classification of Diseases, Ninth* and *Tenth Revision, Clinical Modification* (*ICD-9-CM*, *ICD-10-CM*) coding (Supplementary Table 4) [32–35]. Chart review to assess allergic reactions was performed in the following cases: patients with *ICD-9/10-CM* coding indicating a reaction; patients who received a β-lactam with any preexisting documented β-lactam type I–IV HSR; patients with inpatient or 30-day mortality; patients who had a new β-lactam allergy added to their record within 1 year of their encounter; patients who received an antibiotic from the same class as their documented β-lactam allergy (eg, cephalosporin receipt with any documented cephalosporin allergy); and patients who received diphenhydramine, epinephrine, or hydrocortisone at any point during their encounter. Potential reactions identified through electronic queries or manual review were reviewed by board-certified allergy/immunology physicians to attribute specific antibiotic or other drug-related cause based on timing, likelihood of reactions from antibiotics received, severity and type of reaction, and receipt of additional medications.

HO-CDI was determined through Centers for Disease Control and Prevention's National Healthcare Safety Network reporting by trained infection and prevention personnel [36]. HO-CDI cases were reviewed to confirm onset post–receipt of antibiotics. Thirty-day mortality and 30-day readmissions were determined through a review of an institutional database that analyzed national and statewide death indexes and statewide health-system reporting of mortality and readmission. The cost of inpatient care was unavailable for patients after May 2018 due to changes in data warehouse reporting and excluded if unavailable.

Statistical Analysis

Descriptive statistics were presented for all study variables separately by study period. Differences in demographics, comorbidities, coinfections, and initiation of antibiotics within 48 hours of admission were tested between the 2 study periods to determine if the 2 periods differ significantly on potential confounders using unadjusted *t* tests or χ^2 tests. The treatment effect was then estimated using propensity score–weighted versions of *t* tests and χ^2 tests. The propensity score weights were calculated to adjust for potential confounding demographic and clinical characteristics including additional infectious disease diagnoses, intensive care unit (ICU) stay during encounter, hospital and ICU length of stay, malignancy, asthma, chronic obstructive pulmonary disease, acute and chronic renal failure, hemodialysis, chronic kidney disease, Charlson Comorbidity Index, an internal scoring tool for patient mortality, and allergy severity type [37]. Outcomes were assessed both prior to and after propensity score weighting. Propensity score weighting was not used in comparisons of variables with overlapping patients. Interrupted time series (ITS) analyses were performed on key outcomes of interest to analyze trends between time periods. Analyses were performed in R version 3.6.0 and SPSS IBM SPSS Statistics, version 27 (IBM, Armonk, New York) software, and significance was defined as a P value ≤ .05.

Post hoc analyses for exploratory purposes analyzed demographic and clinical characteristics between cohorts in patients who experienced 30-day mortality using unadjusted *t* test, Fisher exact test, or χ^2 test.

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RESULTS

A total of 6795 patient encounters with discharge coding indicating pneumonia were identified. Of these, 5831 (85.8%) were excluded due to a lack of β-lactam allergy (Supplementary Figure 1). Nine hundred sixty-four patient encounters were included in the final dataset with 341 in the historical cohort and 623 in the intervention cohort, respectively (Table 1). Baseline demographic and clinical variables were balanced after propensity score weighting with the exceptions of patients with concomitant mycoses infections, infective arthritis and osteomyelitis, influenza, and malignancy. There were no differences in specific antibiotic allergies, and variations in several specific antibiotic allergy severity types between cohorts (Supplementary Table 5).

β-lactam use per patient encounter significantly increased in the intervention cohort (70.4% vs 89.3%; $P < .001$) (Table 2). β-lactam use increased in patients with documented mild reactions (78.3% vs 92.6%; $P = .005$) and those with type I

Table 1. Demographics and Clinical Characteristics by Cohort

Variable	Historical Cohort (n = 341)	Intervention Cohort (n = 623)	*P* Value	PS-Weighted *P* Value
Categorical variables				
Sex			.385	.381
Female	226 (66.3)	394 (63.2)		
Male	115 (33.7)	229 (36.8)		
Race			.152	.267
White	310 (90.9)	545 (87.5)		
Other	31 (9.1)	78 (12.5)		
Concomitant infection				
Septicemia	122 (35.8)	247 (39.7)	.266	.696
Urinary tract infection	40 (11.7)	75 (12)	.97	.792
Bacterial infection; unspecified site	15 (4.4)	55 (8.8)	.016	.09
Peri-, endo-, and myocarditis; cardiomyopathy	16 (4.7)	30 (4.8)	>.999	.82
Aspiration pneumonitis	16 (4.7)	24 (3.9)	.648	.519
Mycoses	7 (2.1)	35 (5.6)	.015	.035
Influenza	5 (1.5)	29 (4.7)	.017	.035
Skin and subcutaneous soft tissue infection	6 (1.8)	17 (2.7)	.47	.186
Intestinal infection	4 (1.2)	15 (2.4)	.282	.112
Viral infection	3 (0.9)	17 (2.7)	.091	.249
Peritonitis and intestinal abscess	0 (0)	6 (1)	.095	.075
Infective arthritis and osteomyelitis	0 (0)	12 (1.9)	.011	.011
Diabetes mellitus	118 (34.6)	222 (35.6)	.803	.425
Cardiovascular disease	163 (47.8)	372 (59.7)	<.001	.714
Malignancy	75 (22)	17 (2.7)	<.001	.002
Asthma	48 (14.1)	89 (14.3)	>.999	.964
COPD	119 (34.9)	293 (47)	<.001	.216
Acute and unspecified renal impairment	83 (24.3)	175 (28.1)	.238	.525
Chronic renal impairment	86 (25.2)	206 (33.1)	.014	.745
Hemodialysis	72 (21.1)	226 (36.3)	<.001	.069
ICU stay	42 (12.3)	77 (12.4)	>.999	.973
Receipt of antimicrobial within 48 hours of admission	333 (97.7)	608 (97.6)	>.999	.831
Allergy type				
Drug intolerance	19 (5.6)	45 (7.2)	.396	.304
Mild reaction	69 (20.2)	148 (23.8)	.242	.796
Type I HSR	120 (35.2)	262 (42.1)	.044	.485
Unknown allergy	130 (38.1)	161 (25.8)	<.001	.133
Type II–IV HSR	3 (0.9)	7 (1.1)	>.999	.784
Continuous variables				
Age, y, mean (SD)	68.2 (15.7)	70.5 (15.4)	.034	.69
Charlson Comorbidity Index, mean (SD)	1.8 (1.3)	2.3 (1.4)	<.001	.124
Length of stay, days, median (IQR)	5 (3–8)	5 (3–8)	.831	.85
ICU length of stay, days, median (IQR)[a]	7 (2–14)	5 (2–9)	.218	.451
Internal mortality index[b] [37]	2.9 (1)	2.5 (1)	<.001	.072

Data are presented as No. (%) unless otherwise specified.

