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High-Cost High-Need Patients: The Impact of Reported Penicillin Allergy

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Abstract

Objectives: Over 90% of patients who report a penicillin allergy have the allergy disproved when tested. Unnecessary use of alternative (non-beta-lactam) antibiotics can result in more treatment failures and adverse reactions. We described the prevalence and impact of a reported penicillin allergy in high-cost high-need (HCHN) patients.

Study Design: Retrospective cohort.

Methods: We identified HCHN patients in a care management program of an urban academic medical center (01/01/2014–12/31/2016). We used multivariable logistic regression models to determine the association between a reported penicillin allergy and antibiotic use. We used multivariable Poisson regression models to determine the association between a reported penicillin allergy, with or without multiple drug intolerance syndrome (≥ 3 reported drug allergies), and healthcare utilization.

Results: Of 1,870 HCHN patients, 383 (20%) reported penicillin allergy, 835 (45%) had multiple drug intolerance syndrome, and 290 (16%) had both. HCHN patients reporting penicillin allergy had an increased odds of beta-lactam alternative antibiotic use (adjusted Odds Ratio ([aOR] 3.84 [95%CI 2.17, 6.80])). Healthcare utilization was significantly higher for patients reporting a

penicillin allergy alone (adjusted relative risk [aRR] 1.13 [95% CI 1.03, 1.25]), and with concurrent multiple drug intolerance syndrome (aRR 1.20 [95% CI 1.08, 1.34]).

Conclusions: HCHN patients had a high burden of reported drug allergy. A reported penicillin allergy conferred a 4-fold increased odds of beta-lactam alternative antibiotic use. Reporting penicillin allergy, with and without multiple drug intolerance syndrome, was associated with significantly more healthcare utilization. HCHN care management programs should consider systematic drug allergy evaluations to optimize antibiotic use in these fragile patients.

Précis:

Among high-cost high-need patients, penicillin allergy was commonly reported and was associated with sub-optimal antibiotic choices and increased healthcare utilization.

Keywords

hypersensitivity; penicillin allergy; clindamycin; beta-lactam; skin test; resistance; utilization; antibiotic

INTRODUCTION

High cost high need (HCHN) patients comprise five percent of patients nationwide and account for 50% of health care spending.¹ While less than 5% of Medicare spending is considered potentially preventable, almost three-quarters of the preventable costs are incurred by this HCHN subset.² Addressing modifiable risk-factors present in HCHN patients may improve clinical outcomes while curbing overall US healthcare spending.^{1,3}

Prominent comorbidities in HCHN patients include conditions associated with increased risk of bacterial infection, such as diabetes mellitus, chronic obstructive pulmonary disease, and chronic renal failure.⁴ Acute bacterial lung and urinary tract infections are among the most common reasons for preventable hospitalizations in HCHN patients;^{2,5,6} bacterial pneumonia alone comprised almost one-quarter of preventable hospital costs in HCHN patients in 2006, resulting in an excess spending of \$7.2 billion dollars.⁷

Beta-lactam antibiotics are first-line treatments for many of these bacterial infections, however, approximately 10% of Americans report a penicillin allergy, limiting treatment choice.⁸ Patients with infections who report a penicillin allergy are often administered alternatives to beta-lactam antibiotics that can be less effective, resulting in treatment failures;^{9,10} more toxic, resulting in adverse drug reactions;^{9,10} and broader-spectrum, resulting in higher risks of antibiotic resistance.^{11,12} However, over 90% of patients reporting a penicillin allergy have their allergy disproved when formally evaluated.⁸

Active care management that combines chronic disease management and case management improves care and reduces costs in HCHN patients.^{13–16} Although medication management is a proven feature of successful care management programs for HCHN patients,^{16,17} programs have generally not previously accessed or addressed drug allergies.¹⁸ To assess the potential benefits of proactive drug allergy evaluation in the HCHN population, we

described the epidemiology and impact of reported penicillin allergy on antibiotic use and healthcare utilization in HCHN patients.

METHODS

Study Design and Population

This study was conducted at a large Boston-based academic medical center with an active care management program for HCHN patients. HCHN patients received their primary care at one of 15 affiliated practice sites. We considered a 36-month study period (January 1, 2014 through December 31, 2016) and included only HCHN patients continuously followed by the active care management program for at least 34 of these months. All data were retrieved exclusively from electronic sources. The study was approved by the Partners Human Subjects Committee (Protocol 2017P000456).

