

Penicillin skin testing in advance of need: Multiyear follow-up in 568 test result-negative subjects exposed to oral penicillins

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Background: There are few published data on adverse drug reactions and/or re-sensitization associated with oral penicillin use in penicillin allergy history-positive/penicillin skin test-negative individuals during routine clinical care with multiyear follow-up.

Objectives: We sought to provide long-term follow-up data on the type, severity, and frequency of adverse reactions associated with oral penicillin use in individuals who have histories of penicillin "allergy" yet also have negative results on penicillin skin tests done in advance of need. We also aimed to repeat testing on individuals with penicillin-associated adverse reactions.

Methods: Medical records were reviewed for penicillin use and associated adverse reactions in all 568 penicillin skin test-negative individuals who had received at least 1 course of oral penicillin after testing but before December 31, 2001, during routine care. These individuals were drawn from a group of 1246 penicillin skin test-negative individuals seen initially between November 16, 1994, and August 13, 2001.

Results: The mean length of follow-up was 4.26 ± 1.64 years (range, 0.39-7.12 years). The mean penicillin exposure was 3.94 ± 3.91 courses (range, 1-22 courses). Only 65 (11.4%) of 568 subjects had any penicillin-associated reactions, and 6 subjects had 2 reactions each. A reaction occurred in 27 subjects (4.8%) with their first penicillin reexposure. There were 71 (3.2%) reactions with 2236 total penicillin courses. There were no serious reactions. Repeated testing was done in 33 subjects older than age 18 years. Only 1 subject was positive on repeated penicillin skin testing.

Conclusion: Penicillin use after negative penicillin skin testing done in advance of need is safe, and re-sensitization is rare. (*J Allergy Clin Immunol* 2003;111:1111-5.)

Key words: Adverse drug reaction, allergy, amoxicillin, antibiotic, outcomes, penicillin, penicillin skin test

Penicillin skin testing has not been widely done in advance of need in the outpatient setting because of fear of potential re-sensitization. Saxon et al,¹ in their review of immediate hypersensitivity reactions to β -lactam antibiotics in 1987, stated that "the results of [penicillin skin] testing cannot be used for more than 72 hours" and that "[penicillin] skin testing must be repeated when a future

course of penicillin is contemplated because the patient may have become clinically re-sensitized from the antigenic boost given from the earlier course of penicillin, or from environmental exposure to penicillin." There had been a report by Mendelson et al² 3 years earlier on 240 children and adolescents who were penicillin-skin tested in advance of need; 219 of these subjects were given a 10-day course of oral penicillin after a negative skin test. There were 3 delayed reactions, occurring from 7 to 10 days after starting the penicillin, and all reactors were skin test-negative when retested 4 to 7 weeks later. The remaining 216 patients who did not have an adverse drug reaction with a single course of oral penicillin had a repeated skin test within 1 to 9 months, and only 2 (0.9%) were positive. These 2 remained positive 6 months later on a third test.

In the 15 years since the review of Saxon et al,¹ there have been 4 studies that have addressed the issue of re-sensitization. Two have looked at re-sensitization after parenteral exposure. The first was a small study of 15 subjects by Parker et al³ that looked at hospitalized patients given parenteral β -lactams after a negative penicillin skin test; 3 subjects (20%) became skin test-positive despite having no acute clinical symptoms with the β -lactam therapy. The authors of that study made the point that older patients might be more likely to become sensitized or re-sensitized than the group studied by Mendelson et al.² A second group, led by Lopez-Serrano,⁴ identified 207 penicillin skin test- and oral/parenteral amoxicillin/penicillin challenge-negative individuals who then had a repeated skin test 10 to 30 days later and a second oral/parenteral challenge. The skin test results converted to positive in 5 patients, and in 5 additional patients there was an adverse drug reaction associated with the second oral/parenteral challenge, despite negative skin test results. One additional subject developed hives with a third course of oral amoxicillin (1 month after the formal study) during the course of usual clinical care and was skin test-positive on a third skin test performed after that reaction.