Abbreviations: COPD, chronic obstructive pulmonary disease; HSR, hypersensitivity reaction; ICU, intensive care unit; IQR, interquartile range; PS, propensity score; SD, standard deviation.

[a]Analysis performed on subset of patients with an ICU stay (historical cohort, n = 42; intervention cohort, n = 77).

[b]Analysis performed on subset of patients with available data (historical cohort, n = 289; intervention cohort, n = 602).

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

Variable	Historical Cohort (n = 341)	Intervention Cohort (n = 623)	*P* Value	PS-Weighted *P* Value
Categorical outcomes				
Received β-lactam	240 (70.4)	556 (89.3)	<.001	<.001
Allergy type				
Drug intolerance	n = 19	n = 45		
Received β-lactam	17 (89.5)	41 (91.1)	>.999	
Mild reaction	n = 69	n = 148		
Received β-lactam	54 (78.3)	137 (92.6)	.005	
Type I HSR	n = 120	n = 262		
Received β-lactam	68 (56.7)	225 (85.9)	<.001	
Unknown allergy	n = 130	n = 161		
Received β-lactam	100 (76.9)	148 (91.9)	<.001	
Type II–IV HSR	n = 3	n = 7		
Received β-lactam	1 (33.3)	5 (71.4)	.5	
Readmission	50 (14.7)	102 (16.4)	.546	.806
In-hospital mortality	0 (0)	40 (6.4)	<.001	<.001
Received β-lactam	…	37 (92.5)		
Received alternative therapy	…	34 (85)		
30-day mortality	8 (2.3)	89 (14.3)	<.001	<.001
Received β-lactam[a]	7 (87.5)	80 (89.9)	>.999	
Received alternative therapy[a]	8 (100)	79 (88.8)	>.999	
HO-CDI	4 (1.2)	1 (0.2)	.056	.032
Continuous outcomes, median (IQR)				
Inpatient costs, $[b]	7921 (4611–14 600)	7454 (4624–13 431)	.524	.303
Antibiotic days of therapy	8 (5–13)	8 (5–12)	.98	.9
Antibiotic duration, days	5 (3–8)	5 (3–7)	.426	.62
Antibiotic cost per patient-day, $	68 (28–143)	76 (36–153)	.029	.1

Data are presented as No. (%) unless otherwise specified.

Abbreviations: HO-CDI, healthcare facility–onset *Clostridioides difficile* infection; HSR, hypersensitivity reaction; PS, propensity score.

[a]Data are analyzed in patients with 30-day mortality (historical cohort, n = 8; intervention cohort, n = 89).

[b]Data are analyzed in patients with available data (historical cohort, n = 341; intervention cohort, n = 529).

HSRs (56.7% vs 85.9%; $P < .001$). There was no difference in total DOTs, duration, and antibiotic cost per encounter (Table 3). ITS analyses indicated there was a significant level increase ($P = .011$) and a flattening in slope of β-lactam utilization ($P = .02$). There was a significant level decrease ($P = .024$) and no change in the slope of alternative antibiotics utilization ($P = .053$) (Figure 2). β-lactam use improved in both first encounters (69% vs 88.2%; $P < .001$) and for patients previously admitted with pneumonia during the study time periods (80.5% vs 93.8%; $P = .027$) (Supplementary Table 6).

β-lactams for the treatment of pneumonia increased (69.2% vs 86.8%; $P < .001$) without change in duration or DOTs. Within this grouping, cefepime use per encounter increased (38.4% vs 55.4%; $P < .001$) and was associated with shorter durations. Cefepime was used more frequently in patients with documented type I and unknown reactions (Supplementary Table 7). The use of piperacillin-tazobactam and other cephalosporins increased without changes in duration. Ceftriaxone use and duration was unchanged.

The use of alternative pneumonia antibiotics per encounter significantly decreased (58.1% vs 36%; $P < .001$), as did alternative antibiotic DOTs and duration. Decreases in this category were driven by a reduction in fluoroquinolone use per encounter (48.7% vs 26.3%; $P < .001$), DOTs (3 vs 2; $P = .002$), and duration (3 days vs 2 days; $P = .003$), leading to predicted avoidance of 568 fluoroquinolone DOTs. The use of vancomycin per encounter (54% vs 46.5%; $P = .033$), and gram-positive pneumonia antibiotic DOTs per encounter and duration per encounter decreased between cohorts.

There was no change in the incidence of allergic reactions overall (2.4% vs 1.6%; $P = .738$), nor in type I–IV reactions (0.9% vs 0.6%; $P = .458$) (Table 4). In the subset of patients who received β-lactams and in whom reactions were attributed to β-lactams, there was no change in total reactions (1.3% vs 0.9%; $P = .703$) or type I–IV reactions (1.3% vs 0.2%; $P = .084$). There was no change in allergic reactions attributed to alternative therapy (1.8% vs 0.9%; $P = .221$). In the intervention cohort, 1 patient (0.2%) experienced a type I–IV HSR attributed to β-lactam therapy, compared with 3 patients (0.5%) secondary to alternative therapy.

