

Original article

Oral antibiotic adverse reactions after penicillin skin testing: multi-year follow-up

Background: Long-term follow-up data on adverse drug reactions after oral antibiotic use in penicillin allergy history positive individuals with penicillin skin test done in advance of need are rare.

Methods: Oral antibiotic associated adverse drug reactions in 83 penicillin skin test positive individuals were compared to a sex, age, and length of follow-up matched sample of 166 penicillin skin test negative individuals, all of whom had at least one post penicillin skin test oral antibiotic. The mean post penicillin skin test follow-up interval was 34.5 ± 16.6 months. There were 1655 total oral antibiotic exposures.

Results: In penicillin skin test positive individuals, the adverse drug reaction rate was not significantly different with cephalosporin or non-beta-lactam use ($P = 0.12$). In penicillin skin test negative individuals the adverse drug reaction rate was significantly lower with cephalosporin vs. non-beta-lactam use ($P = 0.005$). Penicillin was safely used in penicillin skin test negative individuals. Overall cephalosporins caused fewer adverse drug reactions independent of penicillin skin test status ($P = 0.005$).

Conclusions: Penicillin skin testing was only able to predict penicillin associated adverse drug reactions in penicillin skin test positive individuals. Excluding accidental penicillin exposure in penicillin skin test positive individuals, non-beta-lactams were associated with adverse drug reactions more often than penicillins or cephalosporins, independent of the penicillin skin test result. Cephalosporins were used as or more safely than non-beta-lactams in both penicillin skin test positive and negative individuals.

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Introduction

Penicillins function as haptens and are a leading cause of true IgE mediated drug allergy. Penicillin and cephalosporins are structurally related. Since the development of cephalosporins, reports have been made about increased rates of cephalosporin associated adverse drug reactions occurring in individuals who had a history of a penicillin associated adverse drug reaction (1). By the 1980s it became apparent that the true level of immunologic cross-reaction was significantly lower than rates based on patient questionnaire studies (2). There have also been reports that penicillin allergic individuals experience adverse drug reactions at greater rates to unrelated classes of antibiotics, non-beta-lactams (3).

There are a number of factors that complicate the clinical management of beta-lactam adverse drug reactions. Most penicillin 'allergic' history positive individuals are not really allergic to penicillin. Penicillin skin testing accurately identifies individuals who make anti-penicillin IgE, but it is inconvenient for most clinicians because of

reagent unavailability. Few penicillin 'allergy' history positive, penicillin skin test positive individuals have been intentionally challenged with penicillin. There is little prospective data on adverse drug reaction rates in penicillin skin test positive and negative individuals to penicillins, cephalosporins, and non-beta-lactam antibiotics (4). There is decay in penicillin allergy over time as measured by penicillin skin testing (5). Finally the actual causes for most antibiotic associated adverse drug reactions are not accurately established (6). The net effect is that oral penicillins and cephalosporins are often unnecessarily avoided when they may be the most appropriate treatment for an outpatient infection.

Adverse drug reactions reported after oral antibiotic use are common, yet generally mild, occurring in between 1 and 8% per oral antibiotic course in unselected outpatients (6). Rashes, including urticaria and macular-papular eruptions, are the most common adverse drug reactions, but are unfortunately poorly characterized in medical records by physicians. Many adverse drug reactions may have non-IgE mediated mechanisms

involved, but with penicillins, and by extension, cephalosporins, the fear of IgE mediated anaphylaxis is well entrenched. Most antibiotic anaphylaxis occurs with parenteral exposures. Anaphylaxis with oral penicillin or cephalosporin is rare (7–9). Because a history of a previous adverse drug reaction associated with penicillin is so common, occurring in up to 10% of the population (10), many individuals are given less than optimal oral antibiotic therapy due to of a fear of a serious adverse drug reaction that is not grounded in reliable data. This leads to a variety of adverse outcomes including increased drug resistance, increased antibiotic associated morbidity, and increased health care costs (11,12). This paper attempts to determine the rates of adverse drug reactions to different classes of oral antibiotics during long-term follow-up in individuals with a penicillin allergy history documented as penicillin skin test positive or negative.