Exposure

The primary exposure of interest was a reported penicillin allergy, defined as any reported allergy or intolerance to any penicillin antibiotic. After being electronically retrieved, allergy data were manually verified by chart review to determine the first date of penicillin allergy “active” status, the reaction(s) listed, and any allergy status changes that occurred during the study period. Given that antibiotic prescribing might not be affected for patients reporting only a penicillin intolerance, we considered a sensitivity analysis definition of a reported penicillin allergy that excluded patients who had penicillin gastrointestinal intolerance only. We separately considered multiple drug intolerance syndrome as an exposure, defined as a reported allergy or intolerance to three or more drugs (one of which may have been a penicillin) at the time of study entry.^{19,20}

Outcomes

The primary outcome was antibiotic use, defined as antibiotic exposure, regardless of duration, captured by any inpatient antibiotic administration or outpatient antibiotic prescribed in the study period. We considered narrow-spectrum beta-lactam antibiotics as any penicillins, other than anti-pseudomonal penicillins or penicillin class antibiotic/beta-lactamase inhibitor combinations, and first or second generation cephalosporins.^{11,21,22} Beta-lactam alternative antibiotics included fluoroquinolones, macrolides, vancomycin, clindamycin, sulfonamides, tetracyclines, aminoglycosides, and linezolid.^{11,21,22}

The secondary outcome was healthcare utilization, which considered inpatient, emergency, and outpatient visit counts. Inpatient visits excluded residential inpatient stays, and emergency visits excluded those that led to an inpatient visit. Outpatient visits were specified as primary care or specialist visits.

Key Variables

Key variables assessed included patient demographics, insurance, comorbidities, corticosteroid use, other drug allergies, and resistant organisms. Comorbidities considered were cardiovascular disease, diabetes, renal disease, and cancer, defined from established diagnostic codes, when available (Supplemental Table 1).^{23–25} Charlson comorbidity index

(CCI) was electronically calculated based on diagnostics codes.^{26,27} Systemic corticosteroid use, a binary variable, was considered yes for any patients with a documented inpatient administration and/or an outpatient prescription for an oral or parenteral steroid. Other reported drug allergies were defined similarly to a reported penicillin allergy (i.e., any reported allergy or intolerance). We captured total number of reported allergies, reported cephalosporin allergies, and reported sulfonamide antibiotic allergies. Colonization or infection with *methicillin-resistant Staphylococcus aureus* (MRSA) was determined by the presence of a MRSA microbiology culture. Colonization or infection with vancomycin-resistant *Enterococcus* (VRE) was determined by the presence of a VRE microbiology culture.

Statistical Analysis

Numbers with frequencies and means with standard deviations (SD) were used to describe categorical and continuous variables, respectively. We used simple regression models (i.e., models with a single independent variable) to assess bivariate relationships. Multivariable regression models were used to assess the relationship between the exposure(s) and outcomes. Because a patient's penicillin allergy status can change during the study period (from no reported penicillin allergy to reported penicillin allergy, or vice versa), we used generalized estimating equations (GEE) to construct regression models to account for the within patient correlation. Multivariable logistic regression models were used to determine the association of penicillin allergy status on antibiotic use and multivariable Poisson regression models were used to determine the association between penicillin allergy status and number of healthcare visits per follow-up year.

We considered patient demographics and CCI as potentially confounding variables warranting inclusion in the final models *a priori*. All other key variables were individually assessed for confounding. While we identified other drug allergies as a confounder, this variable was determined to be collinear with the exposure and was not included in the final models. We report Odds Ratios (OR) with 95% confidence intervals for antibiotic use outcomes and Relative Risks (RR) with 95% confidence intervals (CI) for healthcare visits. All p-values were 2-sided with $p < 0.05$ considered statistically significant. Statistical analyses were performed in SAS version 9.4 (Cary, NC, USA).

RESULTS

Cohort Description

Of 1,870 patients enrolled in the study, 383 (20%) had a reported penicillin allergy at any time during the study period. There were 835 (45%) patients with multiple drug intolerance syndrome, including 290 patients (16%) with both a reported penicillin allergy and multiple drug intolerance syndrome. The 383 patients reporting penicillin allergy had a total of 513 reactions, commonly rash or dermatitis ($n=179$, 35%), unknown ($n=83$, 16%), urticaria or hives ($n=75$, 15%), gastrointestinal upset ($n=74$, 14%), angioedema or swelling ($n=42$, 8%), and anaphylaxis ($n=31$, 6%, Supplemental Table 2). There were 40 patients whose only penicillin reaction was gastrointestinal upset alone. There were 25 patients whose penicillin allergy status changed during the study period: 19 patients had a new penicillin allergy label

applied and 6 patients had their penicillin allergy label resolved (4 [67%] of which were resolved by allergy testing). Therefore, the final cohort consisted of 1,895 penicillin allergy observations in 1,870 unique patients, with a total 5,599 person-years (PY) of follow-up time for analysis.