Five of 556 patients (0.9%) who received a β-lactam in the intervention cohort experienced an HSR attributed to a β-lactam. Patients 1 and 2 were given cefepime with a documented mild penicillin allergy. Patient 3 was given ceftriaxone

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Table 3. Antimicrobial Utilization by Cohort

Variable[a]	Historical Cohort (n = 341)	Intervention Cohort (n = 623)	*P* Value
β-lactam antibiotics			
DOTs per encounter	4 (3–7)	4 (3–6)	.627
Duration per encounter	4 (3–7)	4 (3–6)	.492
Cefepime, ceftriaxone, piperacillin-tazobactam			
Use per encounter[b,c]	236 (69.2)	541 (86.8)	<.001
DOTs per encounter	4 (3–7)	4 (3–6)	.220
Duration per encounter	4 (2–7)	4 (2–6)	.143
Cephalosporins			
Use per encounter[b,c]	280 (82.1)	483 (77.5)	.111
DOTs per encounter	4 (3–7)	4 (3–6)	.260
Duration per encounter	4 (3–7)	4 (3–6)	.181
Cefepime			
Use per encounter[b]	131 (38.4)	345 (55.4)	<.001
DOTs per encounter	4 (3–6)	4 (2–5)	.012
Duration per encounter	4 (3–6)	4 (2–5)	.012
Ceftriaxone			
Use per encounter[b]	137 (40.2)	274 (44)	.283
DOTs per encounter	3 (2–6)	3 (2–5)	.423
Duration per encounter	3 (2–6)	3 (2–5)	.423
Other cephalosporins			
Use per encounter[b,c]	12 (3.5)	43 (6.9)	.043
DOTs per encounter	2 (1–4)	2 (1–2)	.727
Duration per encounter	2 (1–4)	2 (1–2)	.661
Piperacillin-tazobactam			
Use per encounter[b]	10 (2.9)	48 (7.7)	.005
DOTs per encounter	2 (1–3)	3 (1–5)	.282
Duration per encounter	2 (1–3)	3 (1–5)	.282
Antimicrobials other than β-lactams			
Use per encounter[b,c]	101 (29.6)	67 (10.8)	<.001
DOTs per encounter	5 (3–8)	5 (3–7)	.008
Duration per encounter	4 (3–7)	4 (3–6)	.044
Alternative pneumonia antibiotics			
Use per encounter[b,c]	198 (58.1)	224 (36)	<.001
DOTs per encounter	3 (2–5)	2 (1–5)	.027
Duration per encounter	3 (1–5)	2 (1–4)	.023
Fluoroquinolones			
Use per encounter[b,c]	166 (48.7)	164 (26.3)	<.001
DOTs per encounter	3 (1–4)	2 (1–3)	.002
Duration per encounter	3 (1–4)	2 (1–3)	.003
Carbapenems			
Use per encounter[b,c]	10 (2.9)	33 (5.3)	.124
DOTs per encounter	3 (1–5)	4 (3–8)	.068
Duration per encounter	3 (1–5)	4 (3–8)	.070
Aztreonam			
Use per encounter[b]	16 (4.7)	19 (3)	.261
DOTs per encounter	2 (1–7)	2 (1–3)	.526
Duration per encounter	2 (1–7)	2 (1–3)	.526
Aminoglycosides			
Use per encounter[b,c]	20 (5.9)	19 (3)	.051
DOTs per encounter	1 (1–2)	1 (1–1)	.200
Duration per encounter	1 (1–2)	1 (1–1)	.200
Clindamycin			
Use per encounter[b]	33 (9.7)	42 (6.7)	.133
DOTs per encounter	1 (1–3)	1 (1–3)	.883
Duration per encounter	1 (1–3)	1 (1–3)	.883
Gram-positive coverage antibiotics			
Use per encounter[b,c]	185 (54.3)	296 (47.5)	.053

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Table 3. Continued

Variable[a]	Historical Cohort (n = 341)	Intervention Cohort (n = 623)	*P* Value
DOTs per encounter	3 (1–4)	2 (1–3)	<.001
Duration per encounter	3 (1–4)	2 (1–3)	<.001
Vancomycin, intravenous			
Use per encounter[b]	184 (54)	290 (46.5)	.033
DOTs per encounter	2 (1–3)	2 (1–3)	.274
Duration per encounter	2 (1–3)	2 (1–3)	.274
Linezolid			
Use per encounter[b]	7 (2.1)	8 (1.3)	.516
DOTs per patient	5 (1–7)	4 (1–5)	.513
Duration per encounter	5 (1–7)	4 (1–5)	.513
Atypical coverage antibiotics			
Use per encounter[b,c]	157 (46)	324 (52)	.088
DOTs per encounter	3 (1–2)	4 (2–5)	.428
Duration per encounter	3 (2–5)	4 (2–5)	.423

Data are presented as median (interquartile range) unless otherwise specified.

Abbreviations: DOTs, days of therapy; PS, propensity score.

[a]Data reported in patients who received therapy.

[b]Data are No. (%).

[c]Patients receiving multiple antibiotics in category are counted once.

with mild cephalexin and penicillin allergies. Patient 4 was given piperacillin-tazobactam with a preexisting mild cephalexin allergy and ceftriaxone type I HSR. Patient 5 was given amoxicillin-clavulanate with a mild penicillin allergy. Antibiotic selection was consistent with cross-reactivity chart recommendations for patients 1–3. Patient 4 received therapy where the chart recommends a risk benefit assessment for β-lactam use. Nonconsistent antibiotic selection occurred in patient 5.

HO-CDI decreased between cohorts (1.2% vs 0.2%; $P = .032$). There was a significant increase in both inpatient mortality (0% vs 6.4%; $P < .001$) and 30-day mortality (2.4% vs 14.3%; $P < .001$). There was no difference in β-lactam or alternative therapy use between cohorts in patients who experienced mortality at 30 days. No inpatient deaths were attributed to an allergic reaction. A single patient within the mortality cohort experienced a reaction, which resolved 10 days prior to death. There were no changes in 30-day readmission or hospital cost.

Post hoc analyses of patients who experienced 30-day mortality showed that patients in the historical cohort had higher malignancy (50% vs 4.5%; $P = .001$) and diabetes (75% vs 31.5%; $P = .021$). No other significant differences were noted.

DISCUSSION

Results of our analysis demonstrated an increase in β-lactam utilization in patients with documented β-lactam allergies and pneumonia following implementation of a side chain–based cross-reactivity chart and enhanced allergy assessment to guide antibiotic prescribing and ASP surveillance and intervention. There were no increases in β-lactam allergic reactions, including type I–IV HSRs, despite increased use.

