

Original Article

The Effect of Penicillin Allergy Testing on Future Health Care Utilization: A Matched Cohort Study

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What is already known about this topic? An unverified penicillin allergy is a significant public health problem.

What does this article add to our knowledge? Demonstrates that penicillin allergy testing significantly reduces health care utilization, outpatient visits, emergency department visits, and total hospital days, and alters the types of antibiotics used in our study cohort, during over 3 years of follow-up.

How does this study impact current management guidelines? It adds additional support to making the practice of verifying most penicillin allergies in outpatients a routine part of health care.

BACKGROUND: The effect that penicillin allergy testing has on future health care utilization is uncertain.

OBJECTIVE: Determine whether penicillin allergy testing affects future overall health care utilization as measured by outpatient department (OPD) visits, emergency department (ED) visits, and hospital days.

METHODS: Potential cases and control subjects were penicillin allergic Kaiser Permanente Southern California members who had at least 2 visits between 2010 and 2012 and at least 1 year of continuous health plan coverage before their index visit.

RESULTS: It was possible to match 308 (73.2%) of the potential cases to 1251 unique controls, on the basis of age, sex, weighted Charlson comorbidity index, drug class allergies, OPD visits, ED visits, and hospital days during the years before their index visit. Cases and controls were then followed for an average of 3.6 and 4.0 years, respectively. Based on results analyzed using a generalized linear mixed model, cases were estimated to have 0.09 fewer OPD visits ($P < .001$), 0.13 fewer ED visits ($P = .29$), and 0.55 fewer hospital days ($P < .001$) per health plan coverage year during follow-up compared with controls.

Cases were exposed to more penicillins and first- and second-generation cephalosporins and less clindamycin and macrolides. **CONCLUSIONS:** Penicillin allergy testing, primarily done in the setting of an outpatient Allergy consultation, was associated

with significantly less health care utilization during 3.6+ years of follow-up and greater use of narrow-spectrum antibiotics. Penicillin allergy testing has a favorable cost-benefit ratio for the incremental cost of testing versus future health care utilization and improves antibiotic stewardship. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: Adverse reactions; Allergy consultation; Antibiotic stewardship; Charlson comorbidity index; Cost; Drug allergy; Emergency department; Health care utilization; Hospital; Outpatient; Oral challenge; Penicillin allergy testing; Utilization

A nonconfirmed penicillin allergy is a significant public health problem.¹ The Choosing Wisely initiative of the American Board of Internal Medicine Foundation has recommended that physicians “don’t overuse non-beta-lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation.”² The Centers for Disease Control and Prevention, along with the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, and the American Academy of Allergy, Asthma, and Immunology, has recommended using penicillin allergy testing as an important part of antibiotic stewardship.³⁻⁵ Most patients with a history of penicillin allergy tolerate penicillin because most penicillin allergy histories are inaccurate, incomplete, and/or unverified. In Kaiser Permanente Southern California (KPSC), less than 4% of individuals with a history of penicillin allergy are penicillin allergy skin test or oral amoxicillin challenge positive.⁶ There have been a number of studies that have looked at changes in antibiotic use after penicillin allergy testing.⁷⁻¹⁵ There are no publications on the effect penicillin allergy testing has on future health care utilization and antibiotic exposures over a multiple-year period in a large group of individuals with a history of penicillin allergy.

METHODS

This study was reviewed and approved by the KPSC Institutional Review Board. The KPSC currently cares for more than 4 million members and has used an electronic health record (EHR) since 2007.

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This study was funded by ALK and the Kaiser Permanente Health Care Program. Conflicts of interest: E. Macy has received research support from ALK and payment for participation in review activities from BioMarin. Y.-H. Shu declares no relevant conflicts of interest.

Received for publication March 8, 2016; revised January 21, 2017; accepted for publication February 22, 2017.