Material and methods

This study was reviewed and approved by the Kaiser Permanente Southern California Institutional Review Board. All participants provided written informed consent for the initial penicillin skin testing and subsequent medical record review. All patients in this study had their penicillin skin testing at the Kaiser Permanente San Diego Allergy Department and were followed in the San Diego area. This paper complies with the EAACI position paper on nomenclature for allergy (13).

Penicillin skin testing as previously described was performed on 1081 patients between November 16 1994 and May 31 2000, including 265 previously reported on, who were tested prior to May 28 1996 (10). The penicillin skin test panel of reagents used on all patients in this study included native penicillin, penicilloyl polylysine (Pre-Pen™), penicilloate, penilloate, and native amoxicillin (10). The penicillin skin test was considered positive if the test to any reagent was positive. If any puncture test was positive, no intradermal tests were done with the remaining negative reagents. Registered nurses, certified according to the Childhood Asthma Management Program procedures, performed all penicillin skin testing (14). Patients enrolled in this study were referred to the Allergy Department and thus would be expected to have a higher proportion of true antibiotic allergy than a randomly selected population. Patients were offered enrollment in the study if they had a history of a penicillin associated adverse drug reaction and it was felt that knowing whether they were penicillin skin test positive or negative would help in their future clinical management. A record of the penicillin skin test result was placed in the patient's written comprehensive health plan medical record. Patients subsequently received oral antibiotics from both primary care providers and specialists. Many of the patients had no ongoing Allergy Department contact.

Health plan computerized pharmacy records were reviewed for all oral antibiotics dispensed to all 1081 patients from the date of their penicillin skin test up to May 31, 2000. Eighty-five of 101 penicillin skin test positive individuals received at least one oral antibiotic from a health plan pharmacy during the follow-up period. Two potential case subjects were eliminated from the study because they had repeat negative penicillin skin tests and then tolerated oral penicillin early during the potential follow-up period. This left 83 penicillin skin test positive case subjects. Two control individuals were selected for each case, matched for sex, age ($\pm$ 8.4 years), and

follow-up interval ($\pm$ 0.6 years) from the 906 of 980 penicillin skin test negative individuals who also had at least one oral antibiotic from a health plan pharmacy. The comprehensive health plan medical record of these 249 individuals were then manually searched for all oral antibiotic use and all adverse drug reactions reported. The length of follow-up was determined by counting the number of months that an individual had Kaiser Permanente Health Care coverage between the date of the initial penicillin skin test and May 31, 2000.

It was assumed that all health plan pharmacy oral antibiotic dispensings represented a true exposure. Since some individuals also obtained additional oral antibiotics from non-health plan pharmacies, any additional comprehensive health plan medical record of an oral antibiotic use was assumed to be an additional exposure.

An adverse drug reaction for this study was defined as a reaction resulting in an acute change in oral antibiotic usage or a recommendation for future avoidance of that oral antibiotic noted in the comprehensive health plan medical record. It was assumed that any adverse drug reaction that did not warrant one of these two comments in the comprehensive health plan medical record was not significant, because it would probably not influence future oral antibiotic prescribing patterns. Thus minor complaints, such as mild gastrointestinal upset, some mild rashes, yeast infections, and headaches, that were noted in the comprehensive health plan medical record but did not result in a change in therapy or a recommendation for future avoidance, were not defined as adverse drug reactions for the purposes of this study.

The characterization of rashes in this paper is much more accurate for the initial evaluation carried out at the time of the penicillin skin test, because it was obtained by an allergist based on direct interview of the patient. Hives were defined as pruritic rashes with raised migratory individual lesions lasting less than 24 h. All other rashes were reported as maculopapular, fixed drug eruptions, or other. The characterization of rashes that occurred as adverse drug reactions with subsequent oral antibiotic use, as extracted out of the comprehensive health plan medical record, were so variable that they are reported only as rashes.

The SAS statistics program (version 8.2 for Windows) was used for all statistical analysis except the Poisson heterogeneity test, a chi-squared goodness-of-fit test using Poisson expected values, which was computed in MATHCAD 2000. Continuous numerical variables such as age, follow-up interval, and oral antibiotic utilization were analysed with both *t*-tests and Wilcoxon rank-sum tests, and any discrepancy in the results are noted. The various rates, such as adverse drug reaction rates, were compared using the Poisson heterogeneity test. Other categorical data was analysed with contingency tables using Fisher's exact tests. Statistical significance was established at $P < 0.05$, two-tailed.

