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Association of Penicillin or Cephalosporin Allergy Documentation and Antibiotic Use in Hospitalized Patients with Pneumonia

Christian M. Mancini BS[1,2,*], **Megan Wimmer, PharmD**[3,*], **Lucas T Schulz, PharmD, BCIDP**[3], **Yuqing Zhang, DSc**[1,2,4,5], **Xiaoqing Fu, MS**[1,2], **Michael Postelnick, RPh, BCPS AQ-ID**[6], **Tanaya Bhowmick, MD**[7], **Francesca Lee, MD**[8], **Kimberly G. Blumenthal, MD, MSc**[1,2,4]

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

[2]The Mongan Institute, Massachusetts General Hospital, Boston, MA

[3]Department of Pharmacy, University of Wisconsin Health, Madison, WI

[4]Harvard Medical School, Boston, MA

[5]Clinical Epidemiology Research and Training, Boston University School of Medicine

[6]Northwestern Memorial Hospital, Department of Pharmacy, Chicago, IL, USA

[7]Division of Allergy, Immunology, and Infectious Diseases, Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ

[8]Department of Pathology and Internal Medicine, Division of Infectious Diseases, University of Texas Southwestern Medical Center, Dallas, TX

Abstract

Background: Treatment guidelines for pneumonia recommend beta-lactam antibiotic-based therapy. Although reported penicillin allergy is common, more than 90% of patients with reported penicillin allergy are not allergic.

Objective: We evaluated the association of a documented penicillin and/or cephalosporin (P/C) allergy to antibiotic use for the treatment of inpatient pneumonia.

Corresponding Author: Kimberly G. Blumenthal, MD, MSc, Division of Rheumatology, Allergy and Immunology, The Medical Practice Evaluation Center, The Mongan Institute, Massachusetts General Hospital 100 Cambridge Street, 16th Floor, Boston, MA 02114, p-(617) 726-3850, f-(617) 724-7441, kblumenthal@mgh.harvard.edu, twitter: @KimberlyBlumen1.

*Denotes co-first author

Conflicts of Interest

Dr. Blumenthal reports a beta-lactam allergy clinical decision support tool licensed to Persistent Systems. Megan Wimmer, Michael Postelnick, Christian Mancini, Xiaoqing Fu, Yuqing Zhang, Lucas Schulz, Tanaya Bhowmick, and Francesca Lee report no conflicts of interest.

Methods: This was a national cross-sectional study conducted among Vizient, Inc. network hospitals that voluntarily contributed data. Among hospitalized patients with pneumonia, we examined the relation of a documented P/C allergy in the electronic health record to prevalence of first-line beta-lactam antibiotic administration and alternative antibiotics using multivariable log-binomial regression with Generalized Estimating Equations.

Results: Of 2,276 inpatients receiving antibiotics for pneumonia at 95 US hospitals, 450 (20%) had a documented P/C allergy. Compared to pneumonia patients without a documented P/C allergy, patients with a documented P/C allergy had reduced prevalence of first-line beta-lactam antibiotic use (adjusted prevalence ratios [aPR] 0.79 [95%CI 0.69, 0.89]). Patients with high-risk P/C reactions (n=91) had even lower prevalence of first-line beta-lactam antibiotic use (aPR 0.47 [95% CI 0.35, 0.64]). Alternative antibiotics associated with a higher use in pneumonia patients with a documented P/C allergy included carbapenems (aPR 1.61 [95%CI 1.22, 2.13]) and fluoroquinolones (aPR 1.52 [95%CI 1.21, 1.91]).

Conclusions: Inpatients with documented P/C allergy and pneumonia were less likely to receive recommended beta-lactams and more likely to receive carbapenems and fluoroquinolones. Inpatient allergy assessment may improve optimal antibiotic therapy for the 20% of inpatients with pneumonia and a documented P/C allergy.

Keywords

Allergy; Pneumonia; EHR Data

INTRODUCTION

Approximately 10% of patients in the United States (US) report an allergy to penicillin antibiotics and 2% report an allergy to cephalosporin antibiotics.[1,2] However, up to 95% of these patients may be able to tolerate penicillin and other beta-lactam antibiotics; the prevalence of true immunoglobulin (Ig) E-mediated penicillin allergies are estimated to be 0.01 to 1%.[3,4] Even confirmed IgE-mediated allergies appear to resolve at a rate of approximately 10% per year.[5] Patients with a documented penicillin allergy are often prescribed alternative agents that may lead to inferior treatment outcomes or increase the risk of harm, including prolonged hospital length of stays, higher readmission rates, and adverse effects.[6,7] Treatment with fluoroquinolones, clindamycin, and later generation cephalosporins is associated with an increased risk of *Clostridioides difficile* colitis.[7–9] Furthermore, the unnecessary use of broad-spectrum antibiotics contributes to multidrug-resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *enterococcus* (VRE).[7,9]

Pneumonia is a common infection affecting approximately 450 million people per year and is a major cause of death across all age groups.[10] Community-acquired pneumonia (CAP) is the second most common cause of hospitalization in the US with 1.5 million admissions per year; CAP additionally accounts for 4.5 million outpatient and emergency room visits annually.[11] Hospital-acquired pneumonia (HAP) accounts for approximately 22% of all hospital-acquired infections; ventilator-acquired pneumonia (VAP), a particularly morbid subset of HAP, results in 13% mortality.[12,13]