Available online ■■

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2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2017.02.012>

Abbreviations used

CCI- Charlson comorbidity index
 ED- Emergency department
 EHR- Electronic health record
 KPSC- Kaiser Permanente Southern California
 OPD- Outpatient department

Case subjects were selected from the 421 KPSC San Diego members with at least 1 year of health plan coverage and who had been penicillin allergy tested between January 28, 2010, and March 23, 2012. This cohort has been reported on previously in part.⁶ The *index visit* for cases was defined as the date of the health care visit immediately before the date that penicillin allergy testing was performed. The index visit defined the end of the lead-in period. The follow-up period started with the penicillin allergy testing visit. In almost all penicillin allergy tested subjects, an Allergy consultation occurred at the testing visit.

Control subjects were selected from the 241,504 KPSC members in the San Diego service area with at least 1 year of health plan coverage, who were not tested for penicillin allergy, but had an active penicillin *allergy* on at least 2 health care visits between 2010 and 2012. For each control, a health care visit was selected to be the index visit. The next visit was defined as the first follow-up visit, to mimic the visit when penicillin allergy testing was performed in cases. The index visit represented the visit where a decision for penicillin allergy testing was made for case subjects or could have been made for control subjects.

For baseline measurements, age, drug class allergies, and weighted Charlson comorbidity index (CCI) were collected at the index visit date; frequencies of health care utilization per health plan coverage year, including outpatient department (OPD) visits, emergency department (ED) visits, and hospital days, were calculated in the 2 years before the index visit, defined as the lead-in period. Subjects were followed up to the end of the study on March 31, 2015, defined as the end of the follow-up period. For follow-up measurements, drug class allergies and weighted CCI were collected at the end of study; frequencies of health care utilization per coverage year were calculated from the index visits to the end of the follow-up period.

Up to 5 unique controls were matched to a single case on a set of demographic characteristics and health care utilization at baseline. Subjects were matched on sex, type of index visit (OPD, ED, or hospitalization), weighted CCI group (grouped as weighted CCI equal to 0, 1, and 2+), and age (± 5 years) at the nearest index visit dates. The mean time difference between cases and controls for the index visits was 0.45 ± 0.72 years. In the lead-in period, subjects were matched on OPD visits per coverage year (± 0.2), ED visits per coverage year (± 1), and hospital days per coverage year (± 1). To ensure the success of matching, the ranges of matching factors were determined using an iterative process that resulted in no statistically significant differences ($P > .05$) between final matched cases and controls. The nearest-neighbor algorithm was used per iteration to identify the closest controls matched to each case, subjected to the specified restrictions. It was possible to match 308 (73.2%) of the penicillin allergy tested cases to 1251 nontested penicillin *allergic* controls.

Antibiotic courses were collected for both the lead-in and follow-up periods. Antibiotic utilization was calculated as the frequency of antibiotic courses per coverage year. Cases and controls were not matched for lead-in period antibiotic utilization. The definition of

an antibiotic course and how active drug class *allergies* at the index visit and at the end of the follow-up period were determined have been previously described in detail.¹⁵ In brief, an antibiotic course was an uninterrupted exposure to a specific antibiotic by a specific route. There was a maximum of 23 potential drug classes used to characterize drug class *allergies*. All penicillin class antibiotic use, possible penicillin-associated adverse drug reactions, and penicillin *allergy* field comments and status were confirmed by manual chart review of the written comments in the EHR in both cases and controls.

Under a successful matching of individual demographic characteristics and health care utilization at baseline, the effects of penicillin allergy testing were assessed as the differences in health care utilization between matched cases and controls in the follow-up period. The generalized linear mixed model was applied to estimate and test the health care utilization differences.¹⁶ Case status treated as a predictor and a health care utilization was an outcome in a model, where the linear fixed effects of case status were interpreted as the estimated health care utilization difference in the follow-up period between cases and controls. Poisson distribution was assumed for outcomes due to the skewed distributions of health care utilization. Controls relativeness within a matched set was estimated by specifying the compound-symmetry structure. If the model could be converged, the standard variance components structure was specified instead. For categorical outcomes, weighted CCI groups at baseline were tested using the Friedman chi-square test to address the concern of related controls per matched case.¹⁷ Antibiotic courses were additionally measured without being matched at baseline. By assuming no correlations with the matching factors, antibiotic courses used through the end of follow-up were tested using a standard chi-square or Fisher exact test. All statistical analyses were performed using SAS 9.2 statistical software (Carey, NC).