Age, race, and body mass index did not differ by penicillin allergy status (Table 1). Patients reporting a penicillin allergy were more often female (73% vs 56%, $p<0.001$). The most common insurance was an accountable care organization (ACO) external risk (89%), with fewer patients part of a commercial external risk-based contract (11%). Active smoking was uncommon (8%), and former smokers comprised 38% of patients.

The CCI was high on average (4.74 [SD 3.30]), but also not differential by penicillin allergy status. Patients had cardiovascular disease (61%), diabetes (51%), renal disease (45%), and cancer (46%), not differential by reported penicillin allergy status. Systemic corticosteroid use was present in 34% overall, with no difference by penicillin allergy status.

Only 14% of patients had no reported drug allergies overall. One or two drug allergies were present in 42% of patients overall, three or four drug allergies were present in 21% of patients and more than five drug allergies were present in 24% of patients. Compared to patients not reporting penicillin allergy, patients with a reported penicillin allergy more frequently had more total reported drug allergies ($p<0.001$). Reported cephalosporin and sulfonamide antibiotic allergies were present in 3% and 16% of patients overall, more frequently in patients reporting penicillin allergy (cephalosporin 6% vs 2%, $p<0.001$; sulfonamide antibiotic 26% vs 13%, $p<0.001$). MRSA and VRE colonization and/or infection were overall low at baseline (4%), without a difference by penicillin allergy status.

Primary Outcome: Antibiotic Use

Antibiotics in HCHN patients included fluoroquinolones ($n=912$), first generation cephalosporins ($n=576$), macrolides ($n=529$), vancomycin ($n=431$), third generation cephalosporins ($n=380$), sulfonamides ($n=360$), tetracyclines ($n=334$), and clindamycin ($n=184$, Table 2). HCHN patients used beta-lactam alternative antibiotics more frequently than narrow-spectrum beta-lactam antibiotics overall.

The use of narrow-spectrum beta-lactam antibiotics was lower in patients reporting a penicillin allergy (17% vs 47%, $p<0.001$, Table 2). In the multivariable adjusted regression model, patients reporting penicillin allergy had lower odds of narrow-spectrum beta-lactam antibiotic use (adjusted OR 0.16 [95%CI 0.12, 0.23]), compared to those reporting no penicillin allergy (Figure 1A). This association strengthened in the sensitivity analysis that excluded patients with penicillin gastrointestinal intolerance only (adjusted OR 0.11 [95%CI 0.08, 0.16], data not shown).

Alternative antibiotic use was higher in patients reporting a penicillin allergy (80% vs 71%, $p<0.001$, Table 2). Specific alternative antibiotics used more in patients reporting a penicillin allergy were fluoroquinolones (53% vs 47%, $p=0.026$), clindamycin (28% vs 5%, $p<0.001$) and tetracyclines (25% vs 16%, $p<0.001$). In the multivariable regression model, patients reporting penicillin allergy had an increased odds of beta-lactam alternative antibiotic use

(adjusted OR 3.84 [95%CI 2.17, 6.80], Figure 1B), with clindamycin use having the greatest odds ratio (adjusted OR 8.40 [95%CI 5.99,11.79]), compared to those reporting no penicillin allergy. This association between reported penicillin allergy and beta-lactam alternative antibiotic use strengthened in the sensitivity analysis that excluded patients with penicillin gastrointestinal intolerance only (adjusted 5.64 [95% CI 2.78, 11.44]).

Secondary Outcome: Healthcare Utilization

Total number of visits per follow-up year were higher for patients reporting a penicillin allergy (3.03 vs 0.70, $p<0.001$) and those who also had multiple drug intolerance syndrome (2.05 vs 0.44, $p<0.001$, Table 3). Inpatient visits per follow-up year were comparable between patients with and without a reported penicillin allergy, but emergency, primary care, and specialist outpatient visits were more frequent for patients reporting a penicillin allergy (Table 3). All visit types were more frequent in patients reporting multiple drug intolerance syndrome (Table 3).