The Infectious Disease Society of America recommends beta-lactam antibiotics as first-line pneumonia treatment.[14,15] Inpatient CAP treatment consists of a beta-lactam (e.g., ceftriaxone) plus macrolide or respiratory fluoroquinolone monotherapy.[14] Treatment of HAP and VAP includes an anti-pseudomonal beta-lactam (i.e., piperacillin-tazobactam, ceftazidime, cefepime) plus a non-beta-lactam anti-pseudomonal agent, such as an aminoglycoside, polymyxin, or fluoroquinolone, in addition to vancomycin or linezolid depending on risk factors for MRSA or VRE.[15] Across all pneumonia types and treatment regimens, beta-lactam antibiotics are generally considered more effective and less toxic than alternative antimicrobial agents.[16]

In this study, we assessed the association of documented penicillin and/or cephalosporin (P/C) allergies on inpatient antibiotic selection for the treatment of pneumonia in a large national sample of US hospitals.

METHODS

Study Design and Data Collection

This is a secondary analysis of inpatients with pneumonia at short-term acute care hospitals from a large national cross-sectional study of hospitalized patients within Vizient.[17,18] Vizient, Inc is the largest member-driven, health care performance improvement company in the US; over 3,200 acute care hospitals and more than 95% of all US academic medical centers are Vizient members. [19] The Acute Care Hospital Groups within Vizient maintains an email listserv of 147 contacts at Vizient member hospitals that was used to identify hospital participants for this study. Vizient member hospitals completed intake questionnaires from September 18, 2018 through October 12, 2018.[18] Full study participation required hospitals to submit deidentified clinical details for inpatients receiving any antibiotic on a single assessment day within the study period (October 16, 2018 through January 13, 2019). All patient data were entered by employees of the hospital with access to electronic health records (EHRs) and antibiotic utilization data as part of their professional duties (e.g., clinical pharmacist).

In this study, we included all inpatients on antibiotics with a diagnosis of pneumonia from short-term acute care hospitals. Pneumonia was diagnosed by chart review and entered into the data collection field “Infection(s) treated (if known) (select all that apply).” We grouped pneumonia patients into those treated for pneumonia alone, pneumonia with bacteremia, pneumonia with sepsis, and pneumonia with other infections.

The exposure of interest was a P/C allergy documented in the EHR regardless of reaction. Reactions were reviewed by a board certified allergist-immunologist (KGB) and categorized into risk categories: high-risk, medium-risk, and low-risk Table E1. High-risk reactions included reactions that were potentially severe IgE (e.g., anaphylaxis, shortness of breath and wheezing, rash and shortness of breath, angioedema) or other immunologically-mediated phenotypes (e.g., acute interstitial nephritis, Stevens Johnson syndrome), and adverse reactions that may be contraindications such as bone marrow suppression and colitis.

The primary outcome was use of beta-lactam antibiotics indicated for treatment of pneumonia in hospitalized patients: ceftriaxone, piperacillin-tazobactam, cefepime, or ceftazidime. The secondary outcomes considered antibiotic use by drug and drug class. Cephalosporin antibiotics were grouped by generation, except we considered ceftazidime-avibactam and ceftolozane-tazobactam as “novel cephalosporins” and ceftaroline was not grouped. All antibiotics were received or pending administration on the assessment day.

We determined hospital characteristics, including geographic location, setting, and number of staffed beds for participating sites from the Definitive Healthcare database. Geographic location was modified into US census regions: Midwest, Northeast, South, and West.[20] Setting was designated as urban or rural. Definitive Healthcare bed data come from the Medicare Cost Report, as self-reported by hospitals.[21]

Patient characteristics considered as potentially confounding factors included age, sex, race, inpatient location (e.g., intensive care unit), hospital day number, medical comorbidities (i.e., renal disease, diabetes), resistant organism (i.e., MRSA and VRE captured through infection control “flags”) colonization or infection, and type of pneumonia (pneumonia only, pneumonia and bacteremia or sepsis, or pneumonia with another infection). Renal disease was defined as an elevated creatinine on admission or renal failure of any type on the patient’s diagnoses, problem list, or admission note. A patient was considered diabetic if diabetes was listed in diagnoses, problem list, or admission note; if the patient was on diabetes medications at the time of their admission; or if the patient had a documented glycosylated hemoglobin≥6.5%.

Statistical Analysis

Numbers and frequencies were reported for categorical variables. Continuous variables were reported as means with standard deviations or medians with interquartile ranges, as appropriate considering their distributions. We examined the relation of documented P/C allergy to prevalent antibiotic use outcomes in unadjusted analyses, presenting numbers, frequencies, and p-values from Chi squared tests.

For the primary outcome of first-line indicated beta-lactam antibiotics and other commonly used drug classes with significant findings from univariable analyses, we examined the relation of documented P/C allergy to prevalent antibiotic use using log-binomial models with Generalized Estimating Equations models (to take into consideration correlation among patients at the same hospital) to estimate adjusted prevalence ratio (PR) and its 95% confidence interval (CI).[22] Informed by directed acyclic graphs, we considered patient demographics, hospital day, intensive care unit location, resistant organisms, and whether there was pneumonia alone, pneumonia with bacteremia or sepsis, or pneumonia with other infections as potentially confounding variables warranting inclusion in the final models *a priori*.

