Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study

Eric Macy, MD, MS,[a] and Richard Contreras, MS[b] *San Diego and Pasadena, Calif*

Background: Penicillin is the most common drug "allergy" noted at hospital admission, although it is often inaccurate.
Objective: We sought to determine total hospital days, antibiotic exposures, and the prevalence rates of *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus* (VRE) in patients with and without penicillin "allergy" at hospital admission.
Methods: We performed a retrospective, matched cohort study of subjects admitted to Kaiser Foundation hospitals in Southern California during 2010 through 2012.
Results: It was possible to match 51,582 (99.6% of all possible cases) unique hospitalized subjects with penicillin "allergy" to 2 unique discharge diagnosis category–matched, sex-matched, age-matched, and date of admission–matched control subjects each. Cases with penicillin "allergy" averaged 0.59 (9.9%; 95% CI, 0.47-0.71) more total hospital days during 20.1 ± 10.5 months of follow-up compared with control subjects. Cases were treated with significantly more fluoroquinolones, clindamycin, and vancomycin ($P < .0001$) for each antibiotic compared with control subjects. Cases had 23.4% (95% CI, 15.6% to 31.7%) more *C difficile*, 14.1% (95% CI, 7.1% to 21.6%) more MRSA, and 30.1% (95% CI, 12.5% to 50.4%) more VRE infections than expected compared with control subjects.
Conclusions: A penicillin "allergy" history, although often inaccurate, is not a benign finding at hospital admission. Subjects with a penicillin "allergy" history spend significantly more time in the hospital. Subjects with a penicillin "allergy" history are exposed to significantly more antibiotics previously associated with *C difficile* and VRE. Drug "allergies" in general, but most those notably to penicillin, are associated with increased hospital use and increased *C difficile*, MRSA, and VRE prevalence. (J Allergy Clin Immunol 2014;133:790-6.)

Key words: *Adverse drug reaction, antibiotics,* Clostridium difficile*, electronic medical record, hospital use, methicillin-resistant* Staphylococcus aureus*, multiple drug intolerance syndrome, penicillin allergy, prevalence, vancomycin-resistant* Enterococcus *species*

Abbreviations used
ICD-9: International Classification of Diseases, Ninth Revision
MDIS: Multiple-drug intolerance syndrome
MRSA: Methicillin-resistant Staphylococcus aureus
VRE: Vancomycin-resistant *Enterococcus* species

Penicillin "allergy" is the most common drug-class "allergy" noted in the medical records of subjects using health care, including hospitals, in the United States.[1,2] Most subjects with a history of penicillin "allergy" are not allergic and tolerate future penicillin use.[3] In our health plan, over the past 4 years, less than 2% of subjects with a history of penicillin "allergy" had a positive penicillin allergy test result.[4,5] Carrying an inaccurate diagnosis of penicillin "allergy" could adversely affect the quantity and quality of health care used. A majority of hospitalized patients are treated with antibiotics.[6] Hospitalized patients tend to be older and are less likely to have positive penicillin allergy test results.[2,5] Fluoroquinolones, clindamycin, vancomycin, and third-generation cephalosporins are commonly substituted for first-line penicillin-class antibiotics in subjects with an active penicillin "allergy" history.[7] Fluoroquinolones, clindamycin, and third-generation cephalosporins have been previously associated with increased rates of *Clostridium difficile*.[8-10] There is still a widespread but mistaken concern about a possible clinically significant increased rate of adverse reactions associated with first- and second-generation cephalosporin use in subjects with a history of penicillin "allergy" that could be driving even more fluoroquinolone, clindamycin, vancomycin, and third-generation cephalosporin use when a first- or second-generation cephalosporin could be safely used.[11]

There have been only small pilot programs involving penicillin allergy testing in hospitalized patients, including emergency department patients, patients in intensive care units, and preoperative patients published, to date. These reports show that penicillin allergy testing can be performed safely in hospitalized patients and suggest improved outcomes, less vancomycin use, and potential cost savings.[12-20] Less than 0.1% of the approximately 25 million subjects with penicillin "allergy" undergo penicillin allergy testing in the United States annually.[3]

If a subject with a penicillin "allergy" history has a negative penicillin skin test result and oral amoxicillin challenge result, they will have new penicillin-class antibiotic–associated adverse reactions at rates not significantly different from those of random subjects in the population when corrected for sex and other drug "allergy" history.[21] New antibiotic-associated adverse drug reactions will still occur in 0.5% to 5% of all subjects with all therapeutic antibiotic use, depending on the specific antibiotic given and underlying patient characteristics.[21-23] Higher rates of

From [a]the Southern California Permanente Medical Group, Department of Allergy, San Diego Medical Center, and [b]Kaiser Permanente Health Care Program, Department of Research and Evaluation, Pasadena.