There have been 2 studies that examined re-sensitization after oral reexposure only. The first was a trial by Pichichero and Pichichero.⁵ They identified a group of 163 penicillin allergy history-positive subjects, aged 6 months to 18 years, who had negative results on the skin test, the initial 5- to 10-day oral challenge, and a repeated skin test. The subjects received a total of 513 courses of oral β -lactams during routine clinical care during a 5.4-year average follow-up, and only 3 had mild, poten-

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tially IgE-mediated adverse reactions. The 3 reactors did not have a third postreaction skin test. Finally, a well-designed trial was conducted in 46 penicillin allergy history-positive, skin test-negative individuals who were given three 10-day courses of oral penicillin, with repeated skin tests between the challenges, by Solensky et al.⁶ All of the individuals remained skin test-negative, and none of them had any clinical symptoms of allergy to penicillin with any of the oral penicillin challenges.

The aforementioned studies had a number of limitations, either singly or in combination, including the following: (1) complex testing and challenge procedures; (2) a relatively small sample size of adult subjects receiving oral antibiotics only; (3) challenges given outside the setting of clinical infections; (4) lack of repeated skin tests after adverse drug reactions in the clinical setting; and (5) relatively short follow-up periods.

To help address these issues, we identified a large, age-diverse cohort of penicillin skin test-negative individuals who had an initial skin test done in advance of need and who, during a follow-up period of several years, had multiple exposures to oral penicillin-class antibiotics given for infections during routine clinical care. We then identified the subgroup of these individuals, older than age 18 years, who reported at least 1 adverse reaction to a posttest penicillin exposure and tried to repeat the skin test on as many of them as possible.

METHODS

This study was reviewed and approved by the Institutional Review Boards of both Kaiser Permanente Southern California and the University of California at San Diego. Repeated penicillin skin testing was restricted to individuals older than 18 years by the University of California at San Diego Institutional Review Board. All subjects had provided written, informed consent for their initial penicillin skin test and subsequent medical record review, which had been approved separately by the Kaiser Permanente Southern California Institutional Review Board. All subjects in this study had all of their penicillin skin testing done at the Kaiser Permanente San Diego Allergy Department and were followed in the San Diego area.

Penicillin skin testing, as previously described, was performed on 1383 individuals between November 16, 1994 and August 13, 2001.⁷ This includes 1081 subjects who, in whole or in part, were previously reported.⁷⁻⁹ Potential subjects for the current study were derived from the entire pool of 1383. For those 33 subjects who had a repeated penicillin skin test as part of this study, we attempted to evaluate the intradermal skin test sites at 48 hours for delayed reactions through use of the criteria established by Romano et al.¹⁰ The penicillin-class antibiotics that the study subjects received were prescribed on the basis of the clinical judgement of their treating physicians, mostly primary care providers in the Departments of Family Practice, Pediatrics, and Internal Medicine.

Health plan computerized pharmacy records were used to identify all penicillin-class oral antibiotics dispensed to all 1246 penicillin skin test-negative individuals from the date of the initial test to December 31, 2001. There were 568 subjects identified who met the entry criteria of having a negative result from an initial penicillin skin test done in advance of need and also of receiving at least 1 course of penicillin during routine clinical care. There were 113 subjects in the current study who had been partially reported in a previous publication.⁹ The narrative written comprehensive health plan medical record of each of the 568 subjects was reviewed for

any additional penicillin exposure. The clinical characteristics of all adverse reactions attributed to oral penicillin exposure were collected through use of the same methods as chart abstractions done on similar patients in previous publications on this population.^{8,9} These records were written primarily by Family Medicine, Internal Medicine, and Pediatric physicians and often were quite brief. The specific words contained in the narrative medical record were used to categorize the primary features of the reactions into 1 of the following 5 groups: anaphylaxis, gastrointestinal reactions, hives, other rashes, and other reactions. An adverse drug reaction was considered significant and was recorded for the purposes of this study if it resulted in an acute change in the oral penicillin use or a recommendation for future penicillin avoidance.