We performed two sensitivity analyses. In the first, we assessed only patients with high-risk beta-lactam allergies in the multivariable models. In the second, we used E-value to quantify the minimum strength of association that an unmeasured and residual confounder must

have with both the treatment and outcome, while simultaneously considering the measured covariates, to negate the observed treatment–outcome association.[23,24]

All p-values were 2-sided with $p<0.05$ considered statistically significant.[25] Statistical analyses were performed in SAS version 9.4 (Cary, NC, US).

Institutional Review Board

This study was reviewed by the Partners Human Research Committee and determined to be exempt/non-human subjects research (Protocol 2018P001722).

RESULTS

Participating Sites and Patients

From 129 hospitals who submitted complete data for 10,729 hospitalized patients, we identified 2,276 inpatients with pneumonia from 95 short-term acute care US hospitals (Figure 1). All US census geographic regions were represented. Most hospitals were in an urban setting (89%). There were 37 (39%) academic medical centers with mean staffed beds 390 (standard deviation 283). Inpatient allergy consultations were available at 36 (38%) and inpatient penicillin skin testing was available at 28 (29%) of the hospitals. Almost all hospitals (98%) had a formalized antibiotic stewardship program.

Patient Characteristics

Of 2,276 patients receiving antibiotics for treatment of pneumonia, 450 (20%) had a documented P/C allergy and 1,826 (80%) did not have a documented P/C allergy (Table 1). The majority of patients had low or medium risk P/C allergies (n=359, 80%) but 91 patients (20%) had high risk P/C allergies (Figure 2). Hospital characteristics were comparable by allergy status. A similar proportion of patients with and without a documented allergy had access to an inpatient allergist (50% vs 48%) and inpatient penicillin skin testing (50% vs 48%). Patients with a documented allergy had similar age but were more frequently female (62% vs 44%) and white (74% vs 61%), compared with patients without a documented P/C allergy. Inpatient locations and hospital day were not meaningfully different by P/C allergy status. MRSA was more common in patients with documented P/C allergy (13% vs 11%). The number of specified infections in addition to pneumonia were similar P/C allergy status and most patients (78%) had pneumonia only.

Antibiotic Use

First-line indicated beta-lactam antibiotics were less frequently used in patients with a documented P/C allergy (44% vs 57%, Table 2). Patients with a documented P/C allergy less frequently received penicillins (11% vs 33%), 3rd generation cephalosporins (18% vs 23%), and 4th generation cephalosporins (20% vs 13%). Many specific antibiotics were used more frequently in patients with a documented P/C allergy, including carbapenems (10% vs 6%), aztreonam (5% vs <1%), fluoroquinolones (23% vs 14%), clindamycin (4% vs 1%), and polymixins (2% vs <1%).

In the adjusted multivariable regression model, patients with a documented P/C allergy had a reduced prevalence of first-line indicated beta-lactam antibiotic use (aPR 0.79 [95% CI 0.69, 0.89], Table 3, Table E2). Intensive care unit location (aPr 1.18 [95%CI 1.10, 1.25]) and pneumonia with bacteremia or sepsis (aPR 1.25 [95% CI 1.08, 1.45]) were associated with increased first-line beta lactam antibiotic use (Table E2).

Considering only patients with high-risk P/C allergies, adjusted prevalence of first-line indicated beta-lactams was lower (aPR 0.47 [95%CI 0.35, 0.64]). To completely explain away the observed association (i.e., aPR=0.79), the association of potential residual confounder(s) with P/C documentation or use of first-line beta-lactam must be greater than 1.86.

In the adjusted multivariable regression model, patients with a documented P/C allergy had increased prevalence of carbapenem use (aPR 1.61 [1.22, 2.13], Table 3, Table E2). Considering only patients with high-risk P/C allergies, adjusted prevalence of carbapenem use was higher (aPR 2.22 [95%CI 1.29, 3.82]). To completely explain away the observed association (i.e., aPR=1.61), the association of potential residual confounder(s) with P/C allergies or use of carbapenem must be greater than 2.60.

In the adjusted multivariable regression model, patients with a documented P/C allergy had increased prevalence of fluoroquinolone use (aPR 1.52 [1.21, 1.91], Table 3, Table E2). Considering only patients with high-risk beta-lactam allergies, adjusted prevalence of fluoroquinolone use was the same (aPR 1.56 [95%CI 1.12, 2.17]). To completely explain away the observed association (i.e., aPR=1.52), the association of potential residual confounder(s) with P/C allergies or use of fluoroquinolone must be greater than 2.42.

Patients with a documented penicillin allergy had increase prevalence of 4th generation cephalosporin use (aPR 2.15 [95%CI 1.63, 2.83]) and tetracycline use (aPR 1.53 [95%CI 1.01, 2.30], Figure 3). Patients with a documented cephalosporin allergy had increase prevalence of vancomycin use (aPR 1.73 [95%CI 1.06, 2.81]). An increased prevalence of carbapenem use was observed in both patients with a penicillin (aPR 1.61 [95%CI 1.18, 2.21]) and cephalosporin allergy (aPR 2.37 [95%CI 1.28, 4.39]).