In the multivariable adjusted analysis, number of healthcare visits were significantly greater for patients with a reported penicillin allergy compared to those not reporting a penicillin allergy (RR 1.13 [95% CI 1.03, 1.25], Table 4). The relative risk demonstrating increased visits was nearly identical when excluding patients with penicillin gastrointestinal intolerance only. Patients with reported penicillin allergy and concurrent multiple drug intolerance syndrome had a higher incidence of healthcare utilization (RR 1.20 [95% CI 1.08, 1.34], Table 4), compared to those without penicillin allergy and multiple drug intolerance syndrome.

DISCUSSION

We performed a retrospective cohort study of HCHN patients and identified that over 1 in 5 of these patients had a reported penicillin allergy, and almost half had multiple drug intolerance syndrome. Patients had risk factors for bacterial infections, but MRSA and VRE were infrequent, suggesting that narrow-spectrum beta-lactams would be potentially useful treatments in this population. HCHN patients had high antibiotic use overall; HCHN patients with a reported penicillin allergy were about 7-fold less likely to be exposed to narrow-spectrum beta-lactams and over 3-fold more likely to be exposed to beta-lactam alternative antibiotics. HCHN patients with penicillin allergy alone had 13% more healthcare visits; there were 20% more healthcare visits if there was concurrent multiple drug intolerance syndrome.

The HCHN patients had a markedly high prevalence of reported penicillin allergy (20%). While the prevalence of reported penicillin allergy varies among adult populations, it is often reported from 6 to 10%.^{19,28,29} Penicillin allergy reporting increases with increasing age, and our HCHN cohort comprised older adults (mean age 77).³⁰ Hospitalized patients and patients with cancer have even higher reported penicillin allergy prevalences (up to 15%).^{31,32,33,34} Multiple drug intolerance syndrome was identified in almost half (45%) of HCHN patients, but previous studies indicated that general patient populations rarely have multiple drug intolerance syndrome (from 2 to 6%).^{19,20}

Penicillin allergy testing removes false penicillin allergy labels in over 90% of patients who carry a historical penicillin allergy diagnosis.⁸ Testing includes a detailed allergy history, and often procedures such as penicillin skin testing and/or drug administration under medical observation (i.e., a drug challenge). Although penicillin allergy evaluation is broadly encouraged by organizations such as the Centers for Disease Control and Prevention and the National Quality Forum, currently less than 1% of Americans with a documented penicillin allergy report having been tested.^{35–37} Drug allergy testing for other antibiotics is available in some US allergy practices, and can be used to disprove prior drug allergies and clarify true drug reactions in patients with multiple drug intolerance syndrome. Antibiotic allergy evaluations in one Australian center disproved 85% of all reported antibiotic allergies.²¹ While fewer antibiotic allergies may be disproved in a HCHN population, it is quite likely that many antibiotic allergies will be found untrue, which would improve antibiotic prescribing and minimize risks of treatment failure and adverse effects.

The HCHN patients had highly prevalent risk factors for bacterial infections that included diabetes (51%), cancer (46%), and systemic corticosteroid exposure (34%). Additionally, almost half of the patients (46%) were current or former smokers, a strong risk factor for bacterial pneumonia which was the single most common preventable hospitalization reason in HCHN patients.^{2,5,6} Increasing the use of narrow-spectrum beta-lactam antibiotics in HCHN patients may not only serve to improve their clinical outcomes but may reduce utilization and avert healthcare costs. While to date this has not been assessed specifically, one study demonstrated that patients reporting a penicillin allergy who received penicillin allergy evaluations had lower antibiotic costs in the year after their allergy testing compared to the year before their allergy testing.³⁸

The resistant organisms MRSA and VRE were surprisingly uncommon in HCHN patients (4%). This low level of colonization with resistant organisms suggests that, when infected, HCHN patients may have infections treatable with narrow-spectrum beta-lactams. As such, reclaiming the use of narrow-spectrum beta-lactams in HCHN patients previously labelled as penicillin-allergic would be helpful. Prior studies identified that patients reporting penicillin allergy had an increased prevalence of MRSA and VRE,³⁹ and an increased incidence of new MRSA, with more than half of the increased MRSA risk attributable beta-lactam alternative antibiotic prescribing.¹¹ Addressing reported penicillin allergies, therefore, is also a useful antibiotic stewardship tool for fighting antimicrobial resistance.⁸