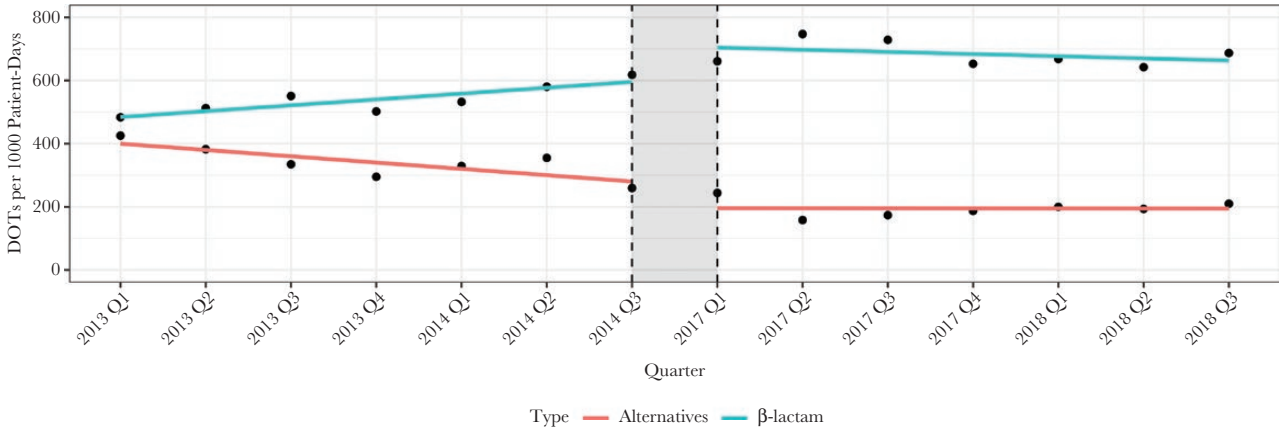

Figure 2. Interrupted time-series analysis of β-lactam and alternative antibiotic days of therapy (DOTs) per 1000 patient-days, by calendar quarter.

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Table 4. Allergic Reactions by Cohort

Variable	Historical Cohort	Intervention Cohort	*P* Value	PS-Weighted *P* Value
Study cohort	n = 341	n = 623		
Any allergic reaction	8 (2.4)	10 (1.6)	.573	.738
Drug intolerance	3 (0.9)	0 (0)	.044	.025
Mild reactions	2 (0.6)	6 (1)	.719	.329
Type I–IV combined reactions	3 (0.9)	4 (0.6)	.703	.458
Type I HSR	1 (0.3)	1 (0.2)	>.999	.521
Type II–IV HSR	2 (0.6)	3 (0.5)	>.999	.616
Allergic reaction (excluding drug intolerance reactions)	5 (1.5)	10 (1.6)	>.999	.781
Received β-lactam	n = 240	n = 556		
Reaction secondary to β-lactam use[a,b]	3 (1.3)	5 (0.9)	.703	
Drug intolerance[b]	0 (0)	0 (0)		
Mild reactions[b]	0 (0)	4 (0.7)	.322	
Type I–IV combined reactions	3 (1.3)	1 (0.2)	.084	
Type I HSR[b]	1 (0.4)	0 (0)	.302	
Type II–IV HSR[b]	2 (0.8)	1 (0.2)	.218	
Received alternative therapy	n = 335	n = 586		
Reaction secondary to alternative use[a,c]	6 (1.8)	5 (0.9)	.221	
Drug intolerance[c]	3 (0.9)	0 (0)	.048	
Mild reactions[c]	2 (0.6)	2 (0.3)	.625	
Type I–IV combined reactions	1 (0.3)	3 (0.5)	>.999	
Type I HSR[c]	0 (0)	1 (0.2)	>.999	
Type II–IV HSR[c]	1 (0.3)	2 (0.3)	>.999	
Allergic reactions secondary to alternative use (excluding drug intolerance reactions)[a,c]	3 (0.9)	5 (0.9)	>.999	

Data are presented as No. (%) unless otherwise specified.

Abbreviations: HSR, hypersensitivity reaction; PS, propensity score.

[a]One allergic reaction was thought to be either from β-lactam or alternate therapy and included in both categories (historical cohort, n = 1).

[b]Data were analyzed in patients who received β-lactam antibiotics (historical cohort, n = 240; intervention cohort, n = 556).

[c]Data were analyzed in patients who received alternative antibiotics (historical cohort, n = 335; intervention cohort, n = 586).

These results are similar to previously reported results from our institution, which detailed significant improvements in β-lactam selection for surgical prophylaxis [27]. Analyses across similar time periods show increased prescribing resulting in 85% and 89% β-lactam use for surgical prophylaxis and pneumonia, respectively. Importantly, this increased β-lactam use has not resulted in increases in allergic reactions in either population. A total of 1094 surgical prophylaxis patients with documented β-lactam allergies received β-lactam antibiotics (98% cefazolin) resulting in 3 (0.3%) reactions. Cefazolin does not share a side chain with other β-lactams, and use of later-generation cephalosporin- or penicillin-based regimens used for the treatment of pneumonia inherently carry more cross-reactivity risk than cefazolin due to increased side chain similarities [11–13]. Despite this, our results also showed low allergic reaction rates in intervention cohort patients receiving β-lactams (0.9%).

This rate is comparable to reports of allergy incidence in individuals exposed to different classes of antibiotics. Macy and Poon reported the incidence of new allergies in outpatients exposed to various classes of antibiotics including penicillins (1.3%), cephalosporins (0.9%), and fluoroquinolones (0.8%) [38]. In another large database study, 1.1% of patients with a history of a penicillin allergy had a new cephalosporin allergy reported within 30 days of receipt of a cephalosporin course compared to 0.4% of those without an antibiotic allergy, or 0.7% with cephalosporin allergies [18]. Patients in our analysis were as likely to develop an allergic reaction from alternative therapy as they were from β-lactam treatment. Results further contribute to the body of literature supporting the safety profile of structurally dissimilar prescribing.