Amoxicillin and amoxicillin/clavulanic acid accounted for >80% of the oral penicillin-class antibiotics used in study subjects. Penicillin VK accounted for most of the rest, with smaller amounts of other penicillins, ampicillin, and dicloxacillin.

The SAS statistics program (version 8.2 for Windows; SAS Institute Inc, Cary, NC) was used for most of the statistical analysis. Calculation of the compound confidence level for the estimate of the expected number of negative to positive skin test conversions was computed by numerical integration with the use of Mathcad 2000 (Mathsoft, Cambridge, Mass). Continuous numeric variables such as age, length of follow-up, and antibiotic use were analyzed with *t* tests and Wilcoxon rank-sum tests. Categorical data were analyzed with contingency tables by χ^2 tests and Fisher exact tests. The number of courses of penicillin per patient-year rates were compared by Poisson regression, PROC GENMOD, by modeling the "number of courses of penicillin" on "reactor status" as a dummy variable with log "length of follow-up" as the offset. The significance reported is the significance of the reactor status dummy variable.¹¹ The post-negative penicillin skin test adverse reaction given index adverse reaction association was examined with an asymmetric conditional lambda coefficient and an asymmetric conditional uncertainty coefficient, as described in the SAS Procedures Guide.¹² Statistical significance was established at $P < .05$, 2-tailed.

RESULTS

Study subject demographics

There were 391 female (68.8%) and 177 male (31.2%) subjects in the overall study cohort. The mean $\pm$ SD age was 39.1 ± 22.6 years (range, 0.2-86.1 years) at the time of the initial skin test. The mean $\pm$ SD time between the index penicillin reaction and the initial negative penicillin skin test was 14.9 ± 15.0 years (range, 0.0-54.8 years). The mean $\pm$ SD length of follow-up was 4.26 ± 1.64 years (range, 0.39-7.12 years). The mean $\pm$ SD penicillin exposure was 3.94 ± 3.91 courses (range, 1-22 courses). There were a total of 71 adverse reactions (3.2%) associated with 2236 total penicillin courses. Table I contains the baseline demographic data for individuals with and without adverse drug reactions occurring during this study, showing reactors compared with nonreactors.

Clinical characteristics of adverse drug reactions

Only 65 individuals had any penicillin-associated adverse reaction, and 6 subjects (9.2%) had 2 reactions each. Table II contains the clinical characteristics of the index adverse reaction and the first post-skin test reexposure reaction for these 65 patients. There was no signifi-

TABLE I. Demographics and clinical characteristics of reactors and nonreactors

	Reactors (n = 65)	Nonreactors (n = 503)	P value
Female (%)	53 (81.5%)	338 (67.2%)	.02*
Age at time of index negative penicillin skin test result (y): mean $\pm$ SD	40.6 $\pm$ 20.4	38.9 $\pm$ 22.9	.60†
Time since index adverse reaction to penicillin at initial negative penicillin skin test (y): mean $\pm$ SD	15.1 $\pm$ 14.1	14.9 $\pm$ 16.1	.46†
Length of follow-up after index negative penicillin skin test result (y): mean $\pm$ SD	4.72 $\pm$ 1.58	4.20 $\pm$ 1.64	.03†
No. of courses of penicillins since index negative penicillin skin test result: mean $\pm$ SD	4.75 $\pm$ 5.10	3.83 $\pm$ 3.72	.50†
No. of courses of penicillins per year of follow-up	1.01	0.91	.11‡
Primary clinical characteristics of index adverse reaction to penicillin (%)			.22§
Anaphylaxis	5 (7.7%)	27 (5.4%)	
Gastrointestinal	1 (1.5%)	16 (3.2%)	
Hives	47 (72.3%)	316 (62.8%)	
Other rashes	8 (12.3%)	53 (10.5%)	
Other	1 (1.5%)	29 (5.8%)	
Unknown	3 (4.6%)	62 (12.3%)	
Reported an adverse reaction associated with the index negative penicillin skin test result	2 (3.1%)	4 (0.8%)	.09§

*Fisher exact test.