RESULTS

There were only 4 positive penicillin allergy test results for the 308 matched cases (1.3%), and only 2 (0.65%) were tested during a hospitalization. The mean time between index visit and penicillin allergy testing visit was 28.2 ± 30.6 days. There were 89 (28.9%) cases 14 years or younger at the time of penicillin allergy testing. Matched case and control subjects' baseline demographic characteristics and health care utilization are presented in Table I. Descriptive statistics for controls were calculated by inversely weighting the size of the matched case-control sets. Cases and controls were matched on weighted CCI groups to increase the matching availability. The lead-in annual frequencies of OPD visits, ED visits, and hospital days were successfully matched at nonsignificant levels ($P > .05$). Note that cases had significantly higher lead-in period antibiotic usage ($P < .001$).

Comparisons in health care utilization during the follow-up period are presented in Table II. There was an average of 3.6 years (a total of 1109.4 patient-coverage years) and 4 years (a total of 5014.5 patient-coverage years) of follow-up for cases and controls, respectively. During the follow-up period, penicillin allergy tested subjects averaged 0.09 fewer follow-up OPD visits ($P < .001$) and 0.55 fewer hospital days ($P < .001$) per coverage year. Also, fewer 0.13 average ED visits were noted for penicillin allergy tested subjects, but the difference was not significant.

The different antibiotics used by cases and controls during the follow-up period, along with new antibiotic *allergies* reported

TABLE I. Baseline demographic characteristics and health care utilization matched for case and control cohorts

Variables	Median (first quartile, third quartile)		Effect [†]	P value [‡]
	Cases	Controls*		
N	308	1251		
Sex: female, n (%)	202 (65.6)	813 (65)		
At index visit date				
Age (y)	39.7 (11.7, 61.5)	35.4 (11.9, 58)	−0.003	.77
Drug class allergies	2 (2, 3)	2 (2, 3)	0.047	.25
Weighted CCI group, n (%)				.21
0	131 (42.5)	564 (45.1)		
1	107 (34.7)	437 (34.9)		
2+	70 (22.7)	250 (20)		
Weighted CCI	1 (0, 1)	1 (0, 1)	−0.046	.44
During 2-y lead-in period				
Health plan coverage (d)	730.5 (730.5, 730.5)	730.5 (730.5, 730.5)	−0.002	.48
OPD visits/coverage year	8.5 (5, 13)	7.6 (4.5, 12)	0.011	.6
ED visits/coverage year	0 (0, 0.5)	0 (0, 0.5)	0.182	.14
Hospital days/coverage year	0 (0, 0)	0 (0, 0)	0.126	.27
Antibiotic courses/coverage year [‡]	1.5 (0.5, 2.9)	1 (0.5, 2)	0.248	<.001

*Medians and quartiles were calculated by inversely weighting the size of each matched case-control set.

[†]Fixed effects of case status and the P values estimated using generalized linear mixed models. Differences in counts of weighted CCI groups were tested using Friedman χ^2 test.[‡]Not matched at baseline.**TABLE II.** Follow-up demographic characteristics and health care utilization for matched case and control cohorts

Variables	Median (first quartile, third quartile)		Effect [†]	P value [‡]
	Cases	Controls*		
N	308	1251		
At end date of study				
Drug class allergies	1 (1, 2)	2 (1, 3)	−0.511	<.001
Weighted CCI	1 (0, 2)	1 (0, 2)	−0.017	.72
During follow-up period				
Health plan coverage (d)	1340 (1157.5, 1556)	1546 (1230, 1784)	−0.119	<.001
OPD visits/coverage year	5 (2.9, 8.3)	4.8 (2.7, 8.5)	−0.089	<.001
ED visits/coverage year	0 (0, 0.3)	0 (0, 0.4)	−0.132	.29
Hospital days/coverage year	0 (0, 0)	0 (0, 0)	−0.553	<.001
Antibiotic courses/coverage year [‡]	0.9 (0.3, 1.9)	0.7 (0.2, 1.5)	0.137	<.001

*Medians and quartiles were calculated by inversely weighting the size of each matched case-control set.

