
Determination of the incidence of sensitization after penicillin skin testing

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Background: Concerns for sensitization after penicillin skin testing are a factor in limiting the timing and population for whom this testing is offered. The sensitizing potential of the penicillin skin test has never been studied directly.

Methods: A total of 329 volunteers underwent prick and intradermal skin testing with penicillin G, benzylpenicilloyl-polylysine, and a minor determinant mixture. Those with negative skin testing had repeat testing 4 weeks later. Medical history and antibiotic use were determined by interview, questionnaire, and electronic pharmacy records.

Results: Seventy-two of the 329 subjects (22%) reported a history of previous β -lactam reaction, of which 10 (14%) had a positive initial skin test. Overall, the initial skin test was positive in 23 of 329 (7%). Of the subjects with a negative initial skin test, 239 completed the second test 4 weeks later. Of these, 6 subjects (2.5%, 95% confidence interval 0.5% to 4.5%) converted to a positive skin test. None had taken a β -lactam antibiotic between the two tests, and none had any previous history of β -lactam reaction. One subject reported having never taken a β -lactam antibiotic before. In comparison to the 233 subjects who did not convert their skin test, the statistically significant factors favoring sensitization were: female sex (odds ratio [OR] 6.53, $P = 0.05$), atopy (OR 5.31, $P = 0.04$), and history of food allergy (OR 6.35, $P = 0.02$). There was a trend toward more recent penicillin use in the newly sensitized subjects, but this was not statistically significant.

Conclusion: Penicillin skin testing may sensitize a small number of individuals to penicillin.

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INTRODUCTION

Despite advances in antimicrobial therapy, β -lactam antibiotics remain an important element in the treatment of infectious diseases. The prevalence of self-reported penicillin allergy ranges from 1 to 10% in the general population, although only 10 to 30% of these patients demonstrate serum-specific immunoglobulin E with skin testing.¹ Penicillin skin testing has been found to have an excellent negative predictive value, and >98% of patients with positive histories of penicillin allergy and negative skin test results can tolerate penicillin without difficulty.² There is controversy, however, regarding the length of time that a penicillin skin test remains valid, with recommendations ranging from 72 hours to no time limit.^{3–5} Survey data of practicing allergists and allergy program directors have similarly revealed a wide range of opinion, as reported by Wickern et al⁶; approximately 1 in 3 responders felt that skin test results were only valid if penicillin was immediately administered, 1 in 3 believed the

results were good indefinitely, and the remaining one-third gave answers ranging from 24 hours to 1 year.⁶

Concern that penicillin skin testing is valid for only a brief period stems from rare anecdotal cases and theoretical concerns. In one study⁴ of penicillin skin testing in 740 patients, a patient with a positive history and negative skin tests subsequently had an acute urticarial reaction to penicillin 6 months after the skin testing without intervening antibiotic. Speculation as to the mechanism of penicillin immunoglobulin E sensitization in this patient included ingestion of an unknown dose of penicillin, sensitization from the skin test itself, or sensitization from environmental exposures. Studies have shown the presence of small amounts of penicillin in milk,^{7,8} meat,⁹ and possibly even soft drinks,¹⁰ although many authors question the significance of these environmental exposures.¹¹ Therapeutic courses of penicillin given after negative skin testing have been reported to induce resensitization at a rate between 0 and 16%.^{5,11–14} The potential contribution of sensitization by the skin testing procedure itself has not been investigated, although some authors cite this potential in recommendations limiting the duration of time for which a negative result is valid.³ The purpose of the present study was to evaluate the incidence of sensitization after penicillin skin testing alone and to identify any predisposing factors predictive of skin test conversion.