A reported penicillin allergy in HCHN patients was associated with a 7-fold lower use of narrow-spectrum beta-lactams and an over 3-fold increased use of alternative antibiotics. These associations magnified to 9-fold less likely to receive a narrow-spectrum beta-lactam and 6-fold more likely to receive beta-lactam alternatives when excluding penicillin gastrointestinal intolerance patients in a sensitivity analysis. A prior population-based outpatient cohort found that patients reporting penicillin allergy had approximately 4-fold increased risks of macrolide and clindamycin exposure and 2-fold increased fluoroquinolone exposure.¹¹ While we found that all beta-lactam alternative antibiotics were used more frequently in HCHN in this study, the largest difference by reported penicillin allergy status was clindamycin use, where an over 8-fold increased odds of use was identified in patients reporting a penicillin allergy. Clindamycin is considered one of the most common causative

antibiotics for *Clostridioides difficile* infection (CDI).⁴⁰ Prior studies support that CDI incidence is greater for patients with a reported penicillin allergy, and that some of the observed increased CDI risk is directly attributable to macrolide, clindamycin, and fluoroquinolone prescribing.¹¹ As such, if routine penicillin allergy evaluations could improve antibiotic prescribing, CDI cases might be averted. Recently, patients with penicillin allergy histories who were penicillin tested were subsequently exposed to less clindamycin and macrolides than matched patients not penicillin tested.⁴¹

Although all patients were high utilizers, reporting a penicillin allergy, both alone and with concurrent multiple drug intolerance syndrome, conferred a 10–20% significant increase in health care utilization. The observed utilization differences were driven by increased emergency and outpatient visits. Given that narrow-spectrum beta-lactams are first-line therapies for many infections,⁸ utilization might be reduced after penicillin allergy label removal. Indeed, one prior matched cohort study determined that patients with penicillin allergy histories who received penicillin allergy evaluations had fewer outpatient visits ($p < 0.001$), emergency visits ($p = 0.29$), and hospital days ($p < 0.001$) per coverage year during follow-up compared with matched controls with penicillin allergy histories who did not receive the penicillin allergy evaluation.⁴¹

This study used a retrospective design. Although we reduced misclassification through manual review of the primary exposure (penicillin allergy) and studied outcomes derived from electronically-captured antibiotic and utilization data, misclassification could still exist. Because drug dosage and duration details were not consistently available, we studied antibiotic and corticosteroid use, regardless of dose and duration. However, drug use did include both inpatient and outpatient use through administration and prescription data. We assessed total healthcare system visits as our measure of healthcare utilization, and did not consider inpatient length of stay nor procedures and tests performed. We assessed many potential confounders in our analysis but could not consider all possible confounders; other illnesses and/or social factors (e.g., living situation) might impact antibiotic choice or healthcare visits. However, because these factors would not be related to the exposure of penicillin allergy, their inclusion into our models would be unlikely to yield different results. Our findings come from one sample of HCHN patients enrolled in the care management program of a single large academic medical center in the Boston area; such patients may not be representative of other HCHN patients in the US.

CONCLUSIONS

This large, retrospective cohort analysis demonstrates that there is a high burden of drug allergy in HCHN patients and substantial room for improvement in the antibiotic choices made for HCHN patients reporting a penicillin allergy. Systematic efforts focused on penicillin and drug allergy management in HCHN patients may benefit both the patients and the healthcare systems tasked with supporting the care of these complex patients in a cost-conscious manner.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosures:

Dr. Blumenthal reports a clinical decision support tool used institutionally for beta-lactam allergy at Partners HealthCare System which is licensed to Persistent Systems.

Abbreviations:

HCHN	High-cost high-need
CCI	Charlson comorbidity index
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
VRE	vancomycin-resistant <i>Enterococcus</i>
SD	standard deviations
OR	Odds Ratios
RR	Relative Risks
CI	confidence intervals
PY	Person-year
CDI	<i>Clostridioides difficile</i> infection

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Take-Away Points:

- Over 20% of high-cost high-need (HCHN) patients reported a penicillin allergy, and 45% had multiple drug intolerance syndrome (≥ 3 reported drug allergies).
- HCHN patients had highly prevalent risk factors for bacterial infections: diabetes (51%), cancer (46%), and systemic corticosteroid exposure (34%).
- A reported penicillin allergy was associated with an almost 4-fold increased odds of any alternative antibiotic use; clindamycin use increased over 8-fold.
- Reporting a penicillin allergy, with or without multiple drug intolerance syndrome, conferred a 10–20% increase in healthcare utilization.
- HCHN patients are ideal candidates for systematic drug allergy evaluations, including penicillin allergy testing, to optimize first-line antibiotic treatments.