Results

Index adverse drug reactions associated with historical penicillin use

The clinical characteristics of the entire cohort's initial penicillin associated adverse drug reaction and time to onset after penicillin exposure are presented in Table 1. Most of the individuals enrolled in this study had a history of hives, anaphylaxis, and/or wheezing. Recollected symptoms of the index penicillin associated adverse drug reaction consistent with an IgE mediated mechanism did not quite reach statistical significance when compared to penicillin skin test results, providing further evidence

Table 1. Index penicillin associated adverse drug reaction symptoms and time to onset in all 1081 individuals seen between November 16 1994 and May 31 2000

	Penicillin skin test positive	Penicillin skin test negative	<i>P</i> for Fisher exact tests
Index penicillin adverse drug reaction symptoms			0.08
Apparent IgE Mediated†	80 (79.2%)	678 (69.2%)	
Vague‡	10 (9.9%)	188 (19.2%)	
Unknown	11 (10.9%)	114 (11.6%)	
Time to onset of index adverse drug reaction after penicillin exposure			0.14
< 1 h	18 (17.8%)	182 (18.6%)	
1–24 h	32 (31.7%)	259 (26.4%)	
> 24–72 h	14 (13.9%)	111 (11.3%)	
> 72 h	18 (17.8%)	136 (13.9%)	
Unknown	19 (18.8%)	292 (29.8%)	
Totals	101 (100%)	980 (100%)	

†Includes anaphylaxis, hives, and/or wheezing.

‡Includes anxiety; drug fever; maculopapular, fixed eruptions, and other rashes; gastrointestinal symptoms; headaches; local swelling; and/or other adverse drug reactions.

that patient history is unreliable in ruling in or out penicillin allergy. Additionally, there was no significance associated with the time to onset of the adverse drug reaction after penicillin exposure when evaluating penicillin skin test results. There were no significant differences in index adverse drug reaction characteristics or time to onset between the 249 study subjects who were evaluated for oral antibiotic associated adverse drug reactions during the post penicillin skin test follow-up interval and the entire cohort.

Penicillin skin test results

The results of all initial penicillin skin tests performed on 1081 sequential individuals seen between November 16 1994 and May 31 2000 are reported in Table 2. Overall only 9.3% ($n = 101$) were penicillin skin test positive. The penicillin skin test was positive to at least one reagent on puncture testing in 13 individuals. There were only four individuals uniquely positive to amoxicillin. It was calculated that 10.9% to 15.8% of the penicillin skin test positive individuals would have been missed if other commonly used testing strategies, not utilizing the entire panel of reagents, were employed.

Adverse reactions associated with penicillin skin testing

In the penicillin skin test positive group, four of 101 (4.0%) individuals noted an adverse reaction associated with the penicillin skin testing procedure. Adverse reactions were much more likely to occur in puncture positive individuals, with three (23%) of 13 noting itching or hives distant from the penicillin skin test sites. Of these, one individual received epinephrine and all three received antihistamines. Only one (1.1%) of 88 intradermal positive individuals had what was considered a systemic

Table 2. Patterns of reactivity to initial penicillin skin testing in all 1081 individuals seen between 11 and 16–94 and 5–31–00

Pattern of reactivity	Number (%)
Negative to all reagents	980 (90.7%)
Positive to at least one reagent	101 (9.3%)
Breakdown of positive tests	
Positive at least to Pre-Pen	75 (74.2%)
Positive at least to penicilloate	21 (20.8%)
Positive at least to amoxicillin	18 (17.8%)
Positive at least to penicilloate	13 (12.9%)
Positive at least to penicillin	10 (9.9%)
Potentially missed if	
Pre-Pen and penicillin used only	16 (15.8%)
Pre-Pen, penicillin, and amoxicillin used only	11 (10.9%)
Allergo-Pen or equivalent† used only	13 (12.9%)

†Allergo-Pen is a product of Allergo Pharma, Germany, and contains penicilloyl polylysine, penicillin, and penicilloate.

reaction ($P = 0.006$, Fisher exact tests), compared to the penicillin skin test puncture positive group. That patient, who had a cough, received epinephrine and antihistamines.