DISCUSSION

In this national cross-sectional study of 2,276 hospitalized patients who received antibiotics for the treatment of pneumonia from 95 US hospitals, the 20% who had an EHR-documented P/C allergy had a 21% lower risk of receiving a first-line indicated beta-lactam for pneumonia compared to those without a documented P/C allergy. A documented P/C allergy was also associated with an increased risk of pneumonia treatment with a fluoroquinolone antibiotic (53% increased use) and carbapenem antibiotic (61% increased use). Patients with higher risk P/C allergy histories had an even lower risk of receiving first-line beta-lactams (53% lower) and higher risk of receiving carbapenems (over 2-fold higher) for pneumonia treatment. Although uncommonly used for pneumonia, patients with a documented P/C allergy also had increased use of aztreonam, clindamycin, and polymixins in unadjusted analyses.

Beta-lactams serve as the backbone of antibiotic treatment of CAP, HAP, and VAP. However, documented beta-lactam allergies led to a 21% reduced selection of the guideline-recommended beta-lactams piperacillin-tazobactam, ceftriaxone, cefepime, and ceftazidime. Prevalence of use for these indicated beta-lactams was markedly lower (53% lower) for patients with documentation suggestive of higher risk P/C allergies, which further suggests that the allergy history is important to antibiotic choice. We additionally observed that a documented P/C allergy was associated with a 52% increased risk of fluoroquinolone treatment. Fluoroquinolones have important Food and Drug Administration "black box" warnings for tendon rupture, torsade de pointes, and abdominal aortic aneurysm/dissection.[26] The increase in fluoroquinolone use may be due to avoidance of ceftriaxone in CAP treatment for patients with documented P/C allergies. However, use of ceftriaxone in patients with penicillin allergy is safe in most patients, even those with high-risk penicillin allergy histories. For patients with a cephalosporin allergy documented in the EHR, many other non-cross-reactive cephalosporins can be safely administered.[1,2] For example, a patient with a nonanaphylactic allergy to cephalexin could be given ceftriaxone.[1,2] US hospitals should identify best practice methods to safely increase guideline-recommended beta-lactam pneumonia treatments among inpatients with documented and unverified P/C allergies.

In our study, patients with a documented P/C allergy were treated with different beta-lactams and beta-lactam alternative antibiotics. There was a 61% increased use of carbapenems in adjusted analysis with unadjusted analyses additionally identifying increased frequency of use of fourth generation cephalosporins (cefepime) and aztreonam. These beta-lactam choices are more broad-spectrum than the recommended cephalosporins for CAP, such as ceftriaxone. The increased use of cefepime and carbapenems in patients with a documented beta-lactam allergy may reflect that provider cross-reactivity concerns are less with 4th generation cephalosporins and carbapenems. Some of the increased use of cefepime and carbapenems in patients with documented beta-lactam allergy may also be a result of the poor efficacy of aztreonam for *Pseudomonas* treatment.[27] In our study, aztreonam was uncommonly used but almost exclusively reserved for patients with a documented beta-lactam allergy (5% vs <1%). While clindamycin was also uncommonly used overall, it was also more commonly used in patients with documented beta-lactam allergy (4% vs 1%); clindamycin is notably not guideline-recommended for the treatment of pneumonia.[14] Selection of more broad-spectrum beta-lactams and beta-lactam alternatives may increase the risk of adverse effects leading to discontinuation of therapy, *Clostridioides difficile* colitis, and/or multidrug-resistant organisms.[6]

The World Health Organization,[28] Centers for Disease Control and Prevention,[29,30] President's Council of Advisors on Science and Technology,[31] and Presidential Advisory Council on Combating Antibiotic Resistant Bacteria[32] have stressed the importance of antibiotic stewardship, both reducing inappropriate antibiotic use and prescribing the most targeted antibiotic.[33,34] Antimicrobial stewardship recently adapted use of penicillin allergy assessments as a method of reducing inappropriate antibiotic use and prescribing targeted antibiotic therapy to improve patient safety and reduce antibiotic resistance.[2,35] Tools to assess documented beta-lactam allergies in inpatient settings include institution-specific guidelines that promote penicillin skin testing and/or beta-lactam test doses or drug

challenges (i.e., giving the indicated drug in a two-step observed setting).[36] Implementation of penicillin allergy skin testing and drug challenges among inpatients have been associated with the safe increased use of beta-lactam antibiotics.[9,36] In a systemic review of over 1,000 inpatients who received penicillin skin testing, 95% of patients were not allergic.[37] However, since penicillin skin testing access is currently quite limited in the inpatient setting – in our study just 38% of hospitals caring for inpatients with pneumonia had access to inpatient allergy consultation and 29% had access to inpatient penicillin skin testing,[18] hospital guidelines that use the reaction history to direct the use of different first-line beta-lactams in patients with documented beta-lactam allergies may be more feasible.[38] Additional strategies include administration of amoxicillin directly to hospitalized patients with low-risk penicillin allergies with the goal of disproving and "delabeling" the penicillin allergy.[39]