†Continuity-corrected *t* approximation to the Wilcoxon rank sum test.

‡Poisson regression (significance of reactor status dummy variable).

§Pearson χ^2 test.

TABLE II. Index adverse reactions compared with first post-negative penicillin skin test result adverse reactions based on narrative medical record

	Post-negative penicillin skin test reactions	Anaphylaxis*	Gastrointestinal	Hives	Other rashes	Other	Unknown
Index reactions	Totals	4	12	16	27	6	0
Anaphylaxis	5	2	1	1	1	0	0
Gastrointestinal	1	1	0	0	0	0	0
Hives	47	1	8	15	18	5	0
Other rashes	8	0	2	0	5	1	0
Other	1	0	1	0	0	0	0
Unknown	3	0	0	0	3	0	0

*See Results section for in-depth descriptions of follow-up medical record review "anaphylaxis" cases.

cant association between the index reaction and the first posttest reaction, as measured by the asymmetric conditional lambda and by the asymmetric conditional uncertainty coefficient. An adverse reaction occurred on the first post-negative skin test penicillin reexposure in 27 (41.5%) of the subjects. Of patients having an adverse reaction with their first post-negative skin test penicillin reexposure, 9 (33.3%) went on to have subsequent penicillin courses with no further reactions. Four of these patients had nonhives rashes, 2 had hives, 2 had other reactions, and 1 had a gastrointestinal reaction. Forty-three subjects (66.2%) had a reaction associated with their last penicillin reexposure during the follow-up period. For all of the subjects who noted an adverse reaction, the first adverse reaction occurred with 2.8 ± 2.8 penicillin exposures (range, 1-14 exposures). There were 43 adverse reactions (66.2%) with rash; nonhives rash was more common than hives; 12 subjects (18.5%) had primary gastrointestinal complaints, and 6 (9.2%) had other reactions, including dizziness, wheez-

ing, and itching without any rash. There were 4 episodes (6.2%) that were nominally described in the narrative medical records as "anaphylaxis."

Further review of these "anaphylaxis" cases revealed that none of these reactions started within 1 hour of antibiotic ingestion; in none of these cases were there systemic symptoms of shortness of breath, faintness, or decreased blood pressure, and all resolved with either no therapy or with antihistamine and/or steroid therapy. Three of 4 of these patients had repeated penicillin skin tests, and all were negative. None of these patients received epinephrine or intravenous fluids. Two patients reacted on their first and only post-negative penicillin skin test penicillin reexposures and 1 patient, despite a second negative skin test result, has to date not received further penicillin. One patient has been lost to follow-up. A third patient reacted after 6 courses of penicillin, had a negative repeated skin test result, and has not received further penicillins to date. The fourth patient with "anaphylaxis" was the most inter-

esting. She reportedly reacted after the second of 3 courses of penicillin given after her first negative penicillin skin test result. She received numerous antibiotics and requests for penicillin "allergy" evaluation because she kept developing recurrent superficial staphylococcal skin infections. She gave a history of "reacting" to virtually all antibiotics except vancomycin and gentamicin. Culture results showed mostly coagulase-negative *Staphylococcus*, but coagulase-positive *Staphylococcus*, which is sensitive to oxacillin and vancomycin, was also noted. She had a negative result on a second skin test done for this study and then had 2 additional courses of penicillin after data collection for this study was closed on December 31, 2001, along with 2 additional negative skin test results. After the fourth negative test result, she was treated with vancomycin. She also had a history of chronic pulmonary embolism (but this was never actually documented), chronic pain, and chronic narcotic use. It was eventually decided that she had Munchausen syndrome.