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Corresponding author: Eric Macy, MD, MS, Department of Allergy, Kaiser Permanente, 7060 Clairemont Mesa Blvd, San Diego, CA 92111. E-mail: eric.m.macy@kp.org.
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adverse drug reactions are seen in female subjects and in subjects with underlying multiple-drug intolerance syndrome (MDIS).[23]

There has been a decreasing rate of positive penicillin skin test results in subjects with a history of penicillin allergy over the last 2 decades.[4,20] Current commercially available *in vitro* blood allergy tests for anti-penicillin IgE or anti-amoxicillin IgE are not useful in detecting clinically significant penicillin allergy because they do not correlate to oral challenge results.[24] Penicillin allergy testing has been safely performed in pregnant women with histories of penicillin "allergy" and colonization with group B streptococcus who require treatment with parenteral penicillin at delivery.[25,26] Resensitization to penicillin after therapeutic use is very rare.[27,28]

The primary goal of this article is to determine the total number of hospital days used, one of the main drivers of health care costs, in hospitalized subjects with an active penicillin "allergy" compared with subjects without a penicillin "allergy" history. The secondary goals are to determine the specific antibiotics used and the prevalence rates of 3 serious infections, *C difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus* (VRE), in cases and control subjects.

METHODS

This study was reviewed and approved by the Kaiser Permanente Southern California Institutional Review Board. The Kaiser Permanente Healthplan uses a completely electronic medical record system, Health Connect (Epic Systems Corporation, Verona, Wis), which has been in operation for all outpatient health care since 2007 and for all inpatient health care since 2009.

Potential cases were defined as the first admission for any patient admitted to a Kaiser Foundation Hospital in Southern California between January 1, 2010, and December 31, 2012, with an active history of penicillin "allergy" at the time of admission. Potential cases were retrospectively placed into 9 primary discharge diagnosis groups based on 3-digit International Classification of Diseases, Ninth Revision (ICD-9), codes. The groups were cancer, cardiovascular, nervous system, abdominal organ system, urology-gynecologic, obstetric, orthopedic-trauma, pulmonary, and "other," which included but was not limited to allergic, dermatologic, endocrinologic, immunologic, infectious, and rheumatologic conditions. These 9 primary discharge diagnosis groups were used for matching control subjects to cases. Within each primary discharge diagnosis group, the following algorithms were used to identify the 2 closest control subjects for each case. All subjects of the same sex as each case with an age ± 1 year and a date of admission ± 1 month were identified. The matching of cases to control subjects was done first by sex, then by closest age, and then by closest date of admission.

For the overall population hospitalization data, the first admission for a unique subject during the study interval was considered the index admission. The index admission for a case was defined as the first admission during the study interval for a subject with an active penicillin "allergy" on the date of that admission. The index admission for a control subject was the admission matched to the case. Total hospital days for unique subjects were determined from the index admission through December 31, 2012. Hospital days were defined as the date of discharge minus the date of admission. However, if an admission and discharge occurred on the same calendar day, it was also considered 1 day.

Drug-class "allergies" were initially determined based on active entries in the drug allergy field of the electronic medical record on the date of index admission and categorized as previously described.[22,23] All new drug "allergy" reports for each subject were then identified through December 31, 2012. A course of an antibiotic was defined as less than 36 hours between administrations of a discrete chemical entity through one specific systemic route: oral or parenteral. Topical and ophthalmic antibiotic use was not considered for this analysis.

The overall prevalence rates for the 3 serious infections tracked, *C difficile*, MRSA, and VRE, were determined as follows: any positive clinical isolate of *C difficile*, MRSA, or VRE or a *C difficile*–, MRSA-, or VRE-associated ICD-9 code, specifically 8.45, 38.12, or 41.12, made during the study interval at any inpatient or outpatient visit and including at least 3 months before the earliest hospitalization and 3 months after the last hospitalization were used to determine prevalence.[9] If the first positive *C difficile*, MRSA, or VRE clinical isolate or ICD-9 code was made during a hospitalization, it was defined as a hospital-acquired case.