While our study data came from a large sample of almost 100 diverse US hospitals, sites voluntarily participated in this study, and as such they were not sampled deliberately as to provide a representative national inpatient cohort. However, while this could impact our prevalence of documented P/C allergy estimate in pneumonia patients (20%), this would be less likely to impact our assessment of the relation of documented P/C allergy to antibiotic use for pneumonia patients. Given that all participating sites had active antibiotic stewardship programs, we consider that if a selection bias were present, it would bias our findings towards the null hypothesis and thus render our findings conservative. Cross-sectional data permitted us to assess antibiotics used or ordered on one day only, without consideration of antibiotic duration or cumulative utilization metrics such as days of therapy per 1000 patient days. We were also unable to determine whether inpatient allergy access or procedures impacted first-line beta-lactam treatment for pneumonia. While clinical data to validate the diagnosis of a bacterial pneumonia (e.g., chest x-ray, sputum culture) were not collected, the chart reviewed pneumonia diagnosis was determined by individuals who routinely perform auditing from health records for antibiotic stewardship practices. We did not have access to clinical data that guide pneumonia treatment, such as microbiology detail or type of pneumonia (CAP, HAP, VAP). Given that increased antimicrobial resistant organisms has been observed in patients with a documented penicillin allergy, it is possible there were differences in pneumonia organisms by P/C allergy. Although prior colonization or infection with resistant gram-negative rods (GNRs) can impact antibiotic treatment decisions, GNRs flags were not captured by our study. However, our multivariable adjustment notably included ICU location (as a proxy for pneumonia severity), pneumonia type, and MRSA/VRE colonization/infection in addition to age, sex, race, and hospital day. We also performed quantitative bias analyses using E-value to further assess unmeasured confounding and found that to completely explain away the weakest significant association we identified would require a potential unmeasured or residual confounder(s) greater than 1.86. This seems unlikely because we are not aware of any such potential confounder(s) and the magnitude would need to be greater than those we already included in our multivariable model.

In summary, we present the largest and most comprehensive US study to date demonstrating the prevalence and impact of documented P/C allergy on the treatment of inpatient pneumonia. The 20% of patients with a documented P/C allergy were treated less commonly

with guideline-indicated beta-lactam antibiotics and more commonly with fluroquinolones and carbapenems. Methods to reduce or eliminate beta-lactam allergies documented in the EHR are needed to increase prescribing of more narrow-spectrum, guideline-recommended beta-lactam agents for the treatment of inpatient pneumonia.

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Abbreviations:

US	United States
Ig	Immunoglobulin
MRSA	Methicillin-resistant *Staphylococcus aureus*
VRE	Vancomycin-resistant *Enterococcus*
CAP	Community-acquired pneumonia
HAP	Hospital-acquired pneumonia
VAP	Ventilator-acquired pneumonia
P/C	Penicillin and/or Cephalosporins
HER	Electronic health record
PR	Prevalence ratio
CI	Confidence Interval

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Highlights Box:

What is already known about this topic?

Pneumonia affects over 450 million people per year, with treatment typically including beta-lactam antibiotics. Patients with unconfirmed penicillin or cephalosporin allergy may not receive beta-lactam antibiotics.

What does this article add to our knowledge?

We present the largest and most comprehensive US study to date demonstrating that pneumonia patients with a documented penicillin and/or cephalosporin allergy were treated less commonly with guideline-indicated beta-lactams.

How does this study impact current management guidelines?

Methods to reduce or eliminate unverified penicillin and/or cephalosporin allergies are needed to increase prescribing of guideline-recommended beta-lactams for the treatment of inpatient pneumonia.

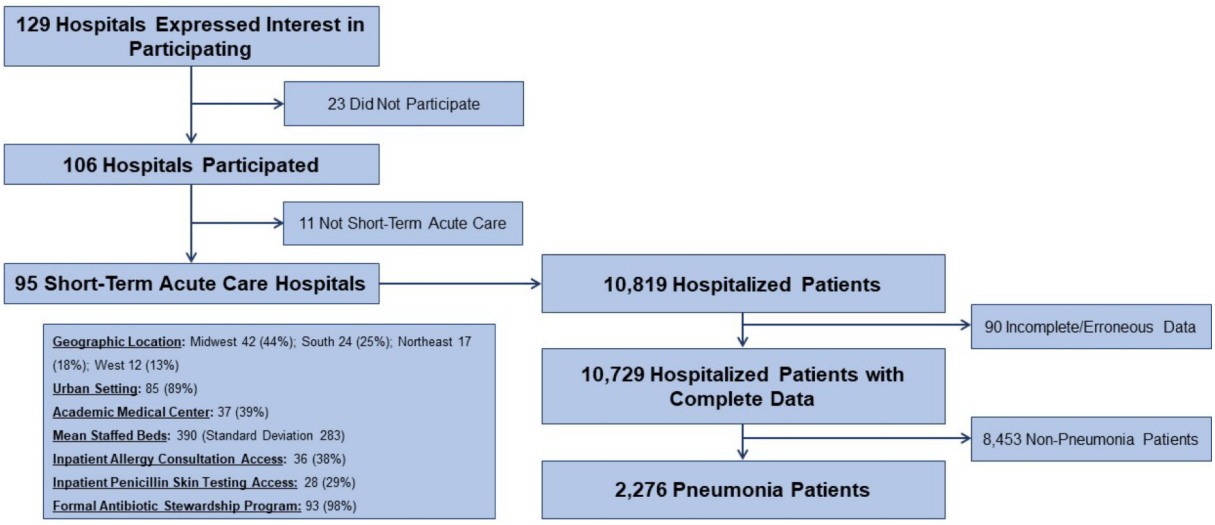

Figure 1. Participating sites and patients.

