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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Abbreviations used
CCI- Charlson comorbidity index
ED- Emergency department
EHR- Electronic heath 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