Total hospital costs were estimated by using the general methods previously used when analyzing health care costs in the Kaiser Permanente Healthcare Program.[29-31] Costs were assigned to health care services by using the Medicare Resource Based Relative Value Scale and Diagnosis-Related Groups (posted at www.CMS.gov). The Diagnosis-Related Groups payments used by Medicare apply only to facility costs. Professional and technical services delivered during hospital stays were calculated independently. It was determined that an average study interval hospital day cost the Kaiser Permanente Health Care program $2,123.56 in 2012 dollars.

The cost of penicillin allergy testing was determined as follows. One registered nurse, with an annual salary and benefits of $118,000, trained in skin testing and oral challenge could perform 8 penicillin allergy tests per 8-hour shift or 2000 per year. The nonpayroll expenses for testing included $69.00 per dose of penicilloyl-poly-lysine (Pre-Pen; ALK-Abelló, Hørsholm, Denmark), $0.12 per amoxicillin 250-mg tablet, and $3.25 per patient for all of the other necessary supplies. The cost for the Kaiser Permanente Health Care program to test a subject for penicillin allergy was $131.37 in 2012 dollars.

All statistical analyses were conducted with SAS EG 4.3 software (SAS Institute, Cary, NC). Percentages and odds ratios were calculated on categorical outcomes. Means and SDs were calculated on continuous variables. Statistical significance was assessed on categorical variables by using χ^2 and t tests for continuous variables. All P values of less than .05 were considered statistically significant.

The primary outcome variables were total hospital days per unique subject from the index admission through December 31, 2013, and the overall study interval *C difficile*, MRSA, and VRE prevalence rates.

RESULTS

Table I displays the demographics, selected health care use, and serious infection rates for all hospitalized patients for the entire health plan during the 3-year study interval of January 1, 2010, through December 31, 2012. This cohort represents approximately a 1% sample of the US population. There were 51,807 unique potential cases, 11.2% of all hospitalized patients, identified with an active history of penicillin "allergy" at the time of an admission during the study interval. It was possible to match 51,582 (99.6%) of the cases at the time of their first admission with an active penicillin "allergy" during the study interval to 2 discharge diagnosis category–matched, sex-matched, age-matched, and date of admission–matched control subjects without an active penicillin "allergy" history. The top 5 most common drug-class "allergies" noted in hospitalized subjects were to penicillin (51,813 [16.7%]), other nonantibiotics (39,509 [12.7%]), narcotics (36,382 [11.7%]), sulfonamide antibiotics (31,765 [10.2%]), and nonsteroidal anti-inflammatory drugs (21,903 [7.1%]). These drug-class allergies alone accounted for 58.4% of all drug "allergies" reported.

The frequencies of the 9 general discharge diagnosis groups used for matching are displayed in Table II. The top 10 specific primary discharge 3-digit ICD-9 codes for study subjects in order of frequency were 786 (respiratory), 715 (osteoarthrosis), 038 (septicemia), 780 (general symptoms), 664 (delivery trauma),

TABLE I. Overall demographics, health care use, and clinical outcomes in health plan hospitalized patients for January 1, 2010, through December 31, 2012

	Female subjects	Male subjects
Total unique hospitalized patients	287,946	174,279
Age,*† mean ± SD	45.0 ± 24.4	50.1 ± 27.4
Body mass index,*† mean ± SD	28.4 ± 7.4	27.6 ± 6.6
Patients with only 1 hospital admission, no. (%)	203,686 (70.7)	118,710 (68.1)
Patients with 2 hospital admissions, no. (%)	48,431 (16.8)	28,990 (16.6)
Patients with ≥3 hospital admissions, no. (%)	35,829 (12.5)	26,579 (15.3)
Total hospital admissions	460,195	300,375
Total hospital days	1,420,083	1,077,985
Hospital days per unique individual† (d), mean ± SD	4.9 ± 9.7	6.2 ± 11.9
Mean follow-up after first hospital admission (mo; maximum = 36 mo), mean ± SD	19.4 ± 10.5	19.7 ± 10.5
Total unique hospitalized patients with a history of penicillin "allergy,"* no. (%)	36,725 (12.8)	15,082 (8.7)
In-hospital deaths,† no. (%)	5,380 (1.9)	5,842 (3.6)
Additional deaths within 3 months of last hospital discharge,† no. (%)	13,438 (4.7)	14,498 (8.3)
Unique patients with ≥1 antibiotic use during hospitalization, no. (%)	165,402 (57.4)	102,860 (59.0)
Total courses of parenteral antibiotics used per hospitalized subjects,† mean ± SD	1.3 ± 2.4	1.7 ± 3.1
Total courses of oral antibiotics used per hospitalized subject,† mean ± SD	0.3 ± 0.9	0.4 ± 1.1
Unique patients undergoing ≥1 surgery during an admission,† no. (%)	196,520 (68.3)	101,595 (58.3)
Admissions for delivery, no. (%)	97,454 (21.2)	None
Unique individuals having ≥1 deliveries, no. (%)	91,715 (31.8)	
C difficile prevalence,† no. (%)	4,890 (1.7)	3,475 (2.0)
MRSA prevalence,† no. (%)	4,612 (1.6)	5,032 (2.9)
VRE prevalence,‡ no. (%)	974 (0.3)	538 (0.3)