[†]Fixed effects of case status and the P values estimated using generalized linear mixed models. Differences in counts of weighted CCI groups were tested using Friedman χ^2 test.[‡]Not matched at baseline.

within 30 days of a course, are listed in Table III. The spectrum of antibiotics given to cases was significantly different compared with that given to controls. Cases were more likely to receive penicillins and first- and second-generation cephalosporins. Controls were more likely to receive clindamycin and macrolides.

There were a total of 38 (12.3%) cases with an active penicillin allergy or allergy noted at the end of the follow-up, yet only 4 (1.3%) were penicillin allergy test positive. There were 139 (45.1%) cases exposed to 337 total courses of a penicillin, and 11 (3.0%) courses resulted in a new penicillin allergy, 10 recorded within 30 days of exposure with 1 additional report made 8 months later. These 11 individuals also tolerated 5 courses of a penicillin before and 2 courses after their newly documented penicillin allergies. There were 23 (7.5%) additional cases with an active penicillin allergy present at the end of the

follow-up period, without any apparent interval exposure to a penicillin or with documented penicillin exposures that were tolerated. In 3 (1%) of these individuals, the penicillin allergy was erroneously reactivated with no interval exposure. In 20 individuals, there had been an initial charting error, failure to inactivate the penicillin allergy after negative testing, yet 7 of these individuals received and tolerated a total of 16 courses of penicillins. In 6 of these patients, there was a note in the problem list documenting a negative penicillin allergy test, but no comment was made in the drug allergy field and the penicillin allergy was not inactivated. In 14 individuals, both a note in the problem list documenting a negative penicillin allergy test and a comment in the penicillin allergy field, documenting a negative penicillin allergy test, were present, but the penicillin allergy still remained active. No cases had repeat penicillin allergy testing

TABLE III. Antibiotics used in cases and controls during the follow-up period

Drug courses	Cases	Controls	<i>P</i> value*
N	308	1251	
Total antibiotic courses	1545	4856	
Unique patients exposed, n (%)	246 (79.9)	998 (79.8)	1.00
Total oral antibiotic courses	1231	3600	
Unique patients exposed, n (%)	237 (76.9)	920 (73.5)	0.25
Total parenteral antibiotic courses	242	862	
Unique patients exposed, n (%)	80 (26)	329 (26.3)	0.97
New <i>allergy</i> noted within 30 d of a specific course, n (%)	19 (1.2)	58 (1.2)	
Unique patients with new <i>allergy</i> within 30 d, n (%)	18 (7.3)	47 (4.7)	0.14
Specific antibiotics			
Penicillin courses	337	40	
Unique patients exposed, n (%)	139 (45.1)	31 (2.5)	<.001
New <i>allergy</i> noted within 30 d of a course (%)	10 (3.0)	0	
First-generation cephalosporin courses	309	488	
Unique patients exposed, n (%)	100 (32.5)	256 (20.5)	<.001
New <i>allergy</i> noted within 30 d of a course	2	6	
Second-generation cephalosporin courses	40	51	
Unique patients exposed, n (%)	21 (6.8)	42 (3.4)	0.009
New <i>allergy</i> noted within 30 d of a course	0	1	
Third- or higher-generation cephalosporin courses	77	332	
Unique patients exposed, n (%)	41 (13.3)	192 (15.3)	0.42
New <i>allergy</i> noted within 30 d of a course	0	6	
Monobactam courses	1	20	
Unique patients exposed, n (%)	1 (0.3)	13 (1)	0.33
New <i>allergy</i> noted within 30 d of a course	0	0	
Carbapenem courses	8	3	
Unique patients exposed, n (%)	3 (1)	3 (0.2)	0.10
New <i>allergy</i> noted within 30 d of a course	0	0	
Cotrimoxazole courses	136	479	
Unique patients exposed, n (%)	65 (21.1)	297 (23.7)	0.36
New <i>allergy</i> noted within 30 d of a course	4	13	
Clindamycin courses	104	919	
Unique patients exposed, n (%)	45 (14.6)	407 (32.5)	<.001
New <i>allergy</i> noted within 30 d of a course	1	11	
Quinolone courses	264	858	
Unique patients exposed, n (%)	97 (31.5)	384 (30.7)	0.84
New <i>allergy</i> noted within 30 d of a course	4	5	
Macrolides courses	151	1022	
Unique patients exposed (%)	97 (31.5)	523 (41.8)	0.001
New <i>allergy</i> noted within 30 d of a course	0	8	