In the penicillin skin test negative group, 16 of 980 (1.6%) subjects noted an adverse reaction; eight faintness, two nausea, and one each had anxiety, cough, vertigo, headache, hives, and itching ($P = 0.11$, Fisher exact tests), compared to the entire penicillin skin test positive group. Only four (25%) of the 16 received any treatment for the reaction; two ammonia smelling salts, one epinephrine and antihistamines, and one antihistamines alone. Treatment of adverse reactions associated with the penicillin skin test was based on the clinical impression of the allergist attending in skin testing.

Demographics of cases and controls

The patient demographics and overall oral antibiotic usage of the 83 cases and 166 controls are presented in Table 3. The cases and controls were well matched and there were no significant differences in age, years since index penicillin adverse drug reaction at the time of initial penicillin skin test, or for years of follow-up. As expected penicillin skin test negative individuals received significantly more penicillin and penicillin skin test positive individuals received significantly more non-beta-lactam antibiotics during follow-up. The two somewhat unexpected findings were that nine penicillin skin test positive individuals received penicillin and that penicillin skin test negative individuals received significantly more total courses of oral antibiotics per study subject per year of follow-up compared to penicillin skin test positive individuals, 2.48 vs. 2.02 ($P = 0.0001$, Poisson heterogeneity test). The overall oral antibiotic usage of the combined groups, 2.3 oral antibiotics/person/year, was not significantly different from the average of unselected

health plan members who received any antibiotics during a follow-up year (data not shown). The nine penicillin skin testing positive individuals who received penicillin represented therapeutic errors.

Specific antibiotics use in study subjects by class

The overall specific antibiotic usage in the study population broke down by class as follows. In the penicillin

class, 86% of the courses were amoxicillin containing products, either amoxicillin or amoxicillin/clavulanic acid. In the cephalosporin class, 76% of the courses were cephalexin. In the non-beta-lactam class; 25% were macrolides with erythromycin accounting for 80% of those; 21% were sulfamethoxazole containing; 20% of the courses were tetracyclines, with doxycycline accounting for 73% of those; 15.7% were ciprofloxacin, the only quinolone represented; 5.5% were clindamycin; and no other class accounted for more than 5% in the remainder.

Table 3. Study subject demographics for penicillin skin tests

	Positive (<i>n</i> = 83)	Negative (<i>n</i> = 166)	<i>P</i> -value
Male	26	52	
Female	57	114	
Age at penicillin skin test $\pm$ SD (years)	29.6 $\pm$ 21.0	29.9 $\pm$ 20.9	NS†
Years since index penicillin adverse drug reaction at penicillin skin test $\pm$ SD	7.9 $\pm$ 11.1	12.1 $\pm$ 13.5	NS†
Years of follow-up after penicillin skin test $\pm$ SD	3.1 $\pm$ 1.6	2.8 $\pm$ 1.3	NS†
Total courses of penicillin	14 (to 9 cases)	387 (to 113 controls)	<i>P</i> < 0.0001‡
Courses/subject/year	0.054	0.84	
Total courses of cephalosporin	129 (to 42 cases)	221 (to 80 controls)	<i>P</i> = 0.69‡
Courses/subject/year	0.50	0.48	
Total courses of non-beta-lactam antibiotic	375 (to 74 cases)	529 (to 116 controls)	<i>P</i> = 0.0004‡
Courses/subject/year	1.39	1.15	
Total courses of oral antibiotics	518 (to 83 cases)	1137 (to 166 controls)	<i>P</i> = 0.0001‡
Courses/subject/year	2.02	2.47	

†Not significant by both *t*-tests and Wilcoxon rank-sum tests.

‡Poisson heterogeneity test.

Adverse drug reactions associated with oral antibiotic use

The adverse drug reactions associated with oral antibiotic use during the post penicillin skin test follow-up period are given in Table 4. The overall adverse drug reaction rate per oral antibiotic course, the adverse drug reaction rate per subject exposed, and the adverse drug reaction rate with the first post penicillin skin test exposure are presented for both penicillin skin test positive and penicillin skin test negative study subjects.