*At index admission.
†$P < .0001$.
‡$P = .0882$.

TABLE II. Discharge diagnosis groups used for case-control matching

Discharge diagnosis group	No. of cases	Percentage
Abdominal organ system	6886	13.4
Cancer	2394	4.6
Cardiovascular	4571	8.9
Nervous system	5686	11.0
Obstetric	7399	14.3
Orthopedic-trauma	5173	10.0
Other	8715	16.9
Pulmonary	7159	13.9
Urology-gynecology	3599	7.0

427 (cardiac dysrhythmias), 486 (pneumonia), 648 (childbirth), 428 (heart failure), and 574 (cholelithiasis). These top 10 specific 3-digit ICD-9 codes accounted for 14,904 (28.9%) of the cases and 30,260 (29.3%) of the control subjects.

Table III displays the patients' demographics, hospital use, antibiotic use, and serious infection rates for female and male cases with an active penicillin "allergy" history compared with 2 primary discharge diagnosis group–matched, sex-matched, age-matched, and date of admission–matched control subjects. Subjects with penicillin "allergy" averaged 0.59 (9.9%; 95% CI, 0.47-0.71) more total hospital days each over a mean follow-up of 20.1 ± 10.5 months. There were 0.68 (12.3%; 95% CI, 0.55-0.82) more hospital days noted for each female case and only 0.35 (5.1%; 95% CI, 0.10-0.59) more hospital days noted for each male case compared with control subjects. There were 0.80 (11.9%; 95% CI, 0.61-0.99) more hospital days noted for each female case over the age of 50 years and only 0.26 (3.5%; 95% CI, −0.03 to 0.56) more hospital days noted for each male case over the age of 50 years compared with control subjects. The odd ratios for *C difficile* prevalence in cases compared with control subjects was 1.234 (95% CI, 1.156-1.317). The odd ratios for MRSA prevalence in cases compared with control subjects was 1.141 (95% CI, 1.071-1.317). The odd ratios for VRE prevalence in cases compared with control subjects was 1.301 (95% CI, 1.125-1.504). Most of the *C difficile* (74.4%), MRSA (86.9%), and VRE (89.7%) infections were determined to be hospital acquired.

The discharge diagnosis group with the largest differential in hospitalization days between cases and control subjects for female subjects was pulmonary diseases (1.1 [19.7%; 95% CI, 0.68-1.53] days), and that for male subjects was cancer (0.77 [9.3%; 95% CI, −0.42 to 1.97] days). The discharge diagnosis group with the smallest differential in hospitalization days between cases and control subjects for female subjects was obstetric (0.11 [3.5%; 95% CI, 0.06-0.22] days), and that for male subjects was cardiovascular (−0.03 [−0.4%; 95% CI, −0.72 to 0.65] days).