(continued)

TABLE III. (Continued)

Drug courses	Cases	Controls	<i>P</i> value*
Vancomycin courses	24	170	
Unique patients exposed, n (%)	14 (4.5)	83 (6.6)	0.22
New <i>allergy</i> noted within 30 d of a course	0	1	
Aminoglycoside courses	63	327	
Unique patients exposed, n (%)	34 (11)	183 (14.6)	0.12
New <i>allergy</i> noted within 30 d of a course	0	0	
Metronidazole courses	55	301	
Unique patients exposed, n (%)	35 (11.4)	174 (13.9)	0.28
New <i>allergy</i> noted within 30 d of a course	1	1	
Tetracycline courses	140	488	
Unique patients exposed, n (%)	74 (24)	240 (19.2)	0.07
New <i>allergy</i> noted within 30 d of a course	2	4	
Nitrofurantoin courses	54	152	
Unique patients exposed, n (%)	26 (8.4)	92 (7.4)	0.6
New <i>allergy</i> noted within 30 d of a course	0	2	
All other antibiotic courses	27	95	
Unique patients exposed (%)	17 (5.5)	59 (4.7)	0.66
New <i>allergy</i> noted within 30 d of a course	0	0	

* χ^2 tests for testing unique patient exposure proportions (Fisher exact tests were used for counts <5 in a table cell).

during the follow-up period. There were also 31 (2.5 %) control subjects exposed to 40 total courses of a penicillin and no serious reactions were noted. Despite their apparent documented tolerance to a penicillin, none of these 31 individuals had their penicillin *allergy* inactivated by the end of the follow-up period. All control subjects still had an active penicillin *allergy* noted in their EHR at the end of the follow-up period.

The study results show that penicillin allergy testing is significantly protective from more OPD visits and more hospital days over 3.6+ years of follow-up observation. Tested subjects received more narrow-spectrum penicillins and first- and second-generation cephalosporins.

DISCUSSION

The Centers for Disease Control and Prevention, the Infectious Disease Society of America, the Society for Healthcare Epidemiology of America, and the American Academy of Allergy, Asthma, and Immunology currently recommend penicillin allergy testing to help improve antibiotic stewardship.³⁻⁵ A strength of this article is that it is the first demonstration that penicillin allergy testing, mostly done in the setting of an outpatient Allergy consultation, results in both a decrease in unfavorable antibiotic exposures and a significantly lower overall health care utilization during the following 3.6+ years. A weakness of this study is that subjects were not prospectively randomized to penicillin allergy testing or routine care. However, such random assignment would be unethical, because it is already well established that penicillin allergy testing directly benefits patients.⁷⁻¹⁵ It is already well accepted that verifying penicillin

allergies is the right thing to do from the patient's point of view, and from an antibiotic stewardship point of view, because it allows more appropriate use of relatively narrow-spectrum penicillin class antibiotics.³⁻⁵ It was also not possible to match baseline antibiotic use per year and the effect of a possible allergy consultation at the same time as the penicillin allergy testing.