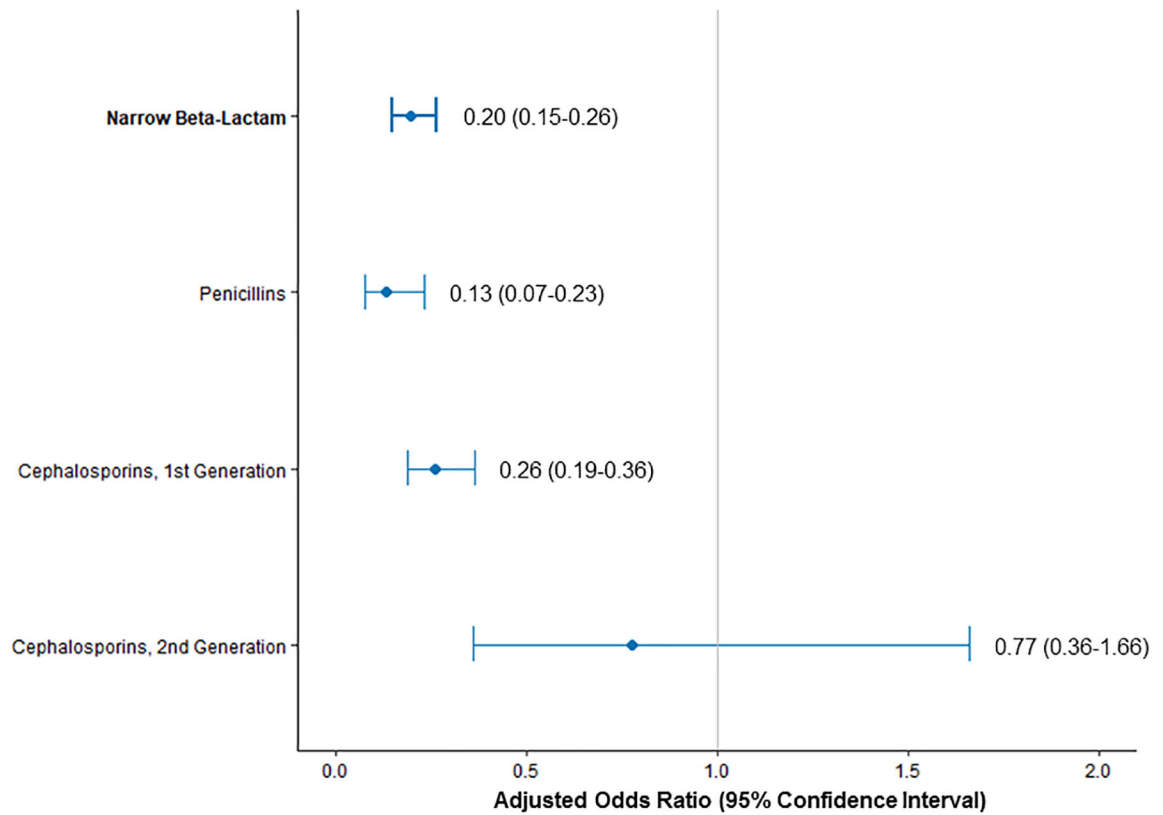


Figure 1A.

The association of reported penicillin allergy on narrow-spectrum antibiotic use in high-cost high-need patients Odds ratios are adjusted for age, sex, race, and Charlson comorbidity index. Penicillins exclude anti-*Pseudomonas* penicillins and penicillins that are combined with beta-lactamase inhibitors (e.g., tazobactam). See methods for details.