Table IV[8,9] displays the top 10 specific antibiotics used by the cases and control subjects. These top 10 antibiotics accounted for 97,271 (84.6%) of the total antibiotic courses used by cases and 171,236 (81.8%) of the total antibiotic courses used by control subjects. There was significantly more ciprofloxacin, vancomycin, and clindamycin given to cases compared with control subjects. Fluoroquinolones were given to 13,053 (25.3%) cases (20,125 total courses) and to 14,853 (14.3%) control subjects (20,302 total courses, $P < .00001$). Cephalosporins were the most common class of antibiotics used in both cases and control

TABLE III. Case and control demographics, health care use, and outcomes

	Female subjects		Male subjects		
	Cases with history of penicillin "allergy," n = 36,583	Control subjects with no history of penicillin "allergy," n = 73,166	Cases with history of penicillin "allergy," n = 14,999	Control subjects with no history of penicillin "allergy," n = 29,998	*P* values between cases and control subjects
Age (y),* mean ± SD	56.7 ± 21.2	56.7 ± 21.2	60.9 ± 20.9	60.9 ± 20.9	Female subjects: $P = .9198$ Male subjects: $P = .9742$
Body mass index,* mean ± SD	28.9 ± 7.5	28.5 ± 7.2	28.1 ± 6.5	27.8 ± 6.2	Female subjects: $P < .0001$ Male subjects: $P < .0001$
Mean follow-up after index admission (mo), mean ± SD (maximum = 36 mo)	20.0 ± 10.5	20.0 ± 10.5	20.4 ± 10.5	20.4 ± 10.5	Female subjects: $P = .9983$ Male subjects: $P = .9977$
Total hospital days per unique subject (d), mean ± SD	6.3 ± 12.4	5.6 ± 10.1	7.1 ± 13.4	6.8 ± 12.2	Female subjects: $P < .0001$ Male subjects: $P = .0076$
Total admissions, mean ± SD	1.8 ± 1.8	1.7 ± 1.6	1.9 ± 1.9	1.9 ± 1.8	Female subjects: $P < .0001$ Male subjects: $P = .0082$
Patients with only 1 admission during the study interval, no. (%)	23,147 (63.3)	48,290 (66.0)	9,212 (61.4)	18,721 (62.4)	Female subjects: $P < .0001$ Male subjects: $P = .0413$
Unique patients undergoing surgery during an admission, no. (%)	23,828 (65.1)	48,242 (65.9)	8,610 (57.4)	17,256 (57.5)	Female subjects: $P = .0084$ Male subjects: $P = .0413$
In-hospital deaths, no. (%)	1,077 (2.9)	2,156 (3.0)	691 (4.6)	1,368 (4.6)	Female subjects: $P = .9799$ Male subjects: $P = .8233$
Additional deaths within 3 months of last discharge, no. (%)	2,747 (7.5)	5,327 (7.3)	1,676 (11.2)	3,498 (11.7)	Female subjects: $P = .1721$ Male subjects: $P = .1271$
Unique patients exposed to ≥1 antibiotic during the index hospitalization, no. (%)	20,471 (56.0)	39,622 (54.2)	8,332 (55.6)	16,562 (55.2)	Female subjects: $P < .0001$ Male subjects: $P = .4940$
Unique patients exposed to ≥1 antibiotic during any hospitalization, no. (%)	24,351 (66.6)	46,645 (63.8)	9,930 (66.2)	19,660 (65.5)	Female subjects: $P < .0001$ Male subjects: $P = .1600$
Courses of parenteral antibiotics used per unique subject, mean ± SD	1.8 ± 3.0	1.6 ± 2.7	2.1 ± 3.5	2.0 ± 3.3	Female subjects: $P < .0001$ Male subjects: $P = .0011$
Courses of oral antibiotics used per unique subject, mean ± SD	0.5 ± 1.2	0.4 ± 1.0	0.5 ± 1.3	0.4 ± 1.2	Female subjects: $P < .0001$ Male subjects: $P < .0001$
C difficile prevalence, no. (%)	1,071 (2.9)	1,686 (2.3)	427 (2.9)	755 (2.5)	Female subjects: $P < .0001$ Male subjects: $P = .0561$

(Continued)

TABLE III. *(Continued)*

	Female subjects		Male subjects		
	Cases with history of penicillin "allergy," n = 36,583	Control subjects with no history of penicillin "allergy," n = 73,166	Cases with history of penicillin "allergy," n = 14,999	Control subjects with no history of penicillin "allergy," n = 29,998	*P* values between cases and control subjects
MRSA prevalence, no. (%)	960 (2.6)	1,631 (2.2)	566 (3.8)	1,053 (3.5)	Female subjects: $P < .0001$ Male subjects: $P = .1574$
VRE prevalence, no. (%)	234 (0.6)	337 (0.5)	68 (0.5)	128 (0.4)	Female subjects: $P = .0001$ Male subjects: $P = .6855$

*At index admission.

