RESEARCH LETTER

Association Between Penicillin Allergy Documentation and Antibiotic Use

Approximately half of hospitalized patients receive antibiotics, and more than 10% of these patients have a penicillin allergy documented in the medical record.[1] Hospitalized patients with ongoing infections who report an allergy to penicillin have an increased risk of adverse drug events, including *Clostridioides difficile* infection, when not treated with a β-lactam antibiotic.[2] Allergy assessment with or without diagnostic testing disproves more than 90% of documented penicillin allergies.[1]

Supplemental content

The inpatient prevalence and effects of documented penicillin allergies has been exclusively investigated in single hospitals or health care systems. We used a large cross-sectional database of inpatients receiving antibiotics to assess the prevalence and association of documented penicillin allergy with inpatient antibiotic use in the US.

Methods | This cohort study used cross-sectional inpatient data collected through Acute Care Hospital Groups within Vizient Inc, Irving, Texas, from September 2018, through January 2019 (eMethods in the Supplement). Data analysis was performed from January 2019, through January 2020. The study was reviewed by the Partners Human Research Committee, Boston, Massachusetts, and was determined to be exempt because it was categorized as nonhuman research.

The exposure was an allergy to any penicillin antibiotic documented in the medical record. The outcomes were antibiotic use overall and for specified indications, considering individual antibiotic classes and 2 antibiotic groupings: (1) β-lactam alternative antibiotics and (2) narrow-spectrum β-lactam antibiotics.

We examined the association of documented penicillin allergy with antibiotic use overall and for specified indications, such as pneumonia, skin and soft-tissue infection, urinary tract infection, and prophylaxis for surgical procedures. We used generalized estimating equations models to account for clustering by hospital with logit link in SAS, version 9.4 (SAS Institute Inc). We report adjusted odds ratios (aORs) with 95% CIs.

Results | Of 10 992 inpatients (5567 [51%] male; mean [SD] age, 57.0 [21.5] years) receiving antibiotics at 106 hospitals, 1741 patients (16%) had a penicillin allergy documented in the medical record. Most penicillin reactions (946 of 2112 [45%]) were cutaneous. Patient characteristics by penicillin allergy status were similar.

Compared with patients without a documented penicillin allergy, patients with a documented penicillin allergy had higher β-lactam alternative antibiotic use (1114 of 1741 [64%] vs 4438 of 9251 [48%]) and lower narrow-spectrum β-lactam antibiotic use (227 of 1741 [13%] vs 2811 of 9251 [30%]).

In the fully adjusted model (**Table**), patients with a documented penicillin allergy had increased odds of β-lactam alternative antibiotic use (aOR, 1.94; 95% CI, 1.74-2.17), with especially high odds of clindamycin use (aOR, 5.34; 95% CI, 3.99-7.13). Patients with a documented penicillin allergy had lower odds of narrow-spectrum β-lactam antibiotic use (aOR, 0.35; 95% CI, 0.31-0.40).

The association between a documented penicillin allergy and β-lactam alternative antibiotic use was stronger among patients receiving antibiotics for urinary tract infection (aOR, 2.07;

Table. Multivariable Assessment of the Association of Documented Penicillin Allergies With Inpatient Antibiotic Use

Antibiotic	Odds ratio (95% CI)[a]	
	Partially adjusted model[b]	Fully adjusted model[c]
β-lactam alternatives[d]	2.04 (1.82-2.27)	1.94 (1.74-2.17)
Vancomycin	1.21 (1.07-1.36)	1.14 (1.01,1.29)
Fluoroquinolones	1.93 (1.64-2.26)	1.91 (1.61-2.25)
Macrolides	0.94 (0.78-1.12)	0.94 (0.78-1.12)
Sulfonamides	1.14 (0.90-1.45)	1.16 (0.91-1.48)
Tetracyclines	1.41 (1.07-1.85)	1.37 (1.03-1.83)
Clindamycin	5.78 (4.39-7.61)	5.34 (3.99-7.13)
Aminoglycosides	1.74 (1.34-2.25)	1.53 (1.16-2.02)
Linezolid	2.30 (1.45-3.63)	2.18 (1.37-3.48)
Narrow-spectrum β-lactams[e]	0.33 (0.29-0.38)	0.35 (0.31-0.40)
Penicillins[f]	0.17 (0.12-0.25)[g]	0.17 (0.12-0.25)[g]
Cephalosporins		
First generation	0.44 (0.37-0.52)	0.47 (0.40-0.55)
Second generation	1.30 (0.79-2.12)	1.34 (0.82-2.18)
Other β-lactams		
Cephalosporins		
Third generation	0.87 (0.75-1.02)	0.92 (0.78-1.08)
Fourth generation	1.44 (1.20-1.72)	1.47 (1.23-1.76)
Carbapenems	1.83 (1.48-2.26)	1.72 (1.38-2.14)
Aztreonam or monobactams	22.49 (14.39-35.15)	18.44 (11.13-30.55)

[a] Documented penicillin allergy compared with no documented penicillin allergy.

[b] Adjusted for age, sex, race/ethnicity, length of hospitalization, inpatient location within the hospital, and number of infections.

[c] Adjusted for age, sex, race/ethnicity, length of hospitalization, number of staffed beds, hospital geographic location, diabetes, cephalosporin allergy, inpatient location within the hospital, and number of infections.