To our knowledge, this is the only report of the use of a cross-reactivity chart combined with enhanced allergy assessment in patients with pneumonia. On a grander scale, despite the availability of and dissemination of high-quality cross-reactivity charts, reports of strategies incorporating structurally dissimilar antibiotic prescribing are limited. Allergy management pathways to date that incorporate recommendations based on a cross-reactivity foundation have utilized computerized guideline applications or medical record alerts. For example, a computerized guideline application with clinical decision support incorporating PST and specialist evaluation along with recommendations for later-generation cephalosporin use in patients with mild reactions, and with or without test dosing in patients with type I HSRs, increased prescribing of penicillins

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and cephalosporins from 38% to 50% in patients with penicillin allergies [39]. Simply removing the electronic medical record warning to avoid cephalosporin use in patients with penicillin allergies increased cephalosporin use from 18% to 27% without differences in anaphylaxis or new allergies at a large, integrated health system [40]. We believe incorporation of active interventions through pharmacist and ASP efforts contributed to improvements. We have described results in surgery and pneumonia populations; however, our evaluation process is for all antibiotic indications in β-lactam allergic patients. Active strategies incorporating side chain–based allergy assessment and active pharmacist review may be an easily implemented, effective, and deployable strategy for ASPs to incorporate into their existing allergy stewardship strategies with the potential for wide-scale influential change.

Our analysis also noted a significant reduction in HO-CDI in the intervention cohort. Patients with penicillin allergies have been shown to have a 23%–26% increased incidence of CDI [18]. A United Kingdom study reported 35% of the increased risk was due to receipt of β-lactam alternatives including fluoroquinolones, clindamycin, and macrolides. Fluoroquinolones alone accounted for 16% of the increased risk [16]. The reduction in HO-CDI was a secondary outcome, likely multifactorial, and influenced by additional institutional initiatives to reduce CDI; however, decreased use and exposure to fluoroquinolones, may have contributed to improvements in this important metric.

There was a significant increase in 30-day mortality and in-hospital mortality in the intervention cohort, though no inpatient deaths were attributed to allergic reactions. Post hoc analyses confirmed the validity of patient identification queries and mortality reporting. In general, individuals in the intervention group were older, had higher Carlson Comorbidity Index scores, and higher risk for mortality as indicated by an internal mortality index [37]. With propensity score weighting, these differences were not significant. In patients who died by 30 days, the only differences between groups were higher malignancy and diabetes in the historical cohort and there was no difference in β-lactam or alternative use between time periods. We are unaware of mortality differences associated with increased β-lactam use or decreased alternative therapy use in patients with pneumonia. The finding that no patients died in the hospital in the historical cohort is noteworthy. Similar β-lactam and alternative use in patients who died suggests this finding is unrelated to antibiotic selection; however, further research is warranted.

This study had several limitations including the single-center, retrospective nature of the analysis. Documented allergies and reactions were limited to those present in the medical record at the time of encounter. Allergy clarification and history may have occurred following patient discussions, which further guided prescribing. Our analysis of allergic reactions may have been impacted if reactions were not properly coded or documented, not identified by investigators during manual chart review, or occurred postdischarge without a new β-lactam allergy charted in the medical record within 1 year. Alternative antibiotic allergic reactions may have been undercounted since postdischarge queries for the addition of new allergies were limited to β-lactam allergies. Potential unaccounted confounders such as risk factors for multidrug-resistant infections, culture and susceptibility variations, and changes in the mix of hospital-associated and community-acquired pneumonia cases were not assessed. Variations in any of these metrics could influence antibiotic selection and our lack of inclusion is an acknowledged limitation.

Antibiotic use could have occurred any time during the encounter and the entirety of use may not have been exclusively for the treatment of pneumonia. For example, a patient may have received various courses of antibiotics depending on concomitant infections. The comparison cohorts were well matched following propensity score weighting for concomitant infections, and commonly used pneumonia antibiotics were reported as a categorical grouping; however, this lack of pneumonia-specific sophistication is a limitation.

Our ASP continued to evolve throughout the extended timeframe of this study. Strategies included enhanced ASP surveillance and intervention in patients at the highest risk of mortality, participation in a statewide initiative to improve antibiotic prescribing in pneumonia and urinary tract infections, regularly updated institutional guidelines for common infectious diseases that often encouraged structurally dissimilar prescribing, and active syndrome-specific interventions targeting pneumonia and other common infectious diseases [41–43]. In general, these strategies emphasized appropriate antibiotic selection and duration. For example, a pneumonia care bundle was implemented, which alerted pharmacists to prescribed antibiotics for the treatment of pneumonia through an alert built in commercially available pharmacy surveillance software. Active surveillance, communication, and intervention by pharmacists were expected to ensure that a suite of predefined quality measures was met. Structurally dissimilar antibiotic selection was implied, and treatment duration was emphasized. These overlapping ASP strategies encouraged active scrutiny of antibiotic use and likely contributed to results. Further investigations comparing effective strategies to optimize antibiotic use in patients with β-lactam allergies are encouraged.

We describe results of a real-world implementation of a cross-reactivity chart to guide structurally dissimilar antibiotic prescribing in patients with pneumonia. Adoption was aided by targeted active pharmacist intervention, ASP oversight, and multidisciplinary buy-in to promote β-lactam use. Initiatives to improve structurally dissimilar β-lactam prescribing may present a resource-friendly, deployable approach that can work in combination with the suite of available allergy management strategies.

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In conclusion, implementation of a β-lactam side chain–based cross-reactivity chart combined with enhanced allergy assessment was associated with increased utilization of β-lactams and reduced non-B-lactam alternative therapy use in patients with pneumonia without increasing allergic reactions.

Supplementary Data

Supplementary materials are available at *Open Forum 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: Clinical Characteristic and Diagnostic Coding Queries

Code Description	CCS Coding[28]
Concomitant infection	
Pneumonia (except that caused by tuberculosis or sexually transmitted disease)	122
Septicemia	2
Urinary tract infection	159
Bacterial infection; unspecified site	3
Peri-; endo-; and myocarditis; cardiomyopathy	97
Aspiration pneumonitis	8.4
Mycoses	4
Influenza	123
Skin and subcutaneous soft tissue infection	197
Intestinal infection	135
Viral infection	7
Peritonitis and intestinal abscess	148
Infective arthritis and osteomyelitis	201
Diabetes mellitus	49, 50
Cardiovascular disease	100, 101, 107 - 112, 114, 115
Malignancy	11 - 47
Asthma	128
COPD	127
Acute and unspecified renal impairment	157
Chronic renal impairment	158
Hemodialysis	58

Abbreviations: CCS, Clinical Classifications Software; COPD, chronic obstructive pulmonary disease.