TABLE IV. The top 10 antibiotics used by cases and control subjects during hospitalizations

	Cases (51,582)	Control subjects (103,164)
1	Vancomycin: N = 16,685 n = 10,872 (21.2%)	Cefazolin: N = 38,117 n = 32,614 (31.6%)
2	Ciprofloxacin*: N = 15,154 n = 10,888 (21.1%)	Ceftriaxone*: N = 30,220 n = 21,726 (21.1%)
3	Clindamycin*: N = 14,447 n = 12,579 (24.4%)	Vancomycin: N = 20,099 n = 12,772 (12.4%)
4	Ceftriaxone*: N = 11,683 n = 8,570 (16.6%)	Metronidazole: N = 18,392 n = 14,341 (13.9%)
5	Metronidazole: N = 11,427 n = 8,542 (16.6%)	Ciprofloxacin*: N = 17,461 n = 13,416 (13.0%)
6	Cefazolin: N = 8,489 n = 7,490 (14.5%)	Piperacillin: N = 14,561 n = 11,157 (10.8%)
7	Gentamicin: N = 6,025 n = 5,329 (10.3%)	Azithromycin: N = 12,837 n = 10,045 (9.7%)
8	Azithromycin: N = 5,812 n = 4,610 (8.9%)	Ampicillin: N = 7,153 n = 6,536 (6.3%)
9	Moxifloxacin*: N = 3,908 n = 3,194 (6.2%)	Gentamicin: N = 6,480 n = 5,809 (5.6%)
10	Ceftazidime*: N = 3,641 n = 2,741 (5.3%)	Ceftazidime*: N = 5,916 n = 4,641 (4.5%)

N, Courses of antibiotic; *n (%)*, unique subjects exposed.
*Antibiotics associated with an increased risk of *C difficile*.[8,9]

subjects. There were 16,279 (31.6%) cases exposed to 27,080 total courses of cephalosporins. There were 51,364 (49.8%) control subjects exposed to 81,678 total courses of cephalosporins ($P < .0001$). There were 8,202 (15.9%) cases exposed to 9,756 total courses of first-generation cephalosporins. There were 34,178 (33.1%) control subjects exposed to 41,348 total courses of first-generation cephalosporins ($P < .0001$). There were 10,138 (19.7%) cases exposed to 16,653 total courses of third- or higher-generation cephalosporins. There were 24,110 (23.4%) control subjects exposed to 38,508 total courses of third- or higher-generation cephalosporins ($P < .0001$).

Subjects with an active penicillin "allergy" history had significantly higher overall rates of drug "allergy" reported at their index admission ($P < .0001$, data not shown). Even when discounting their probable inaccurate penicillin "allergy," cases were still more than twice as likely to have MDIS compared with control subjects. Subjects with a history of penicillin "allergy" were also more likely to have at least 1 new drug "allergy" documented during the follow-up period compared with control subjects ($P < .0001$, data not shown).

The calculated cost for our health care program to test the 51,582 cases for penicillin allergy was $6,776,327.34 (at $131.37 each). The increased hospital use in the cases accounted for 30,433 extra hospital days. Given an average cost of $2,123.56 for a hospital day in our health care program, this amounts to $64,626,630.48 more in health care expenditures over the 3-year study interval or about 9.5 times as much as penicillin allergy testing would cost. It would only cost $2,987,091.06 (44.1% as much) to test the 22,738 female cases of 50 years or older for penicillin allergy, and they alone accounted for 18,190 (59.8%) of the extra hospital days.

When attempting to match cases to control subjects accounting for drug allergy number, it was not possible to match more than one third of the cases. Cases not matched by drug-class "allergy" number were significantly more likely to be male, younger, and have more overall hospital use. Nonmatched cases also had significantly higher *C difficile*, MRSA, and VRE prevalence compared with matched cases. There was a strong positive correlation between increasing drug-class "allergy" number and all of the 4 outcome variables for both cases and their drug-class "allergy" number–matched control subjects (data not shown).