Of 129 hospitals who expressed interest in participating in this study, 95 (74%) acute care hospitals submitted their hospital characteristics and complete, cross-sectional patient data on 10,729 inpatients on antibiotics. This analysis considers the 2,276 (21%) treated for pneumonia.

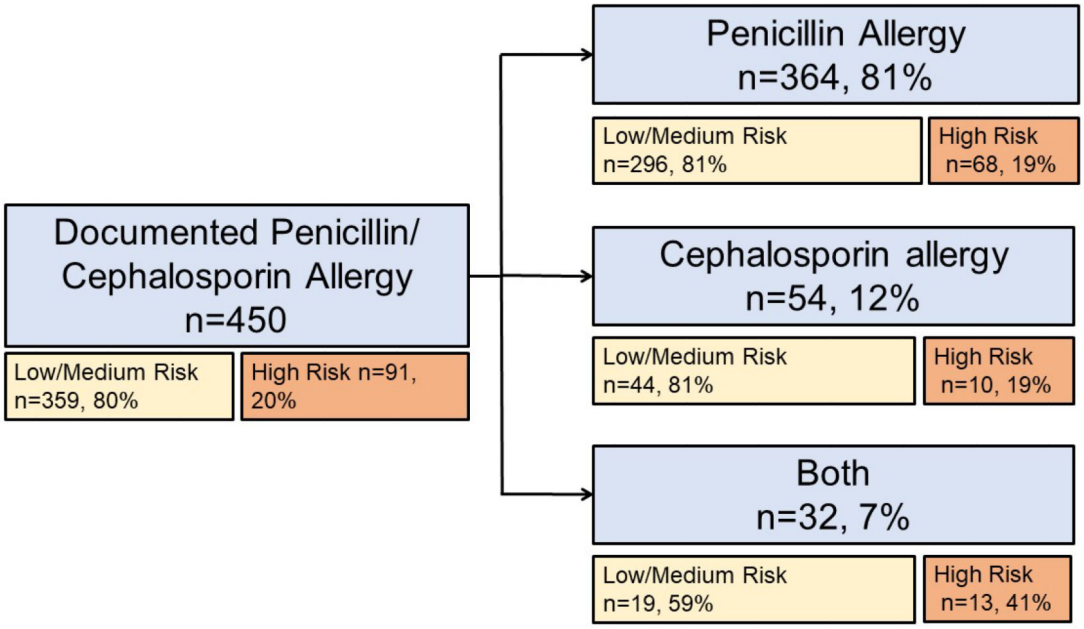

Figure 2.

Penicillin and/or cephalosporin allergies documented in hospitalized inpatients with pneumonia (n=450). Risk categories were determined from coded and free text (i.e., “other”) reaction entries.

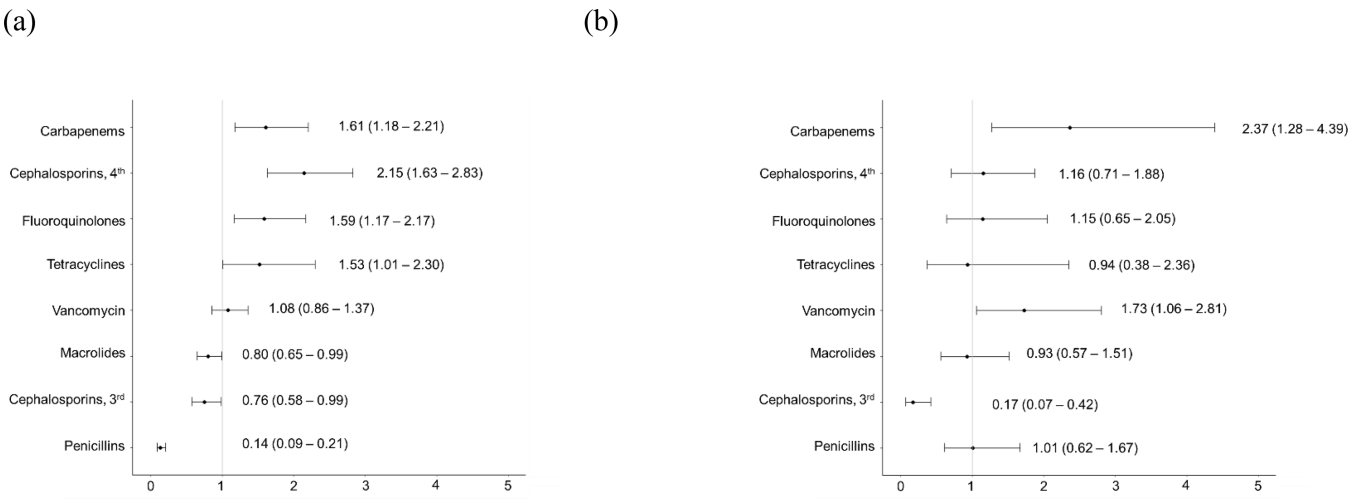

Figure 3:

Multivariable assessment of the impact of a documented (a) penicillin allergy and (b) cephalosporin allergy on inpatient antibiotic use for US inpatients receiving antibiotics for pneumonia. The adjusted prevalence ratios and 95% confidence intervals are displayed. Adjusted prevalence ratios are adjusted for age, sex, hospital day, number of staffed beds, geographic location, and diabetes.