Repeated-skin test subjects

Thirty-three individuals (59.0%) with reactions, of the 56 who were older than 18 years, could be contacted and agreed to retesting. Only 1 individual was positive on retesting. The mean time from the reexposure reaction to the repeat skin test was 3.0 ± 2.0 years (range, 0.0-6.7 years).

We were able to collect data on delayed reactions at the sites of intradermal skin tests at 48 hours in 29 (87.9%) of 33 subjects, including the 1 subject who was acutely positive. All of the intradermal skin test sites were negative for delayed reactions. In terms of a hypothesis that the true rate of delayed reactions to penicillin in the population is 10%, the observed value of 0 of 29 cases would reject this at the 5% level.

The repeated skin test-positive patient was retested 1.8 years after his reexposure reaction, which was hives and which occurred on his first and only post-negative test penicillin reexposure. This patient's first skin test had been done 2 months after his index amoxicillin-associated adverse reaction, which was hives. His penicillin reexposure was in the form of amoxicillin/clavulanic acid and occurred 8 months after his first test. The patient reacted only to the penilloate reagent on his positive repeat test.

Retested subjects were an average of approximately 10 years older than nonretested subjects (exact Wilcoxon rank-sum test, $P = .0770$ [t test, $P < .05$; however, the underlying distribution was asymmetric]). This was because the 9 individuals under the age of 18 years were not recruited for repeated testing as directed by the Institutional Review Board restrictions. There were no significant differences between those retested and those not retested for the following characteristics: sex (exact Pearson χ^2 test, $P = 1.0000$); length of follow-up (exact Wilcoxon rank-sum test, $P = .4781$); time of adverse reaction onset (exact Wilcoxon rank-sum test, $P = .8212$); and type of reaction (exact Pearson χ^2 , $P = .1480$). The number of courses of penicillin used was not significantly different (Wilcoxon rank-sum test [not exact], $P = .93$). The course number of the penicillin associated with the

adverse drug reaction was not significantly different (Wilcoxon rank-sum test [not exact], $P = .87$).

For only 1 of the 33 adult subjects who had a repeated skin test was the result positive. This rate was then extrapolated to the entire cohort. The calculated percentage of repeated positive test results after an initial negative result from a skin test done in advance of need, restricting retesting to adult patients (>18 years old) who had a penicillin-associated adverse reaction, was 0.38% ($[1/33] \times [56/445]$). The calculated rate with a compound 95% CI was 0.0038 (0.0009 to 0.0171).

Overall adverse reaction rates

There were 309 penicillin courses used during 306.9 subject-follow-up-years in the reactor group and 1929 penicillin courses used during 2112.9 subject follow-up years in the nonreactor group. There was a 4.8% chance of a reaction with the first penicillin reexposure; the rate (95% CI) was 27/568 (0.05 [0.03 to 0.07]). There was a 3.2% chance of a reaction with any individual course of penicillin; the rate (95% CI) was 71/2236 (0.03 [0.02 to 0.04]). There was an 11.4% chance of at least 1 reaction over the duration of the follow-up; the rate (95% CI) was 65 of 568 (0.11 [0.09 to 0.14]).

DISCUSSION

Severe IgE-mediated adverse drug reactions with oral penicillins are rare but do occur.¹³ Oral penicillin given even to skin test-positive individuals does not always result in a serious or even identifiable adverse drug reaction.^{9,14,15} Sogn et al,¹⁶ in their 1984 review on penicillin allergy, concluded that if one needed to give penicillin to a penicillin allergy history-positive individual, "[desensitization] is usually necessary." They based this guideline on the limitations of the commercially available tests at the time, the potential dangers of testing with non-commercial reagents, and the paucity of good outcome safety data. Our earlier article provides evidence that testing in advance of need with a complete panel of well-characterized reagents⁷ is safe and that multiple courses of oral penicillins are well tolerated in most skin test-negative individuals. Our data suggest that most penicillin-associated adverse drug reactions in skin test-negative individuals, including most hives, might not be IgE-mediated. This conclusion is based on the assumption that penicillin skin testing identifies true anti-penicillin IgE-positive individuals. Given the lack of positive tests for delayed reactions in our population, we also provide some evidence that penicillin-specific T cells might not mediate many of these reactions either.¹⁰ Historically we have rarely seen positive delayed reactions with intradermal skin tests (data not shown) but had not routinely collected this information before this study.