Supplement Table 2: Documented Allergy Grouping Definitions

Antibiotic Grouping[29]	Example Reactions
Drug intolerance	Confusion, diarrhea, dizziness, gastrointestinal upset, headache, nausea, vomiting
Mild reaction	Itching, morbilliform or macropapular eruption without hives
Type I HSR	Anaphylaxis, angioedema, bronchospasm, difficulty breathing, hives, edema, hypotension, urticaria
Unknown	Reaction experienced was not documented or reported
Type II-IV HSR	Acute interstitial nephritis, drug fever, DRESS, hemolytic anemia, serum sickness, Stevens-Johnson syndrome, toxic epidermal necrolysis

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; HSR, hypersensitivity reactions.

Supplement Table 3: Antibiotic Category Definitions

Antibiotic Grouping	Antibiotics Included
β-lactam antibiotics	Amoxicillin/clavulanic acid, amoxicillin, ampicillin/sulbactam, ampicillin, cefazolin, cefditoren, cefepime, cefpodoxime, ceftaroline, ceftriaxone, cefuroxime, cephalexin, nafcillin, penicillin G, piperacillin/tazobactam
Cephalosporins	Cefazolin, cefditoren, cefepime, cefpodoxime, ceftaroline, ceftriaxone, cefuroxime, cephalexin
Other cephalosporins	Cefditoren, cefpodoxime, ceftaroline, cefuroxime, cephalexin
Penicillins	Amoxicillin/clavulanic acid, amoxicillin, ampicillin/sulbactam, ampicillin, nafcillin, penicillin G, piperacillin/tazobactam
β-lactam pneumonia antibiotics	Cefepime, ceftriaxone, piperacillin/tazobactam
Antibiotics other than β-lactams	Amikacin, azithromycin, aztreonam, ciprofloxacin, clindamycin, colistimethate, daptomycin, doxycycline, ertapenem, fosfomycin, gentamicin, levofloxacin, linezolid, meropenem, metronidazole, minocycline, nitrofurantoin, tigecycline, tobramycin, vancomycin intravenous
Alternative pneumonia antibiotics	Amikacin, aztreonam, ciprofloxacin, clindamycin, ertapenem, gentamicin, levofloxacin, meropenem, tobramycin
Fluoroquinolones	Ciprofloxacin, levofloxacin
Carbapenems	Ertapenem, meropenem
Aminoglycosides	Amikacin, gentamicin, tobramycin
Gram positive coverage pneumonia antibiotics	Linezolid, vancomycin intravenous
Atypical coverage antibiotics	Azithromycin, doxycycline

Supplement Table 4: Allergic Reaction Coding Queries

Code Description[32-35]	*ICD-9-CM*	*ICD-10-CM*	E code
Allergic urticaria	708	L50.0	
Allergy status to drugs, medicaments and biological substances		Z88	
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	
Anaphylactic reaction due to food		T78.0	
Angioneurotic edema, not elsewhere classified/angioneurotic edema, initial encounter	995.1	T78.3	
Antibiotics causing adverse effects in therapeutic use			E930
Cholinergic urticaria		L50.5	
Dermatitis due to substances taken internally	693		
Dermatographic urticaria	708.3	L50.3	
DRESS	995.27		
Eosinophilia	288.3	D72.1	
Generalized skin eruption due to drugs and medicaments taken internally		L27.0	
Idiopathic urticaria	708.1	L50.1	
Localized skin eruption due to drugs and medicaments taken internally		L27.1	
Other adverse food reactions, not elsewhere classified		T78.1	
Other anaphylactic reaction	995.0	T78.2	
Other pruritus	698.8	L29.8	
Other specified urticaria/contact urticaria	708.8	L50.6	
Poisoning by antibiotics	960	T36	
Poisoning by, adverse effect of and underdosing of other systemic anti-infectives and antiparasitics		T37	
Rash and other nonspecific skin eruption	782.1	R21	
Stevens-Johnson syndrome	695.13	L51.1	
Toxic epidermal necrolysis	695.15	L12.3, L51.2	
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	
Unspecified adverse effect of drug or medicament		T88.7	
Unspecified pruritic disorder/pruritus, unspecified	698.9	L29.9	
Urticaria, unspecified	708.9	L50.9	
Vibratory urticaria	708.4	L50.4	

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms.

Supplement Table 5. Documented β-lactam Allergies by Cohort

Variable[a]	Historical (N=341)	Intervention (N=623)	*P* Value
Allergy Type			
Cephalosporin (any)	70 (20.5)	143 (23)	0.431
Drug intolerance	12 (3.5)	11 (1.8)	0.138
Mild reaction	12 (2.9)	44 (7.1)	0.035
Type I HSR	25 (7.3)	56 (9)	0.444
Unknown	20 (5.9)	28 (4.5)	0.435
Type II-IV HSR	1 (0.3)	4 (0.6)	0.661
Cefazolin	2 (0.6)	7 (1.1)	0.505
Drug intolerance	0 (0)	0 (0)	-
Mild reaction	1 (0.3)	6 (1)	0.432
Type I HSR	0 (0)	0 (0)	-
Unknown	1 (0.3)	1 (0.2)	> 0.999
Type II-IV HSR	0 (0)	0 (0)	-
Cefepime	1 (0.3)	11 (1.8)	0.066
Drug intolerance	0 (0)	0 (0)	-
Mild reaction	0 (0)	2 (0.3)	0.542
Type I HSR	1 (0.3)	4 (0.6)	0.661
Unknown	0 (0)	4 (0.6)	0.303
Type II-IV HSR	0 (0)	1 (0.2)	> 0.999
Ceftriaxone	2 (0.6)	19 (3)	0.11
Drug intolerance	0 (0)	0 (0)	-
Mild reaction	1 (0.3)	4 (0.6)	0.661
Type I HSR	1 (0.3)	14 (2.2)	0.026
Unknown	0 (0)	1 (0.2)	> 0.999
Type II-IV HSR	0 (0)	0 (0)	-
Other cephalosporins	66 (19.4)	126 (20.2)	0.811
Drug intolerance	12 (3.5)	11 (1.8)	0.138
Mild reaction	10 (2.9)	43 (6.9)	0.015
Type I HSR	23 (6.7)	41 (6.6)	> 0.999
Unknown	20 (5.9)	28 (4.5)	0.435
Type II-IV HSR	1 (0.3)	3 (0.5)	> 0.999
Penicillin - general or specific (eg ampicillin)	301 (88.3)	541 (86.8)	0.591
Drug intolerance	12 (3.5)	43 (6.9)	0.043
Mild reaction	65 (19.1)	131 (21)	0.521
Type I HSR	105 (30.8)	222 (35.6)	0.148
Unknown	117 (34.3)	142 (22.8)	< 0.001
Type II-IV HSR	2 (0.6)	3 (0.5)	> 0.999
Piperacillin/tazobactam	8 (2.3)	8 (1.3)	0.332
Drug intolerance	0 (0)	1 (0.2)	> 0.999
Mild reaction	4 (1.2)	1 (0.2)	0.056
Type I HSR	2 (0.6)	4 (0.6)	> 0.999