Table 1.

Characteristics of pneumonia patients and hospitals by documented allergy status.

	Documented P/C Allergy (n = 450)	No P/C Allergy (n = 1,826)
Hospital Characteristics		
Geographic Location		
Midwest	231 (51)	884 (48)
Northeast	85 (19)	346 (19)
South	106 (24)	459 (25)
West	28 (6)	137 (8)
Urban Setting	420 (93)	1,674 (92)
Bed Size		
< 100	15 (3)	94 (5)
100–399	158 (35)	690 (38)
≥ 400	277 (62)	1,042 (57)
Academic Medical Center	243 (54)	919 (50)
Number of Staffed Beds (Mean ± SD)	527 ± 331	497 ± 327
Inpatient Allergy Consultation Access	225 (50)	869 (48)
Inpatient Penicillin Skin Testing Access	225 (50)	869 (48)
Formal Antibiotic Stewardship Program	448 (100)	1,817 (100)
Allergist Part of Antibiotic Stewardship Program	17 (4)	83 (5)
Patient Characteristics		
Age (Mean ± SD)	63 ± 19	61 ± 21
Female	277 (62)	795 (44)
Race		
White	334 (74)	1,122 (61)
Black	72 (16)	419 (23)
Asian	4 (1)	32 (2)
Other	40 (9)	253 (14)
Inpatient Location		
General Medical Floor	215 (48)	782 (43)
General Surgery Floor	27 (6)	109 (6)
Adult ICU	89 (20)	449 (25)
Cardiology/Telemetry	53 (12)	160 (9)
Oncology	12 (3)	79 (4)
Pediatric Floor	11 (2)	43 (2)
Pediatrics or Neonatal ICU	1 (<1)	36 (2)
Other	32 (7)	136 (7)
Hospital Day (Median, IQR)	4 [2, 8]	4 [2, 8]
Renal Disease	97 (22)	411 (23)
Diabetes	160 (36)	567 (31)
MRSA Colonization/Infection	57 (13)	193 (11)

	Documented P/C Allergy (n = 450)	No P/C Allergy (n = 1,826)
VRE Colonization/Infection	13 (3)	46 (3)
Infection(s) Treated		
Pneumonia only	351 (78)	1,422 (78)
Pneumonia and bacteremia	9 (2)	35 (2)
Pneumonia and sepsis	28 (6)	120 (7)
Pneumonia and other infections*	59 (13)	234 (13)

Abbreviations: P/C, penicillin and/or cephalosporin; SD, standard deviation; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin resistant *Enterococcus*.

*Other infections include: skin and soft tissue infections, surgical prophylaxis, urinary tract infection, intrabdominal infection, medical prophylaxis, *Clostridioides difficile*, neutropenic fever, endocarditis, and other

Table 2.

Antibiotic use among inpatients with pneumonia by documented beta-lactam allergy status

	All (n = 2,276)	Documented P/C (n = 450)	No Documented P/C Allergy (n = 1,826)	P-Value
First-line Indicated Beta-Lactam Antibiotics *	1241 (55)	199 (44)	1042 (57)	< 0.001
Beta-Lactam Antibiotics				
Penicillins †	650 (29)	48 (11)	602 (33)	<0.001
Cephalosporins, 1st generation	42 (2)	8 (2)	34 (2)	0.91
Cephalosporins, 2nd generation	24 (1)	8 (2)	16 (1)	0.09
Cephalosporins, 3rd generation	503 (22)	79 (18)	424 (23)	0.01
Cephalosporins, 4th generation	327 (14)	91 (20)	236 (13)	<0.001
Novel cephalosporins ‡	14 (1)	2 (<1)	12 (1)	0.61
Ceftaroline	6 (<1)	2 (<1)	4 (<1)	0.40
Carbapenems	158 (7)	44 (10)	114 (6)	0.01
Aztreonam/Monobactams	25 (1)	24 (5)	1 (<1)	<0.001
Non-Beta-Lactam Antibiotics				
Macrolides	550 (24)	99 (22)	451 (25)	0.23
Vancomycin	526 (23)	113 (25)	413 (23)	0.26
Fluoroquinolones	361 (16)	102 (23)	259 (14)	<0.001
Doxycycline	171 (8)	46 (10)	125 (7)	0.01
Metronidazole	119 (5)	33 (7)	86 (5)	0.03
Sulfamethoxazole-trimethoprim	112 (5)	25 (6)	87 (5)	0.49
Aminoglycosides	67 (3)	17 (4)	50 (3)	0.24
Linezolid	53 (2)	17 (4)	36 (2)	0.02
Clindamycin	30 (1)	17 (4)	13 (1)	<0.001
Polymixins ¶	19 (1)	10 (2)	9 (<1)	<0.001

Abbreviations: P/C, penicillin and/or cephalosporin;

* Piperacillin-tazobactam, ceftriaxone, cefepime, ceftazidime

† Amoxicillin, amoxicillin-clavunate, ampicillin, ampicillin-sulbactam, nafcillin, oxacillin, penicillin G, and piperacillin-tazobactam

J Allergy Clin Immunol Pract. Author manuscript; available in PMC 2022 August 01.