METHODS

Three hundred twenty-nine volunteer subjects over 18 years of age who were not pregnant or taking systemic steroids, antihistamines, or β -blockers were enrolled in the study,

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Table 1. Comparison of the Background Characteristics of Subjects Overall and Grouped by Results of Penicillin Skin Testing or Reported History of Previous β -Lactam Reaction

	N	% Total subjects	% Male	Mean age	Hx asthma	Hx allergic rhinitis	Hx urticaria	Hx food allergy	Other drug allergy	Atopic	On immuno-therapy	Previous penicillin ever	Penicillin within last 3 years	Previous cephalosporin ever	Cephalosporin within last 3 years
All Patients	329	100%	56%	35.8	12%	30%	4%	9%	4%	25%	7%	92%	34%	26%	11%
Patients grouped by skin testing															
Initial ST negative	306	93%	58%	35.5	9%	29%	4%	8%	5%	24%	7%	92%	31%	26%	11%
Initial ST positive	23	7%	30%	39.5	39%	43%	9%	13%	0%	43%	17%	100%	65%	22%	13%
Second ST negative	233	97.5%	57%	37.2	11%	32%	5%	7%	4%	26%	9%	91%	29%	28%	11%
Second ST positive (converters)	6	2.5%	17%	41.8	17%	17%	0%	33%	17%	67%	0%	83%	50%	0%	0%
Patients grouped by history of previous β -lactam reaction															
History-negative	257	78%	59%	34	9%	26%	4%	7%	4%	23%	7%	90%	38%	25%	10%
History-positive	72	22%	43%	42.2	22%	42%	7%	14%	4%	31%	7%	100%	18%	29%	14%
ST, skin test.															

which was approved by the local institutional review board. Each subject consented to receive two penicillin skin tests timed 4 weeks apart. Prestudy analysis by Poisson distribution predicted that a sample size of 225 would provide a 95% confidence interval greater than zero if the observed rate of conversion was 1.78% or greater. Approximately half of the volunteer subjects were medical students undergoing initial military officer training. The remaining subjects were patients, staff, and students at Wilford Hall Medical Center at Lackland AFB, TX.

Subjects were surveyed by interview and questionnaire for demographic factors and medical history including asthma, allergic rhinitis, urticaria, food or other drug reactions, atopy (defined as at least one positive immediate skin prick test), or concurrent immunotherapy for either aeroallergens or Hymenoptera. A list of 49 commonly used β -lactam antibiotics was provided, and subjects were questioned regarding the time of last use and presence of any reactions. Reactions were grouped into the following categories: 1) a rash, 2) urticaria, 3) angioedema, 4) gastrointestinal symptoms, 5) respiratory symptoms, 6) cardiovascular symptoms, or 7) unknown/childhood reaction. The subjects then received standard prick skin testing on the anterior forearm with penicillin G (Geneva Pharmaceuticals, Broomfield CO; 10,000 units/mL), benzylpenicilloyl-polylysine (PrePen, Hollister-Stier Labs, Spokane, WA; 6×10^{-5} M), minor determinant mixture (MDM, prepared and verified as previously described; 10^{-2} M),¹⁵ saline, and histamine (1 mg/mL). Negative prick skin testing was followed by intradermal (ID) skin testing with 0.02 mL of the same materials with the exception of histamine, which was 0.1 mg/mL. A positive skin prick test was defined as a mean wheal diameter of 3 mm greater than the negative control with surrounding flare, and a positive ID test was defined as a mean wheal diameter of 5 mm and at least 3 mm larger than the negative control, also with surrounding flare. After 4 weeks, subjects were brought back and surveyed for use of any intervening β -lactam antibiotics. Antibiotic use was also verified by querying the pharmacy database for each subject during the study period and for the last 5 years. Repeat penicillin skin testing as described above was then performed to evaluate for sensitization during the 4-week interim period.

RESULTS

Background demographics, medical history, and penicillin or cephalosporin use for the 329 volunteer subjects are shown in Table 1.

Prevalence of Positive History of Reaction to β -Lactams in the Study Group

Seventy-two of the 329 subjects (22%) had a history of a previous reaction to a β -lactam antibiotic. Of these, 10 of 72 (14%) had a positive skin test, and 62 of 72 (86%) had a negative skin test. Compared with the 257 subjects with a negative history, the statistically significant factors favoring the presence of a previous reaction to a β -lactam antibiotic

included: older age ($P < 0.003$), asthma ($P < 0.01$), female sex ($P < 0.01$), food allergy ($P < 0.04$), and allergic rhinitis ($P < 0.05$). Other differences between the history-positive and history-negative groups were not statistically significant (Table 1). Among the 72 subjects with a reported previous β -lactam reaction, there were a total of 75 reactions: 70 reactions to either penicillin, ampicillin, or amoxicillin, and 5 reactions to a cephalosporin (67 subjects reported a reaction to a penicillin alone, 2 reported reactions only to a cephalosporin, and 3 reported reactions to both penicillin and a cephalosporin). The characteristics of these reactions are reported in Table 2. Of the 70 penicillin reactions, 57% could not recall the exact drug, 17% reported penicillin G as the causative agent, 16% amoxicillin, and 10% ampicillin. Of the 5 cephalosporin reactions, cephalexin was implicated in 2, cefaclor in 2, and cefuroxime in 1.