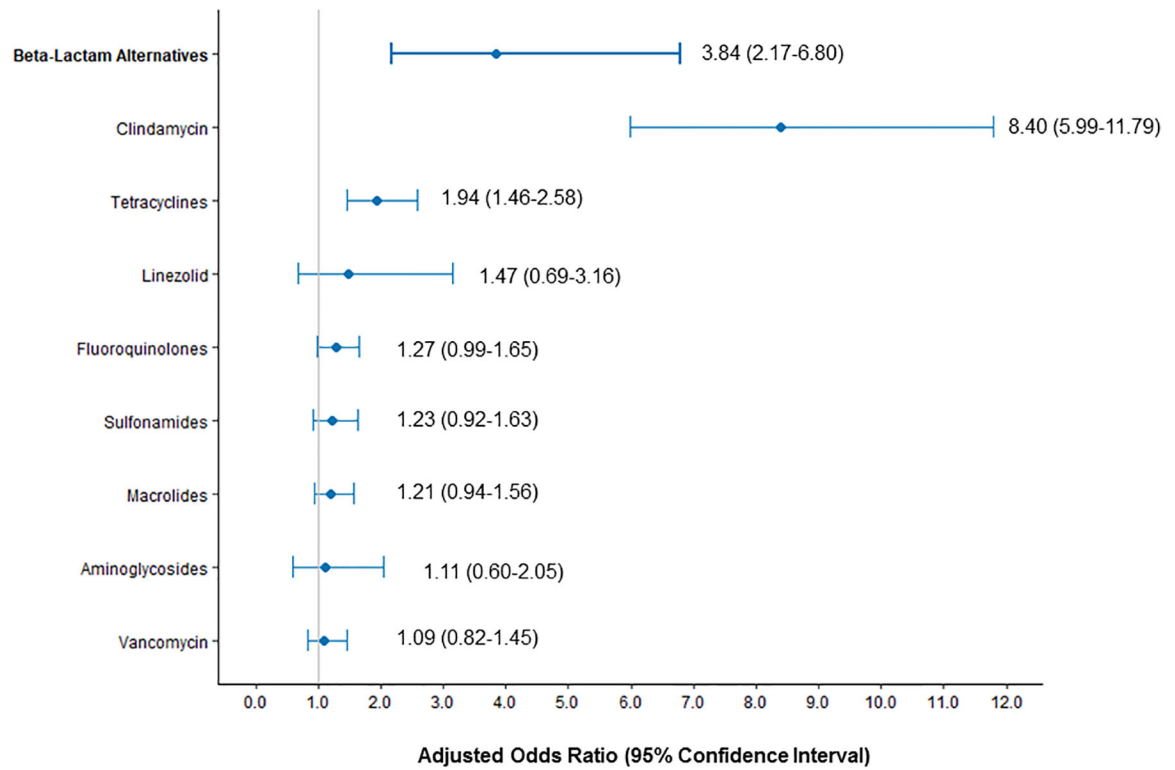


Figure 1B.

The association of reported penicillin allergy on beta-lactam alternative use. Odds ratios are adjusted for age, sex, race, and Charlson comorbidity index.

Table 1.

High-cost high-need patient characteristics by reported penicillin allergy status.

	All Patients (n = 1,895)			Reported Penicillin Allergy (n = 383)			No Reported Penicillin Allergy (n = 1,512)			P-value ^b
	n	Person-year	%PY ^a	n	Person-year	%PY	n	Person-year	%PY	
Age in years (SD)			77 (12.3)			78 (12.2)			77 (12.3)	0.13
Female sex	1,132	3,338	60	279	806	73	853	2,532	56	<0.001
Race/ethnicity										0.65
White	1,617	4,779	85	321	926	84	1,296	3,853	86	
Black	122	356	6	26	75	7	96	282	6	
Hispanic	50	150	3	12	36	3	38	114	3	
Asian	35	105	2	6	18	2	29	87	2	
Other	40	117	2	13	38	3	27	79	2	
Unknown	31	93	2	5	15	1	26	78	2	
BMI										0.27
<18.5	34	102	2	6	18	2	28	84	2	
18.5-<25.0	438	1,284	23	82	232	21	356	1,053	23	
25.0-<30.0	622	1,848	33	120	352	32	502	1,495	33	
30.0+	801	2,366	42	175	505	46	626	1,861	41	
Insurance										0.69
ACO external risk	1,681	4,967	89	344	995	90	1,337	3,972	88	
Commercial external risk	206	611	11	38	110	10	168	501	11	
Other ^c	8	21	<1	1	2	<1	7	19	<1	
Smoking status										0.18
None	876	2,572	46	191	543	49	685	2,029	45	
Former	714	2,117	38	140	410	37	574	1,707	38	
Current	151	449	8	22	64	6	129	385	9	
Unknown	154	461	8	30	90	8	124	371	8	
Charlson comorbidity index	1,895	5,599	4.74 (3.30)	383	1,107	4.80 (3.22)	1,512	4,493	4.72 (3.31)	0.76
Comorbidities										
Cardiovascular disease	1,154	3,401	61	233	666.9	60	921	2,734	61	0.71
Diabetes	967	2,856	51	195	566	51	772	2,290	51	0.76