Adverse drug reactions per course of oral antibiotic

The overall adverse drug reaction rate, 72 adverse drug reactions in 1655 oral antibiotic courses (4.4%), was not significantly different between penicillin skin test positive (5.0%) and negative (4.0%) groups (*P* = 0.38, Poisson heterogeneity test). However, taking the specific oral antibiotic classes into account, the observed overall adverse drug reaction rates within penicillin skin test groups by oral antibiotic class were not the same (*P* = 0.05, Poisson heterogeneity test). This is due primarily to penicillin reactions among penicillin skin test positives. If we exclude accidental penicillin exposure, the overall adverse drug reaction rates within penicillin

Table 4. Adverse drug reactions associated with different classes of oral antibiotics in penicillin skin test positive and penicillin skin test negative study subjects

Antibiotic class	Penicillin skin test		<i>P</i> -value
	Positive (<i>n</i> = 83)	Negative (<i>n</i> = 166)	
Penicillin	3 adverse drug reactions in 3 cases (3 rashes) Adverse drug reaction/course = 21.4% (14 total courses)	14 adverse drug reactions in 13 controls (11 rashes) Adverse drug reaction/course = 3.6% (387 total courses)	0.001†
	3 adverse drug reactions with first post penicillin skin test exposure (33.3%) (9 cases exposed)	3 adverse drug reactions with first post penicillin skin test exposure (2.7%) (113 controls exposed)	< 0.0001†
Cephalosporin	7 adverse drug reactions in 7 cases (6 rashes) Adverse drug reaction/course = 5.4% (129 total courses)	7 adverse drug reactions in 6 controls (6 rashes) Adverse drug reaction/course = 3.2% (221 total courses)	0.31†
	1 adverse drug reaction with first post penicillin skin test exposure (2.4%) (42 cases exposed)	0 adverse drug reaction with first post penicillin skin test exposure (0.0%) (80 controls exposed)	0.17†
Non-beta-lactam	16 adverse drug reactions in 14 cases (5 rashes) Adverse drug reaction/course = 4.2% (375 total courses)	25 adverse drug reactions in 22 controls (10 rashes) Adverse drug reaction/course = 4.7% (529 total courses)	0.75†
	8 adverse drug reactions with first post penicillin skin test exposure (10.8%) (74 cases exposed)	8 adverse drug reactions with first post penicillin skin test exposure (6.9%) (116 controls exposed)	0.36†

†By Poisson heterogeneity test.

skin test groups were not significantly different ($P = 0.79$, Poisson heterogeneity test).

Adverse drug reactions with first post penicillin skin test exposure

The overall adverse drug reaction rate with first post penicillin skin test exposure, ignoring specific oral antibiotic classes, was significantly different between the penicillin skin test positive and negative groups ($P = 0.01$, Poisson heterogeneity test). The difference was due primarily to penicillin adverse drug reactions in penicillin skin test positive individuals. In the penicillin skin test positive group, the adverse drug reaction rate with first post penicillin skin test oral antibiotic exposure, if we exclude penicillin adverse drug reactions, though lower with cephalosporins (2.4%) than non-beta-lactam antibiotics (10.8%), was not significantly different ($P = 0.12$, Poisson heterogeneity test). There was an unexplained but significantly increased adverse drug reaction rate with the first post penicillin skin test non-beta-lactam antibiotic exposure compared to subsequent non-beta-lactam antibiotic exposure, eight out of 74 vs. eight out of 301 ($P = 0.002$, Poisson heterogeneity test), in penicillin skin test positive individuals. This was the only subgroup where there was a significant increase in first post penicillin skin test oral antibiotic exposure adverse drug reactions.

Within the penicillin skin test negative group, the adverse drug reaction rate with first post penicillin skin test exposure was significantly lower with cephalosporins (0.0%) than non-beta-lactam antibiotics (6.9%) ($P = 0.02$, Poisson heterogeneity test). Cephalosporins were associated with significantly fewer reactions than non-beta-lactam antibiotics ($P = 0.005$, Poisson heterogeneity test) after first post penicillin skin test exposure across penicillin skin test groups. The number of adverse drug reactions, both overall and with first post penicillin skin test exposure, for cephalosporins was always less than expected, though not always significantly so, independent of penicillin skin test result.