Prevalence of Positive Initial Skin Testing in the Study Group

Twenty-three of 329 subjects (7%) had a positive initial skin test. Of these, 10 of 23 (43%) had a history of previous reaction to a β -lactam antibiotic, and 13 of 23 (57%) did not. Compared with the 306 subjects with a negative initial skin test, the statistically significant factors favoring a positive initial skin test included: asthma ($P < 0.0001$), female sex ($P < 0.01$), and atopy ($P < 0.05$). Trends in the other factors were not statistically significant. One subject with a history of a reaction to penicillin G (38 years ago) had anaphylaxis during initial ID skin testing. The 23 subjects with positive initial skin testing had a total of 31 positive cutaneous reactions: 15 to Prepen, 12 to penicillin G, and 4 to MDM. One of 23 (4%) was positive only to MDM. Nine of 23 subjects (39%) were positive with skin prick testing alone, with the remaining 14 (61%) positive only on ID testing.

Rate of Sensitization

Of the 329 subjects initially enrolled, 23 were excluded from subsequent sensitization analysis because of a positive initial skin test. An additional 67 subjects with a negative initial skin test did not complete the second skin test, leaving 239 sub-

jects (49 of which had a history of previous reaction to a β -lactam antibiotic) for the analysis of the rate of sensitization between the two tests. The main reason for withdrawal in the 67 subjects (54 of which were history-negative and 13 history-positive) was transfer away from the area (ie, because of completion of military training). Of the 239 subjects with negative initial skin testing, 6 (2.5%, 95% confidence interval 0.5 to 4.5%) had a positive second skin test 4 weeks later (Table 1). None of these 6 subjects had a previous history of reaction to a β -lactam antibiotic, and none had taken a β -lactam antibiotic between the two tests. The statistically significant factors associated with sensitization (compared with the 233 patients who did not convert their skin test) were: female sex (5 of 6 subjects, odds ratio [OR] 6.53, $P = 0.05$), atopy (4 of 6 subjects, OR 5.31, $P = 0.04$), and presence of food allergy (2 of 6 subjects, OR 6.35, $P = 0.02$).

With regard to duration since last β -lactam use, of the newly sensitized subjects, one had completed a 21-day course of amoxicillin-clavulanate 3 weeks before her initial negative skin test, one had taken amoxicillin 5 months before, and another had taken penicillin approximately 3 years before. Two other subjects had not had a β -lactam antibiotic for at least 3 years, and one subject reported having *never* taken a β -lactam antibiotic. None reported taking a cephalosporin previously. When comparing the duration since last penicillin use to the 233 subjects not sensitized by skin testing, there was a trend toward more recent penicillin use in the newly sensitized patients (50% vs 29% having taken penicillin within the last 3 years), but this was not statistically significant ($P = 0.19$).

The wheal and flare responses for the initial and followup skin tests in the six newly sensitized subjects are shown in Table 3. Four of 6 were skin test positive to Pen G alone; 1 was positive to both Pen G and PrePen, and 1 was positive to Pen G, PrePen, and MDM. Subjects who converted their skin test to positive were also offered followup penicillin skin testing to evaluate for persistence of their sensitization. Only one patient was available for long-term followup, and underwent repeat skin testing at 2, 4, 9, 12, 15, and 19 months after

Table 2. Characteristics of the Previous β -Lactam Reactions Reported by 72 Subjects

	N	% With "rash"	% With urticaria	% With angioedema	% With GI symptoms	% With respiratory symptoms	% With cardiovascular symptoms	% With childhood or unknown previous reaction	Avg # sx's per pt	Years since last reaction
Penicillin reactions										
ST neg	61	59%	38%	11%	8%	10%	10%	25%	1.5	21.2
ST pos	9	44%	44%	78%	11%	11%	11%	11%	1.9	16.5
Cephalosporin reactions										
ST neg	4	100%	100%	50%	0%	50%	25%	0%	3.3	5.3
ST pos	1	0%	0%	0%	100%	0%	0%	0%	1.0	2.0
Total reactions:	75	59%	41%	21%	9%	12%	11%	21%	1.6	20.5

GI, gastro-intestinal; ST, skin test.