Patients experiencing adverse reactions (reactors) were more likely to be female and had a longer duration of follow-up. There were no significant differences seen between the types of index adverse reactions reported in reactors versus nonreactors. Reactors tended toward

reporting more adverse reactions with the initial negative skin test itself, but overall adverse reactions to the penicillin skin test were rare events in this study, in 6 (1.0%) of 601 tests (568 initial tests and 33 repeated tests).

Given the historical concern that any adverse reaction to penicillin represented a potential allergy and could lead to anaphylaxis, it is easy to see how 10% of many outpatient populations carry a history of "penicillin allergy."⁷ After only a little more than 4 years of average follow-up, 11.4% of our study subjects had experienced an event that would historically have been called "penicillin allergy." If instead one assumes that only individuals who had both a clinically significant adverse drug reaction and a positive penicillin skin test could have a true IgE-mediated penicillin allergy, then the rate of penicillin allergy falls to 0.38% in our cohort.

This type of chart review for adverse drug reactions raises an interesting question of what anaphylaxis is.¹⁷ Using primary care physician-reported or patient-reported anaphylaxis as the case definition seems to overestimate true anaphylaxis. If anaphylaxis is defined as an acute event caused by IgE-mediated mast cell degranulation with at least 2 of the characteristics hypotension, shortness of breath, and/or systemic hives, then none of the patients identified as having "anaphylaxis" in our follow-up actually had anaphylaxis. In addition, none of the adverse drug reactions in the entire study resulted in emergency department treatment and/or hospitalization.

Given that the mean time to the repeated skin test after the penicillin reexposure reaction was 3 ± 2 years, one could argue that some potential positives "decayed." The single subject with a positive repeated test result had his first positive test 1.8 years after his second reaction. For comparison, the mean time between index penicillin reaction and positive skin test result for the other 137 penicillin-positive patients (9.9% of the 1383 whom we tested during the period when this study was ongoing) was 9.1 ± 11.8 years (data not shown).

We did not repeat the test in nonreacting patients, analogous to the 1984 study of Mendelson et al² or the 2002 study of Solensky et al.⁶ Clinically, though, if a patient exposed to oral penicillin does not react it is difficult to argue that he or she is at significantly increased risk compared with a random patient receiving oral penicillins. This argument is confounded by studies on penicillin allergy history-negative individuals. The National Institute of Allergy and Infectious Disease trial, which used major and minor determinants, reported in 1992 that 4% of 600 hospitalized patients were penicillin skin test-positive.¹⁴ An older American Academy of Allergy study that did not use minor determinants reported in 1977 that 7% of 1229 subjects, both inpatients and outpatients, were penicillin skin test-positive.¹⁵ The calculations become even more complex because several percent of even unselected populations have some sort of adverse reaction with oral penicillin use.¹⁸

In summary, we provide data that penicillin skin testing in advance of need is safe and, if negative, allows the majority of individuals who carry a history of "penicillin

allergy" to safely use multiple courses of oral penicillin-class antibiotics. Reactions that occur are tolerable but unpredictable. In our study, 3.2% of penicillin courses resulted in a report of an adverse reaction, a rate not significantly different from that of random outpatients.^{18,19} Historical reaction type did not predict future reaction type. Repeated positive penicillin skin test results were extremely rare. This could be due to initial false-negative penicillin skin test results secondary to initial test error, rapid decay of potential true-positive tests, new sensitization, or true resensitization. Further work will be needed to clarify what is happening in these rare individuals.

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