Clinical characteristics of adverse drug reactions

There were no serious non-IgE mediated adverse drug reactions seen in this study population, specifically no Stevens–Johnson syndrome, toxic epidermal necrolysis, hepatitis, hemolytic anemia, or nephritis. There were no serious IgE mediated adverse drug reactions, specifically no anaphylaxis. There were only three (33%) adverse drug reactions reported in the nine penicillin skin test positive individuals who, at least initially, were inadvertently exposed to a total of 14 courses of oral penicillin. All had rashes starting more than 24 h after the first post penicillin skin test penicillin exposure. None received any treatment beyond discontinuing the penicillin and taking an oral antihistamine. One individual tolerated a total of three courses of penicillin and three patients tolerated two

courses of penicillin, each after having no reaction with their first accidental post positive penicillin skin test penicillin exposure. Based on rashes occurring with the first post penicillin skin test penicillin exposure, three rashes out of nine exposures in the penicillin skin test positive group and three rashes out of 113 exposures in the penicillin skin test negative group, the sensitivity of the penicillin skin test as described is 50% and the specificity is 94.8%.

The most common adverse drug reactions in the penicillin skin test positive group for all oral antibiotics were rashes, accounting for 14 out of 26 (53.8%) adverse drug reactions. The most common adverse drug reactions in the penicillin skin test negative control group were also rashes, accounting for 27 (58.7%) out of 46 reactions. In penicillin skin test positive individuals, rashes were more likely to occur in cephalosporin associated adverse drug reactions, 6/7 (85.7%), compared to non-beta-lactam antibiotic associated adverse drug reactions, 5/16 (31.3%) ($P = 0.03$, Fisher exact tests). The lack of detail in the comprehensive health plan medical record made accurate characterization of post penicillin skin test adverse drug reaction rashes impossible.

Gastrointestinal adverse drug reactions, including upset stomach, vomiting, and/or diarrhea, were the next most common, accounting for 11 out of 26 reactions (42.3%) in the penicillin skin test positive group. In the penicillin skin test negative group gastrointestinal adverse drug reactions were also the next most common, accounting for 16 (34.8%) out of 46 reactions. All of the gastrointestinal adverse drug reactions were probably not IgE mediated, but were among the most debilitating reported in the entire cohort.

Cephalosporin use in penicillin skin test positive individuals

The seven adverse drug reactions that occurred after cephalosporin exposure in 42 penicillin skin test positive individuals are particularly instructive. One individual tolerated three courses of cefaclor and one course of cephalexin prior to a cefaclor-associated rash on day 2. One individual tolerated one course of cephalexin prior to a cefixime-associated rash on day 7. One individual had no cephalosporin exposure prior to cefixime-associated hives on day 10. One individual tolerated seven courses of cephalexin prior to cephalexin-associated hives. One individual tolerated one course of cefaclor prior to cefuroxime-associated hives. One individual tolerated one course of cephalexin prior to a cephalexin-associated rash on day 2. One individual had no cephalosporin exposure prior to cefixime-associated diarrhea on day 2. In summary, three of the seven individuals tolerated at least one full course of the exact cephalosporin to which they eventually had the adverse drug reaction on subsequent administration. Additionally, although cephalexin accounted for 76% of the cephalosporin use, it accounted

for only two out of seven (29%) of the adverse drug reactions.

Only one (2.4%) of 42 penicillin skin test positive individuals had a rash with their first post penicillin skin test cephalosporin exposure, vs. three rashes (33%) out of nine penicillin skin test positive individuals after their first penicillin exposure ($P = 0.003$, Poisson heterogeneity test). The adverse drug reaction rate with first post penicillin skin test cephalosporin exposure in penicillin skin test negative individuals was not significantly different compared to penicillin skin test positive individuals ($P = 0.16$, Poisson heterogeneity test).

High antibiotic utilizers

There were 39 penicillin skin test negative individuals who in the course of this study received at least one penicillin, one cephalosporin, and one non-beta-lactam antibiotic. This subgroup, which represented only 23.5% (39 out of 166) of the control patients, used 46.3% (526 out of 1137) of the total oral antibiotics and reported 54.3% (25 out of 46) of the total adverse drug reactions. Their adverse drug reaction rate per course of oral antibiotic 25/526 (4.8%) vs. 21/611 (3.4%) was not significantly different ($P = 0.29$, Poisson heterogeneity test) from other 127 control patients. Their oral antibiotic use, 4.04 courses/year of follow-up vs. 1.86 courses/year of follow-up, was significantly greater ($P < 0.0001$, Poisson heterogeneity test). This group used 148 courses of penicillin, 124 courses of cephalosporin, and 254 courses of non-beta-lactam antibiotic, and reported nine adverse drug reactions with penicillins, three adverse drug reactions with cephalosporins, and 13 adverse drug reactions with non-beta-lactam antibiotics.