Unknown	2 (0.6)	2 (0.3)	0.618
Type II-IV HSR	0 (0)	0 (0)	-
Anti-staphylococcal penicillin	1 (0.3)	4 (623)	0.661
Drug intolerance	0 (0)	1 (0.2)	> 0.999
Mild reaction	0 (0)	1 (0.2)	> 0.999
Type I HSR	0 (0)	0 (0)	-
Unknown	1 (0.3)	2 (0.3)	> 0.999
Type II-IV HSR	0 (0)	0 (0)	-

Data are No. (%).
Abbreviations: HSR, hypersensitivity reactions.
[a]Patients may have had multiple allergies documented.

Supplement Table 6. B-lactam Use by Allergy Severity Type and Admission

Variable	Historical	Intervention	*P* Value
First encounter	n = 300	n = 510	
	207 (69)	450 (88.2)	< 0.001
Drug intolerance	n = 19	n = 42	
	17 (89.5)	38 (90.5)	> 0.999
Mild reaction	n = 60	n = 115	
	46 (76.7)	105 (91.3)	0.015
Type I HSR	n = 100	n = 213	
	54 (54)	181 (85)	< 0.001
Unknown	n = 118	n = 134	
	89 (75.4)	122 (91)	0.001
Type II-IV HSR	n = 3	n = 6	
	1 (33.3)	4 (66.7)	0.524
Previous encounter	n = 41	n = 113	
	33 (80.5)	106 (93.8)	0.027
Drug intolerance	n = 3	n = 0	
	3 (100)	0 (0)	-
Mild reaction	n = 9	n = 33	
	8 (88.9)	32 (97)	0.387
Type I HSR	n = 20	n = 49	
	14 (70)	44 (89.8)	0.067
Unknown	n = 12	n = 27	
	11 (91.7)	26 (96.3)	0.526
Type II-IV HSR	n = 1	n = 0	
	1 (100)	0 (0)	-

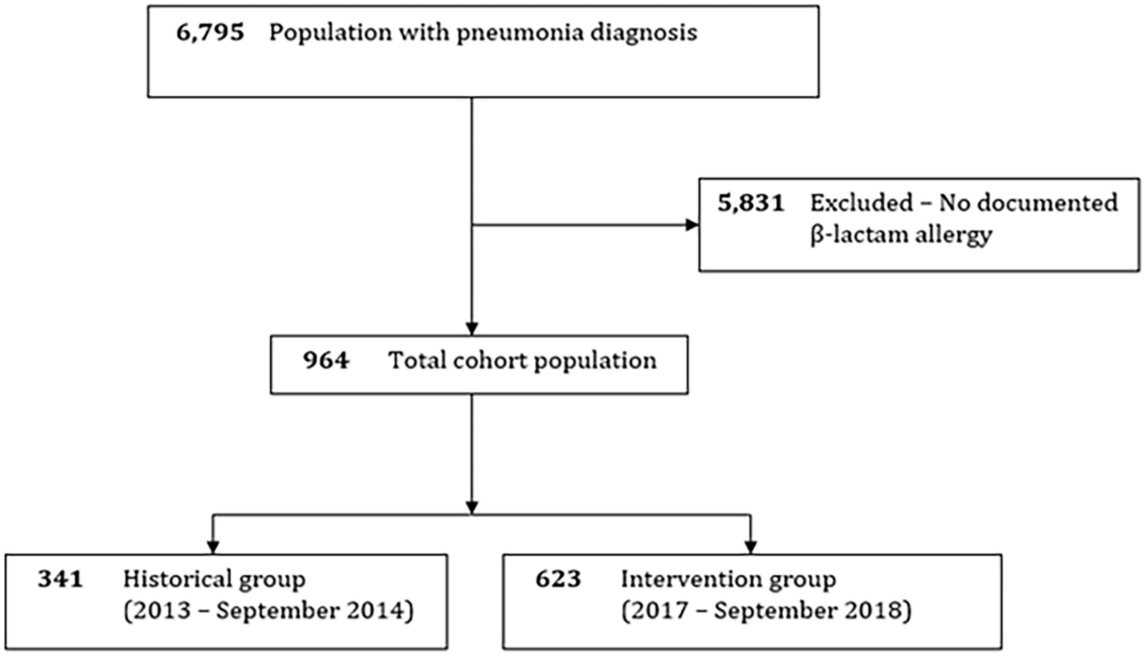
Data are No. (%).
Abbreviations: HSR, hypersensitivity reactions; PS, propensity score.