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‡Ceftazidim-avibactam, ceftolozane-tazobactam

¶Colistimethate and polymyxin

Table 3.

Adjusted prevalence ratios for antibiotic use considering beta-lactam allergy compared to no beta-lactam allergy.

	All P/C Allergy (n=450)		High-Risk P/C Allergy (n=91)	
	Unadjusted Prevalence Ratio (95% CI)	**Prevalence Ratio Adjusted (95% CI)**	**Unadjusted Prevalence Ratio (95% CI)**	**Prevalence Ratio Adjusted (95% CI)**
First-Line Indicated Beta-Lactams*	0.77 (0.68, 0.88)	0.79 (0.69, 0.89)†	0.47 (0.35, 0.63)	0.47 (0.35, 0.64)†
Carbapenems	1.57 (1.18, 2.08)	1.61 (1.22, 2.13)‡	2.15 (1.25, 3.70)	2.22 (1.29, 3.82)‡
Fluoroquinolones	1.60 (1.28, 2.00)	1.52 (1.21, 1.91)†	1.59 (1.14, 2.22)	1.56 (1.12, 2.17)†

Abbreviations: P/C, penicillin and/or cephalosporin;

*Piperacillin-tazobactam, ceftriaxone, cefepime, ceftazidime

†Adjusted for age, white race, sex, hospital day, ICU location, resistant organism colonization/infection and type of pneumonia

‡Adjusted for, ICU location, and pneumonia type

Table E1.

Documented penicillin and/or cephalosporin reactions considered high-risk in patients with pneumonia

High Risk Reactions
Acute Interstitial Nephritis
Anaphylaxis
Rash, GI upset, and itching
Rash, itching, and swelling
Angioedema
Hypotension
Stevens Johnson syndrome/toxic epidermal necrolysis/Drug rash eosinophilia and systemic symptoms (DRESS) syndrome/Acute generalized exanthematous pustulosis (AGEP)
Swelling
Rash and skin peeling
Peripheral eosinophilia
Tongue got puffy
Neutropenia
Patient notes bone marrow suppression
Colitis
Bronchospasm and fever
Shortness of breath and wheezing
Rash and shortness of breath
Shortness of breath
Shortness of breath and other
Cough and shortness of breath
Medium Risk Reactions
Rash and GI Upset
Rash
Hives and diarrhea
Rash, hives and fever
Rash and hives
Rash, hives and itching
Rash and itching
Rash and fever
Rash and vomiting
Mental status change
Hives
Hives and itching
Low Risk Reactions
Diarrhea and itching
Diarrhea
Dizziness
Fever

Itching and flushing
GI Upset
Not documented
Myalgia
Patient denies having this allergy
Tolerated a penicillin class antibiotic
Itching
Nausea
Nausea and vomiting
Palpitations
Vomiting

Table E2.

Multivariable association between documented penicillin and/or cephalosporin allergy and prevalence of antibiotic treatment for pneumonia

	First-Line Beta-Lactam Treatment	
	PR [95% CI]	**p-value**
Age	1.00 (1.00, 1.00)	0.05
Female	1.00 (0.94, 1.06)	0.95
White	0.98 (0.90, 1.07)	0.72
Hospital day	0.99 (0.99, 1.00)	< 0.001
Intensive care unit location	1.18 (1.10, 1.25)	< 0.001
MRSA or VRE colonization/infection	0.96 (0.86, 1.08)	0.49
Type of pneumonia		
Pneumonia only	1.00 (0.90, 1.12)	0.99
Pneumonia with bacteremia or sepsis	1.25 (1.08, 1.45)	0.002
Pneumonia with other infections	ref	ref
	Carbapenem Treatment	
	PR [95% CI]	**p-value**
Intensive care unit location	2.01 (1.52, 2.65)	<0.001
MRSA or VRE colonization/infection	2.11 (1.56, 2.85)	<0.001
	Fluoroquinolones Treatment	
	PR [95% CI]	**p-value**
Age	1.00 (1.00, 1.01)	0.23
Female	1.00 (0.85, 1.19)	0.97
White	1.20 (0.95, 1.53)	0.13
Hospital day	1.00 (0.99, 1.01)	0.53
Intensive care unit location	0.69 (0.55, 0.87)	0.002
MRSA or VRE colonization/infection	0.74 (0.52, 1.06)	010
Type of pneumonia		
Pneumonia only	1.05 (0.78, 1.40)	0.76
Pneumonia with bacteremia or sepsis	0.89 (0.57, 1.38)	0.59
Pneumonia with other infections	ref	ref

Abbreviations: PR, prevalence ratio; CI, confidence interval; MRSA, methicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant Enterococcus; ref, reference