Discussion

There are two sets of risks that need to be addressed in the evaluation of oral antibiotic associated adverse drug reactions. There are the risks associated with any diagnostic test used, and then the risks associated with future oral antibiotic exposure. This paper provides useful data on both sets of risks as they relate to penicillin 'allergy' history positive individuals undergoing penicillin skin testing and then receiving a variety of oral antibiotics.

Penicillin skin testing is safe when used to evaluate individuals with any potential IgE mediated adverse drug reaction history, with risks well within those tolerated with any skin testing procedure (15). Penicillin should never be given to individuals with a history of a penicillin class antibiotic associated severe non-IgE mediated adverse drug reaction such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatitis, hemolytic anemia or nephritis. Penicillin skin tests should never be used to evaluate individuals with histories of severe non-

IgE mediated adverse drug reactions, because no useful information is obtained. History can tell you who not to test, but history is a poor predictor of who will be penicillin skin test positive (16).

The use of amoxicillin, penicilloate, and penilloate identifies a significant fraction of uniquely penicillin skin test positive individuals missed by penicillin and Pre-Pen™ alone. No special significance, such as being at increased risk of anaphylaxis, could be assigned to those individuals penicillin skin test positive to amoxicillin, penicilloate, or penilloate, because all adverse drug reactions seen in this study were mild. One commonly asked question is, 'Do you have to penicillin skin test with all of the minor determinants if you intend to treat with oral penicillin?' Testing with Pre-Pen™ and penicillin identified 84.2% of the patients that a complete panel including Pre-Pen™, penicillin, amoxicillin, penicilloate, and penilloate would have identified. The sample size needed to show a difference between these two testing strategies with results significant at the 0.05 level 80% of the time if the first strategy would result in 3.1% of the patients reacting and the second would result in 2.7% of the patients reacting, would be 28 124 in each group (using nQuery Advisor 2.0™). The assumptions here are directly taken from the data presented in this paper. The first assumption is that only 9.3% of penicillin associated adverse drug reaction history positive individuals are penicillin skin test positive, the second is that only 33% of penicillin skin test positive individuals will react to oral penicillin, the third is that 2.7% of penicillin skin test negative individuals will react to the first post penicillin skin test penicillin therapeutic course, and the final assumption is that partial penicillin skin testing identifies 84.2% of the positives identified by complete penicillin skin testing. Thus in the average physician's practice it is unlikely that a difference could be noted over the physician's lifetime. We would like to think that the risk of life-threatening penicillin associated adverse drug reactions would be correspondingly lower in those individuals screened out by complete penicillin skin testing, but data to support this hypothesis are not yet available for oral penicillin use. Deaths have been reported with single doses of oral penicillin, although these reports are rare (8). In summary, caution is always recommended and we should continue to strive to try to use the 'safest', most complete, test available.

Adverse reactions during penicillin skin testing do occur and were significantly more likely to have an apparent immunologic cause in penicillin skin test puncture positive individuals, although penicillin skin test positive individuals were overall no more likely to report some adverse reaction compared to penicillin skin test negative individuals.

An unexpected but comforting finding was that only three of the nine penicillin skin testing positive individuals who accidentally received oral penicillin had any adverse

drug reaction, and all of these were rashes that started more than 24 h after exposure. This may provide part of the answer to why the time to onset of index adverse drug reaction symptoms prior to penicillin skin testing does not correlate as well as we would like to think it should with the penicillin skin testing result. This is also supported by the lack of anaphylaxis seen with oral antibiotic use over the course of this study even in non-study patients in our entire health care program, where we monitor for drug associated adverse drug reactions and see all of the allergy problems that require referral in a single office.