We provide additional evidence that penicillin allergy tested individuals safely receive more penicillins and first- and second-generation cephalosporins and less clindamycin and macrolides. They do not note new drug intolerances at an increased rate. Our baseline vancomycin use was already very low, because of our current antibiotic stewardship efforts, and no significant reduction was noted. Our baseline use of all cephalosporins was relatively high to start with in individuals with an unconfirmed penicillin allergy, as previously reported.¹⁸

We confirm the findings of Fox and Park¹⁹ in documenting that penicillin allergy testing is safe and effective in children, given that about 29% of our cases were 14 years or younger. There were no episodes of penicillin- or cephalosporin-associated serious cutaneous adverse reactions or anaphylaxis in any of the matched cases or controls during the follow-up period.

Failure to completely inactivate or erroneous reactivation of a penicillin allergy in the EHR of patients who were penicillin allergy test negative, including oral challenge negative, and either not exposed to any penicillin class antibiotics or tolerated therapeutic penicillins, still occurs in our health care program, but at a much lower level than reported in other health care programs that have multiple medical record systems, 7.5% versus 37.6%.²⁰ A surprisingly high percentage, 2.5%, of all penicillin allergic control patients received a penicillin during this study. They all tolerated the exposure and still did not have their penicillin allergy removed.

We have previously shown, and again confirm here, that there will be a predictable rate of allergy reported in large populations given any antibiotics.^{21,22} If an individual has negative penicillin allergy testing, they will report a new penicillin allergy about 3% of the time after every course of a penicillin. We have previously shown that only about 1 in 33 individuals who were penicillin allergy test negative, receive a therapeutic penicillin, and then noted a new reaction that was reported as an allergy were repeat penicillin allergy test positive.²³

The cost-benefit ratio of penicillin allergy testing in our matched cohort can be roughly calculated as follows. The reduction in health care utilization in the cases, compared with controls, was -0.089 OPD visits per year at \$145 per visit (\$12.9),²⁴ -0.132 ED visits per year at \$1233 per visit (\$162.8),²⁵ and -0.553 hospital days per year at \$3146 per hospital day (\$1739.7),²⁶ for a total of \$1915.4 less in health care expenses per patient per year. Compared with the one-time cost of \$145 for penicillin allergy testing reagents and nursing time for the penicillin allergy testing, the savings will be very significant in the long run.²⁷ (Note that the Allergy consultation was already included as one of the follow-up OPD visits.) Given the above, penicillin allergy testing the 308 matched cases might have saved our health plan more than \$2 million over 3.6 years. The cost of penicillin allergy testing and health care utilization may be higher in other health care systems.

This article provides new and compelling evidence that health plans should actively encourage penicillin allergy testing of patients with higher than average health care utilization and an unverified penicillin allergy. Penicillin allergy testing results in

more use of narrow-spectrum penicillins and first- or second-generation cephalosporins, thus improving patient safety and supporting antibiotic stewardship efforts. The data also support the testing of hospitalized individuals, or individuals likely to be hospitalized, which is consistent with the previously documented, significantly increased morbidity associated with an unverified penicillin allergy in hospitalized patients.²⁷

Penicillin allergy testing, in the setting of an Allergy consultation, resulted in lower rates of overall health care utilization, with most of the impact on hospital days, and potentially significant cost savings for health plans. Because our case cohort was initially selected from a group with higher average baseline health care utilization, and controls were matched to the case baseline measurements, the estimates of health care utilization might be less representative of a healthier population.

It may still be worthwhile to test all individuals with an unverified penicillin allergy to ensure they receive optimal antibiotic therapy, but a favorable cost-benefit ratio for testing very low utilizing individuals has not been confirmed. Further research using a population-based sampling design to better estimate the health care utilization and costs associated with penicillin allergy testing may be worthwhile.

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