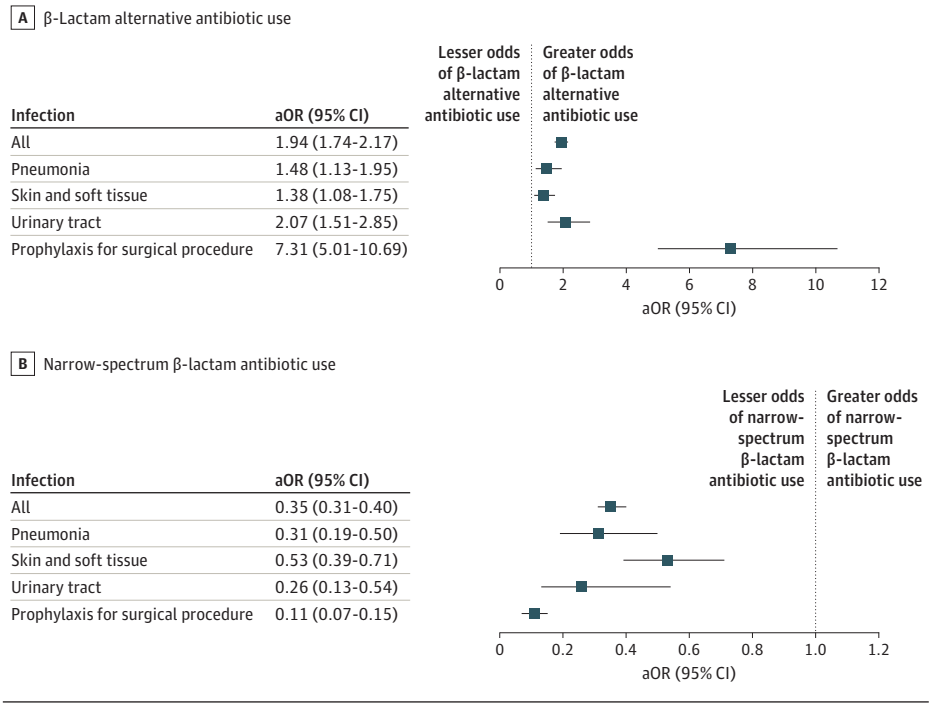
[d] Includes vancomycin, fluoroquinolones, macrolides, sulfonamides, tetracyclines, clindamycin, aminoglycosides, and linezolid.

[e] Includes all penicillins except antipseudomonal penicillins and first- and second-generation cephalosporins.

[f] Other than antipseudomonal penicillins.

[g] Similar when considering amoxicillin-clavulanic acid, ampicillin-sulbactam, and piperacillin-tazobactam together: adjusted odds ratio, 0.18 (95% CI, 0.14-0.22).

Figure. Association of Documented Penicillin Allergies With Inpatient Antibiotic Use Among US Inpatients



Adjusted odds ratios (aORs) are adjusted for age, sex, race/ethnicity, length of hospitalization, number of staffed beds, hospital geographic location, diabetes, cephalosporin allergy, inpatient location within the hospital, and number of specific infections treated.

95% CI, 1.51-2.85) and as prophylaxis for surgical procedures (aOR, 7.31; 95% CI, 5.01-10.69]) (**Figure**, A). The association between a documented penicillin allergy and narrow-spectrum β-lactam antibiotic use was stronger among patients receiving antibiotics for pneumonia (aOR, 0.31; 95% CI, 0.19-0.50), urinary tract infection (aOR, 0.26; 95% CI, 0.13-0.54), and as prophylaxis for surgical procedures (aOR, 0.11; 95% CI, 0.07-0.15]) (Figure, B).

Discussion | In this cross-sectional study of 10 992 inpatients receiving antibiotics from 106 US hospitals, 16% of patients with a documented penicillin allergy had almost 2-fold higher odds of receiving a β-lactam alternative antibiotic. We reported the largest increased odds of a specific β-lactam alternative for clindamycin, an antibiotic associated with *C difficile* infection risk, for which use was more than 5-fold more likely. We identified more than 7-fold increased odds of alternative antibiotic use for inpatients with a documented penicillin allergy receiving antibiotics as prophylaxis for a surgical procedure, a narrow-spectrum β-lactam antibiotic indication for reducing infection risk at the surgical site.[1,3] Patients with a penicillin allergy documented in their medical record also had more than 18-fold increased odds of aztreonam use.

When considering that a small number of the inpatients reporting penicillin allergy would have been truly allergic to penicillin, at least 90% of these antibiotic substitutions were likely unnecessary.[1,4] Although penicillin allergy evaluations are recommended as part of inpatient antibiotic stewardship,[5] most hospitals do not have access to penicillin allergy assessment.[6] However, allergy history alone is associated with a high negative predictive value (96.5%; 95% CI, 94.1%-97.8%) for excluding true penicillin allergy.[4]

Although our study data came from a large sample of hospitals, these data may not be nationally representative. Cross-sectional data did not permit determination of cumulative antibiotic use metrics.

The 16% of inpatients with a penicillin allergy documented on their medical record were treated more commonly with alternatives that may be inferior and/or associated with more adverse drug events. Hospitals may target patients prescribed clindamycin or patients with planned surgical procedures for inpatient penicillin allergy interventions.

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