	All Patients (n = 1,895)			Reported Penicillin Allergy (n = 383)			No Reported Penicillin Allergy (n = 1,512)			^b p-value
	n	Person-year	% PY ^a	n	Person-year	% PY	n	Person-year	% PY	
Renal disease	865	2,544	45	178	509	46	687	2,035	45	0.87
Cancer	862	2,557	46	181	531	48	681	2,026	45	0.79
Systemic corticosteroid use	651	1,919	34	137	394	36	514	1,525	34	0.98
Total reported drug allergies										< 0.001
0	258	764	14	4	9	<1	254	755	17	
1–2	789	2,336	42	89	253	23	700	2,083	46	
3–4	403	1,185	21	104	299	27	299	886	20	
5 or more	445	1,315	24	186	545	49	259	769	17	
Other reported drug allergies										< 0.001
Cephalosporin antibiotics	53	153	3	24	69	6	29	84	2	
Sulfonamide antibiotics	298	868	16	99	284	26	199	585	13	
Prior resistant organisms										
MRSA colonization or infection	134	398	7	30	88	8	104	310	7	0.82
VRE colonization or infection	57	168	4	10	28	3	47	140	3	0.53

^aPercentage of person-year was calculated as person-year/total person-year. Age and Charlson comorbidity index numbers shown are means (standard deviations)

^bUnadjusted p-values for reported penicillin allergy were calculated using GEE logistic model.

^cOther includes: Non-risk other, non-risk PPO/other, United, none.

Abbreviations: BMI, body mass index; ACO, accountable care organization; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*

Table 2.

Unadjusted association of reported penicillin allergy status and antibiotic use

	All Patients (n = 1,895)			Reported Penicillin Allergy (n = 383)			No Reported Penicillin Allergy (n = 1,512)			P-value ^b
	n	Person-year	%PY ^a	n	Person-year	%PY	n	Person-year	%PY	
Narrow-spectrum beta-lactams^c	767	2,275	41	66	188	17	701	2,087	47	< 0.001
Penicillins ^d	317	940	17	13	36	3	304	905	20	< 0.001
Cephalosporins, 1 st generation	576	1,707	31	51	143	13	525	1,563	35	< 0.001
Cephalosporins, 2 nd generation	50	150	3	9	27	2	41	123	3	0.64
Beta-lactam alternatives^e	1,367	4,041	73	306	889	80	1,061	3,152	71	< 0.001
Fluoroquinolones	912	2,695	48	204	587	53	708	2,108	47	0.026
Macrolides	529	1,561	28	122	354	32	407	1,206	27	0.075
Vancomycin	431	1,269	23	90	258	23	341	1,011	23	0.81
Clindamycin	184	536	10	108	312	28	76	224	5	< 0.001
Sulfonamides	360	1,068	19	84	245	22	276	823	18	0.14
Tetracyclines	334	984	18	96	282	25	238	702	16	< 0.001
Aminoglycosides	64	188	3	14	39	4	50	149	3	0.78
Linezolid	35	101	2	10	27	2	25	75	2	0.23
Other beta-lactams										
Beta-lactamase penicillins	395	1,167	21	18	46	4	377	1,121	25	< 0.001
Cephalosporins, 3 rd generation	380	1,128	20	68	196	18	312	932	21	0.14
Carbapenems	40	115	2	8	21	2	32	95	2	0.94

^aPercentage of person-year was calculated as person-year/total person-year.^bUnadjusted p-values for penicillin allergy were calculated using GEE logistic regression model.^cIncludes penicillins and cephalosporins in the 1st and 2nd generations.^dOther than beta-lactamase penicillins^eBeta-lactam alternatives included fluoroquinolones, macrolides, parenteral vancomycin, clindamycin, sulfonamides, tetracyclines, aminoglycosides, and linezolid. Patients may use beta-lactam alternatives multiple times.^fBeta-lactamase penicillins included piperacillin-tazobactam, amoxicillin-clavulanate/clavulanic acid and ampicillin-sulbactam.

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Table 4.
Association between reported penicillin allergy and other drug allergy status on healthcare visits

Healthcare Visits	Unadjusted		Adjusted model ^a		Adjusted model ^b	
	RR (95% CI)	P-value	RR (95% CI)	p-value	RR (95% CI)	P-value
Reported penicillin allergy ^c	1.12 (1.01, 1.24)	0.034	1.14 (1.04, 1.27)	0.008	1.13 (1.03, 1.25) ^d	0.014
Reported penicillin allergy with concurrent multiple drug intolerance syndrome ^e	1.19 (1.06, 1.33)	0.002	1.22 (1.09, 1.36)	< 0.001	1.20 (1.08, 1.34)	< 0.001

^a Age, sex, race-adjusted

^b Age, sex, race, and charlson comorbidity index-adjusted.

^c The reference group is patients without a reported penicillin allergy.

^d In the sensitivity analysis excluding the 40 patients with penicillin gastrointestinal intolerance only, aRR 1.13 [95% CI 1.02, 1.25].

^e The reference group is patients without penicillin allergy and multiple drug intolerance syndrome.