DISCUSSION

An "allergy" history to active penicillin or any other drug is not a benign finding at hospital admission. We show that any drug "allergy" history is associated with increased hospital use over the next several years and significantly higher rates of serious infections. There was good matching for overall antibiotic use between cases and control subjects in our study but very significant differences in the specific antibiotics used. Cases

were significantly more likely to receive fluoroquinolones, vancomycin, and clindamycin than control subjects. Cases were more likely to receive third-generation cephalosporins compared with control subjects, if they received any cephalosporins. The top 10 antibiotics used by initially matched cases included 5 of the antibiotics most associated with *C difficile*: ciprofloxacin, clindamycin, ceftriaxone, moxifloxacin, and ceftazidime.[9,10] Control subjects only had ceftriaxone, ciprofloxacin, and ceftazidime on their top 10 lists. The increased prevalence rate of *C difficile* observed in cases could be explained by their increased use of fluoroquinolones, clindamycin, and third-generation cephalosporins. The increased prevalence rate of VRE in cases could be explained by their almost 2-fold increased rate of vancomycin use along with their higher use of fluoroquinolones and third-generation cephalosporins. There is no good theory at present to explain the increased prevalence rate of MRSA seen in hospitalized subjects with a history of penicillin "allergy" other than just more time in the hospital.

When looking at cases rematched to control subjects by drug-class "allergy" number, we noted a strong positive correlation between total hospital use and all 3 serious infections with increasing drug-class "allergy" number. Penicillin "allergy" is not specifically implicated. As expected, subjects with high drug-class "allergy" numbers were more likely to be older women.[23] MDIS was more than twice as likely to be present in both male and female cases, even when discounting their underlying but probably inaccurate penicillin-class antibiotic "allergy" compared with control subjects. MDIS has previously been associated with increased overall inpatient and outpatient health care use but, interestingly, not mortality.[23]

Reddy et al[32] recently published an abstract also showing significantly increased rates of *C difficile*, MRSA, and VRE infections in patients with a history of penicillin "allergy" admitted to a university hospital in Pennsylvania from 2009 through 2011. We now confirm their observation in a much larger and more diverse population, noting similar increased prevalence rates for all 3 serious infections.

We also noted that both parenteral and oral cephalosporins are widely, safely, and appropriately used in hospitalized subjects with an active penicillin "allergy" history. Cephalosporins were the most common antibiotic class given to both cases with penicillin "allergy" and nonallergic control subjects in our cohort. There was only 1 questionable, serious, potentially IgE-mediated reaction associated with cephalosporin use in 16,279 cases with penicillin "allergy" exposed to 27,080 courses of cephalosporins. There were 4 more convincing, serious, potentially IgE-mediated reactions in 51,364 control subjects without a history of penicillin "allergy" exposed to 81,678 courses of cephalosporins. Control subjects were much more likely to receive a first-generation cephalosporin compared with cases. Cases were more likely to get a third-generation cephalosporin if they received any cephalosporins. These high rates of cephalosporin use in cases occurred despite a warning present in the drug-ordering software that recommended not using any cephalosporins in subjects with an active penicillin "allergy" history. There was no evidence for an increased rate of anaphylaxis in patients with an active penicillin "allergy" history receiving cephalosporins.

Penicillin "allergy" is the easiest drug "allergy" to verify currently.[1] We expect that more than 98% of hospitalized subjects with a history of penicillin "allergy" tested would have negative results.[4] Penicillin allergy testing as soon as possible after admission would be important to derive the maximum benefit of knowing whether a person truly was allergic to penicillin-class antibiotics. It will not be possible to test all patients admitted to the hospital with a history of penicillin "allergy." Few subjects will have a clinical history that contraindicates allergy testing or rechallenge. Some will be taking medication with antihistaminic properties that will preclude accurate skin testing. On the basis of previous experience, it will be possible to test the vast majority of hospitalized subjects with a history of penicillin "allergy."[19,20,33]

Even if only 95% of the subjects with a history of penicillin "allergy" had negative penicillin allergy test responses and only 50% of the additional hospital days could then be avoided in the group with negative penicillin allergy test results, this could still save about 4 times as much as it would cost to perform the penicillin allergy testing in the Kaiser Permanente Health Care program. Targeting penicillin allergy testing to women 50 years or older could potentially increase the cost/benefit ratio by about one third. The Kaiser Permanente Health Care program has significant cost advantages over many other health care programs. For other programs with higher average per-day hospital costs, the potential for savings could be greater as long as their testing-associated costs are not proportionally greater.

There appears to be the potential for significant cost savings and improvement in clinical outcomes by performing penicillin allergy testing at hospital admission on subjects with an active penicillin "allergy" history, especially female subjects 50 years of age or older. Further research will be needed to determine whether correcting all inaccurate drug "allergy" records will result in less hospital use and fewer serious infections.

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