Supplement Table 7. Antibiotic Selection by β-lactam Allergy Severity

Variable	Historical (N=341)	Intervention (N=623)	*P* Value
Drug intolerance	n = 19	n = 45	0.396
β-lactams	17 (89.5)	41 (91.1)	> 0.999
β-lactam pneumonia antibiotics	15 (78.9)	38 (84.4)	0.865
Cephalosporins	16 (84.2)	40 (88.9)	0.918
Cefepime	7 (36.8)	23 (51.1)	0.441
Ceftriaxone	8 (42.1)	24 (53.3)	0.584
Other cephalosporins	1 (5.3)	5 (11.1)	0.660
Piperacillin/tazobactam	1 (5.3)	1 (2.2)	0.509
Alternative pneumonia antibiotics	10 (52.6)	18 (40)	0.513
Fluoroquinolones	8 (42.1)	14 (31.1)	0.577
Carbapenems	0 (0)	3 (6.7)	0.549
Aztreonam	1 (5.3)	2 (4.4)	> 0.999
Aminoglycosides	2 (10.5)	0 (0)	0.085
Clindamycin	0 (0)	2 (4.4)	> 0.999
Gram positive coverage pneumonia antibiotics	10 (52.6)	22 (48.9)	> 0.999
Vancomycin	10 (52.6)	22 (48.9)	> 0.999
Linezolid	0 (0)	0 (0)	-
Atypical coverage antibiotics	7 (36.8)	27 (60)	0.155
Mild reaction	n = 69	n = 148	0.242
β-lactams	54 (78.3)	137 (92.6)	0.005
β-lactam pneumonia antibiotics	54 (78.3)	133 (89.9)	0.036
Cephalosporins	54 (78.3)	132 (89.2)	0.053
Cefepime	33 (47.8)	75 (50.7)	0.806
Ceftriaxone	33 (47.8)	79 (53.4)	0.538
Other cephalosporins	2 (2.9)	14 (9.5)	0.1
Piperacillin/tazobactam	1 (1.4)	13 (8.8)	0.041
Alternative pneumonia antibiotics	39 (56.5)	39 (26.4)	< 0.001
Fluoroquinolones	34 (49.3)	25 (16.9)	< 0.001
Carbapenems	2 (2.9)	4 (2.7)	> 0.999
Aztreonam	0 (0)	2 (1.4)	> 0.999
Aminoglycosides	6 (8.7)	5 (3.4)	0.108
Clindamycin	7 (10.1)	11 (7.4)	0.682
Gram positive coverage pneumonia antibiotics	40 (58)	56 (37.8)	0.008
Vancomycin	40 (58)	55 (37.2)	0.006
Linezolid	2 (2.9)	1 (0.7)	0.238
Atypical coverage antibiotics	34 (49.3)	92 (62.2)	0.1
Type I HSR	n = 120	n =262	0.044

β-lactams	68 (56.7)	225 (85.9)	< 0.001
β-lactam pneumonia antibiotics	67 (55.8)	220 (84)	< 0.001
Cephalosporins	67 (55.8)	207 (79)	< 0.001
Cefepime	37 (30.8)	140 (53.4)	< 0.001
Ceftriaxone	37 (30.8)	106 (40.5)	0.091
Other cephalosporins	2 (1.7)	19 (7.3)	0.048
Piperacillin/tazobactam	4 (3.3)	24 (9.2)	0.069
Alternative pneumonia antibiotics	79 (65.8)	109 (41.6)	< 0.001
Fluoroquinolones	67 (55.8)	81 (30.9)	< 0.001
Carbapenems	5 (4.2)	18 (6.9)	0.424
Aztreonam	9 (7.5)	10 (3.8)	0.199
Aminoglycosides	3 (2.5)	9 (3.4)	0.76
Clindamycin	13 (10.8)	17 (6.5)	0.208
Gram positive coverage pneumonia antibiotics	58 (48.3)	133 (50.8)	0.741
Vancomycin	57 (47.5)	131 (50)	0.731
Linezolid	2 (1.7)	4 (1.5)	> 0.999
Atypical coverage antibiotics	50 (41.7)	124 (47.3)	0.357
Unknown	n = 130	n = 161	
β-lactams	100 (76.9)	148 (91.9)	<0.001
β-lactam pneumonia antibiotics	99 (76.2)	145 (90.1)	0.002
Cephalosporins	98 (75.4)	144 (89.4)	0.002
Cefepime	53 (40.8)	104 (64.6)	<0.001
Ceftriaxone	58 (44.6)	62 (38.5)	0.351
Other cephalosporins	7 (5.4)	4 (2.5)	0.228
Piperacillin/tazobactam	4 (3.1)	9 (5.6)	0.455
Alternative pneumonia antibiotics	67 (51.5)	56 (34.8)	0.006
Fluoroquinolones	54 (41.5)	43 (26.7)	0.011
Carbapenems	3 (2.3)	8 (5)	0.356
Aztreonam	6 (4.6)	4 (2.5)	0.350
Aminoglycosides	9 (6.9)	5 (3.1)	0.170
Clindamycin	12 (9.2)	12 (7.5)	0.739
Gram positive coverage pneumonia antibiotics	76 (58.5)	84 (52.2)	0.34
Vancomycin	76 (58.5)	81 (50.3)	0.205
Linezolid	3 (2.3)	3 (1.9)	> 0.999
Atypical coverage antibiotics	65 (50)	80 (49.7)	> 0.999
Type II-IV HSR (combined)	n = 3	n = 7	> 0.999
β-lactams	1 (33.3)	5 (71.4)	0.5
β-lactam pneumonia antibiotics	1 (33.3)	5 (71.4)	0.5
Cephalosporins	1 (33.3)	4 (57.1)	> 0.999
Cefepime	1 (33.3)	3 (42.9)	> 0.999
Ceftriaxone	1 (33.3)	3 (42.9)	> 0.999

Other cephalosporins	0 (0)	1 (14.3)	> 0.999
Piperacillin/tazobactam	0 (0)	1 (14.3)	> 0.999
Alternative pneumonia antibiotics	3 (100)	2 (28.6)	0.167
Fluoroquinolones	3 (100)	1 (14.3)	0.033
Carbapenems	0 (0)	0 (0)	-
Aztreonam	0 (0)	1 (14.3)	> 0.999
Aminoglycosides	0 (0)	0 (0)	-
Clindamycin	1 (33.3)	0 (0)	0.3
Gram positive coverage pneumonia antibiotics	1 (33.3)	1 (14.3)	> 0.999
Vancomycin	1 (33.3)	1 (14.3)	> 0.999
Linezolid	0 (0)	0 (0)	-
Atypical coverage antibiotics	1 (33.3)	1 (14.3)	> 0.999

Data are No. (%) unless otherwise specified.
Abbreviations: HSR; hypersensitivity reactions; PS, propensity score.

Supplement Figure 1: Cohort Flow Diagram