Most of the published data on penicillin allergy history positive, penicillin skin test positive individuals subsequently receiving cephalosporins have involved individuals who were hospitalized, had a positive penicillin skin test, and then received a single parenteral cephalosporin course immediately after testing (2,6). Most antibiotic utilization is now oral. Penicillin skin testing is often done in advance of acute need (10,17). Many individuals receive multiple courses of oral antibiotics. Cephalosporins are already commonly given to penicillin 'allergy' history positive individuals (2). There was no significant difference in the cephalosporin utilization rate between the penicillin skin testing positive and negative groups in this study ($P = 0.69$, Poisson heterogeneity test).

Despite amoxicillin accounting for more than 80% of all penicillin class antibiotic use in our cohort, only 17.8% of the penicillin skin test positive individuals were positive to the amoxicillin determinant. This is significantly less than the 125 out of 203 (61.6%) seen by Blanca and co-workers (18). In the study by Blanca an additional 87 individuals were described who had allergy symptoms with penicillin exposure despite negative penicillin skin testing. They did not report on the total number of individuals tested to find these individuals during the years 1985–95. Additionally they reportedly used a five times more concentrated solution of amoxicillin (20 mg/ml vs. 4.0 mg/ml) for penicillin skin testing than can be dissolved in water (19).

No rate of re-sensitization to penicillin after penicillin skin testing could be calculated because repeat penicillin skin testing was not routinely carried out. A study to repeat penicillin skin test penicillin skin test negative individuals who report an adverse drug reaction after penicillin is ongoing to help answer this important question. Solensky and co-workers have recently reported repeat penicillin skin testing 43 penicillin skin test negative subjects who all tolerated three courses of oral penicillin. They found no repeat positive penicillin skin tests (20). In the current study, most penicillin skin test negative individuals (97.3%) tolerated their first post test penicillin exposure. If a penicillin skin test negative individual received any penicillin, he/she used an average of 3.4 courses. Those 13 penicillin skin test negative individuals who reported a penicillin associated adverse

drug reaction received an average of 7.1 courses of penicillin each. Penicillin skin test negative individuals have adverse drug reaction rates to penicillin that are not significantly different from their adverse drug reaction rates to non-penicillin oral antibiotics. There were 87 penicillin skin test negative individuals who were exposed to penicillin and at least one other non-penicillin oral antibiotic in this study. This group noted 13 penicillin associated adverse drug reactions with 325 penicillin courses (4.0% rate) and 25 non-penicillin associated adverse drug reactions with 548 courses of non-penicillin oral antibiotics (4.6% rate) ($P = 0.70$, Poisson heterogeneity test).

In this study there appears to be a subpopulation of penicillin skin testing negative individuals who are at significant risk for adverse drug reactions (3,21,22). They are the individuals who use the most oral antibiotics. These penicillin skin test negative individuals may use more oral antibiotics because they know they are not truly 'allergic'.

The adverse drug reaction rates to oral antibiotics seen in this study are very similar to those reported by Herman and Jick (23); 3.5% had adverse drug reactions with oral amoxicillin in an unselected population. Individuals with histories of penicillin 'allergy' had an overall adverse drug reaction rate to oral antibiotics of 4.4% per course in this study. In the present study there was no significant difference in cephalosporin or non-beta-lactam antibiotic associated adverse drug reaction rates in the penicillin skin test positive cohort compared to the negative controls. Penicillin skin testing was not shown to be clinically useful to rule in or rule out cephalosporin associated adverse drug reactions. There may be a low degree of immunologic cross-reactivity between penicillins and cephalosporins (24). Alternatively, certain individuals may rarely make unique IgE to both. The current study does not support either of these alternatives, but instead argues that it is safer to use cephalosporins when clinically indicated over non-beta-lactam antibiotics in penicillin skin test positive individuals. The true dual allergy rate will be difficult, and may be impossible, to tease out of the relatively common mild adverse drug reactions which occur with all antibiotic usage.

In summary, the more antibiotic exposures a person has, the more likely he/she is going to report an adverse drug reaction. Penicillin skin testing was only able to predict penicillin associated adverse drug reactions in penicillin skin test positive individuals. Penicillin can be safely used in penicillin skin test negative individuals. Ignoring accidental penicillin exposure in penicillin skin test positive individuals, non-beta-lactam antibiotics were associated with more adverse drug reactions than penicillins or cephalosporins, independently of the penicillin skin test result. Cephalosporins can be used as safely or more safely than non-beta-lactam antibiotics in penicillin skin test positive and negative individuals.

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