Table 3. Initial and Followup Skin Test Responses in the 6 Newly Sensitized Subjects

Initial Skin Test																				
Subject	PenG				Pre-Pen				MDM				Saline				Histamine			
	Prick		ID		Prick		ID		Prick		ID		Prick		ID		Prick		ID	
	w	f	w	f	w	f	w	f	w	f	w	f	w	f	w	f	w	f	w	f
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	3	12	40
2	0	0	6.5*	0	0	0	4	0	0	0	4	0	0	0	0	0	8	12	8	12
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	3	11	33
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	4	10.5	37.5
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4.5	17.5	9.5	32.5
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	15	10.5	18
Followup Skin Test																				
Subject	PenG				Pre-Pen				MDM				Saline				Histamine			
	Prick		ID		Prick		ID		Prick		ID		Prick		ID		Prick		ID	
	w	f	w	f	w	f	w	f	w	f	w	f	w	f	w	f	w	f	w	f
1	0	0	11	28	0	0	7.5	7.5	0	0	0	0	0	0	0	0	4	4	14	32.5
2	0	0	5	10	0	0	0	0	0	0	0	0	0	0	0	0	5	17.5	10	39
3	0	0	5	5	0	0	3	3	0	0	0	0	0	0	0	0	5	10	15	35
4	2	3	7	7	3†	4	5	5	0	0	9	11	0	0	0	0	3	3	10	50
5	0	0	5	19	0	0	0	0	0	0	0	0	0	0	0	0	3	10	12.5	31
6	0	0	5	8.5	0	0	3	3	0	0	0	0	0	0	0	0	4	4	4	11.5

* In subject 2, there was no erythema on the initial skin test, with definite erythema on the followup skin test.

† In subject 4, the followup skin test prick skin testing for Pre-Pen was considered to be borderline (just at 3 mm), and it was decided to confirm sensitivity by continuing with intradermal testing, which was positive for all 3 determinants.

Wheal and flare sizes are shown, in mm, as the mean sum of orthogonal diameters (length + width/2).

MDM, minor determinant mixture; ID, intradermal skin test; w, wheal; f, flare.

her skin test had converted to positive. Her skin test remained positive to both Pen G and PrePen at the 2-, 4-, 9-, and 12-month repeat tests, but reverted to negative for all reagents at 14 and 19 months. She did not receive any penicillin throughout this time.

Intertest Antibiotic Use

In the 4-week period between the two skin tests, 6 of 239 subjects (2.5%) had taken a β -lactam antibiotic as prescribed by another physician (3 on amoxicillin, 2 cephalexin, 1 cefuroxime). Four of these subjects were history-negative and 2 were history-positive. None of these subjects converted to a positive second skin test.

DISCUSSION

The purpose of this study was to determine the incidence of sensitization after penicillin skin testing alone. In our study population we found a 2.5% rate of sensitization (95% confidence interval 0.5 to 4.5%), defined as conversion from a negative to positive skin test over a period of 4 weeks without intervening medication exposure. This low rate is similar to that found in the general nonallergic population overall, in which people having received a course of penicillin without reaction have an incidence of sensitization estimated between 2 and 4%.^{1,3,17} Other studies evaluating patients with a previous history of allergy to penicillin have found rates of

resensitization from 0 to 16% after oral or parenteral administration of the drug.^{5,11-14} In one of these studies, Mendelson et al¹¹ challenged 219 healthy children with a self-reported history of penicillin or cephalosporin allergy and negative skin testing with a 10-day course of oral penicillin, followed by repeat skin testing 1 to 9 months later. They found that two patients (1% of total group, or 1.5% of those whose history was specifically positive to penicillin) had a positive skin test after the challenge. This is in contrast to Pichichero and Pichichero,¹³ who studied 247 children whose penicillin allergy had been physician-diagnosed and found a significantly higher resensitization rate of 14% when re-tested within 3 to 4 weeks. Parker et al¹² performed repeat skin testing on 18 hospitalized adult patients with previous history of a penicillin reaction who received β -lactam antibiotics after negative skin testing, and found that 3 (16%) had become sensitized within a period of 4 weeks to year.

Another study in Spain by Lopez-Serrano et al¹⁴ evaluated 249 patients with histories of reactions to β -lactam antibiotics for the rate of sensitization after re-exposure to penicillin. They performed initial penicillin skin testing and radioallergosorbent testing, followed if negative by controlled challenge with both intramuscular benzylpenicillin and oral amoxicillin, and evaluated for resensitization 10 to 30 days later with an additional skin test, radioallergosorbent test, and

drug challenge. They found that 11 of 207 patients (5%) with an initial negative evaluation were positive with the second test and/or drug challenge.¹⁴

Most recently, Solensky et al⁵ subjected 48 patients with a history of penicillin allergy and negative skin testing to three serial 10-day oral courses of penicillin, 5 weeks apart, with skin testing performed before each course and 4 weeks after the final course. None of the 46 patients that completed the study converted their skin test to positive, yielding a resensitization rate of 0%.⁵

The route of administration of the drug is also likely an important factor in resensitization, as reactions to penicillin are less likely when given orally.¹⁹ The study with the highest resensitization rate by Parker et al¹² evaluated hospitalized patients, of whom 15 of 18 (83%) had received their antibiotic parenterally.

All of these studies involved patients with a previous history of penicillin allergy and included both skin testing and a medication challenge, either of which may have contributed to subsequent sensitization. Our study evaluated the sensitization potential of the skin testing procedure alone, and found a small but measurable sensitization rate in our population of volunteer subjects, the majority of whom (78%) did not have a history of reaction to penicillin. Interestingly, all six subjects that were sensitized between the two studies were history-negative (had no previous history of reaction to a β -lactam antibiotic). In comparison to the other 233 subjects who did not convert their skin test, the factors favoring conversion were female sex, atopy, and history of food allergy.

Sex has not been reported as a risk factor for sensitization to penicillin overall,⁷ although it is interesting to note that of the 11 patients with "booster" sensitization in the study by Lopez-Serrano et al,¹⁴ 7 (67%) were female, and the majority (83%) of our subjects that converted a negative to positive skin test were female. In most large studies, neither atopy or food allergy have been otherwise associated with increased risk for sensitization to penicillin.⁷

The six newly sensitized subjects also had a trend toward more recent administration of penicillin when compared with the 233 patients not sensitized, although not statistically significant. Some studies have found that more recent penicillin administration can be related to higher incidence of sensitization,^{4,18} whereas others have found no significant relationship between time since last penicillin administration (or previous clinical reaction) and sensitization.^{2,11,13} It has been noted by many authors that sensitization to penicillin appears to decline with time.^{4,11,18} Notably, the study with the lowest resensitization rate (0%) in the previous discussion included patients with the longest mean length of time elapsed since last exposure (25 years, with only six patients exposed within 10 years).⁵ In the study by Lopez-Serrano et al,¹⁴ which had a resensitization rate of 5%, 6 of the 11 resensitized patients had their previous penicillin reaction within 3 years.

Similarly, the individuals newly sensitized in our study were also identified in close temporal relationship to their initial penicillin skin test (4 weeks). If sensitization in these

individuals decreases with time, studies looking for resensitization with longer intervals between initial and subsequent testing may miss such patients. In the one sensitized subject who was available for followup testing, her skin test remained positive for 12 months before reverting to negative. In the study by Mendelson et al,¹¹ the two patients resensitized in their study were identified 6 weeks after initial testing, and remained skin test-positive 6 months later.

Our study differs from previous investigations of sensitization in that we sought to evaluate the potential for sensitization from the penicillin skin testing procedure alone. We did not confirm clinical sensitization with a medication challenge. Another feature is that the majority of our subjects were history-negative, and this population may differ in regard to sensitization by penicillin skin testing, because all of the newly sensitized patients in this study were history-negative. The small number of conversions (6) also limits the power of the statistical analysis.

CONCLUSION

Penicillin skin testing may sensitize a small number of individuals to penicillin.

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