

Evaluation of penicillin hypersensitivity: Value of clinical history and skin testing with penicilloyl-polylysine and penicillin G

A cooperative prospective study of the penicillin
study group of the American Academy of Allergy

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A multicenter cooperative study of almost 3,000 patients by members of the Penicillin Study Group of the American Academy of Allergy has confirmed the usefulness of skin tests to penicillin G (Pen G) and penicilloyl-polylysine (PPL) in the evaluation of penicillin hypersensitivity. Nineteen percent of 1,718 patients with a history of penicillin allergy had positive skin tests to either or both agents, vs 7% of 1,229 patients with no such history. Among patients with a history of penicillin allergy where a detailed history was available, positive skin tests were noted in 46% with a history of anaphylaxis, 17% with a history of urticaria or angioneurotic edema, and 7% with a history of a maculopapular reaction. PPL Generally gave somewhat higher reaction rates than Pen G, but both skin tests were needed to elicit the maximum number of reactors. After skin tests were completed, 379 patients were challenged with penicillin. Six percent of patients with a positive history had an allergic reaction vs 2% of patients with a negative history. However, 67% of the 9 challenged patients with a positive skin test had an allergic reaction, and half of these were immediate or early systemic reactions. Only 3% of the 346 challenged patients with a negative skin test had a reaction to challenge and only one fourth of these had early reactions thought to be possibly mediated by IgE.

The question of penicillin hypersensitivity frequently poses a major problem in the management of infectious diseases. A significant portion of the population have been labeled allergic to penicillin, and this large group of patients may be denied optimal antibiotic therapy for serious infections if we are to rely on the history alone.

The Penicillin Study Group of the American Academy of Allergy has completed a long-term multicenter cooperative study of the value of the clinical

history combined with skin testing to penicillin G (Pen G) and penicilloyl-polylysine (PPL) in the evaluation of the current state of penicillin hypersensitivity in individual subjects. Almost 3,000 patients have been studied by investigators in various centers who supplied data for this report. The recent introduction of penicilloyl-polylysine as a skin testing agent for clinical use adds relevance to these data.

MATERIALS AND METHODS

The study was initiated shortly after PPL became available to the Study Group on an investigational basis. Phase I of the study was primarily concerned with the correlation of the history of penicillin allergy and skin test results. Data on the initial 1,160 patients in Phase I of this study have been previously published¹ and are included in Table I only for summary purposes. An additional 511 patients studied using this same protocol as Phase I, but not previously reported, are also included in Table I. Information on the most recently studied 1,276 patients was collected by 33

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TABLE I. History of penicillin allergy vs skin test results in 2,947 patients (all groups combined)

	No. of patients	PPL+		PG+		Skin test+*	
		No.	%	No.	%	No.	%
Total	2,947	318 (441)†	11 (15)	193 (305)	7 (10)	412 (567)	14 (19)
History							
Negative	1,229	65 (122)†	5 (10)	39 (84)	3 (7)	87 (155)	7 (13)
Positive	1,718	253 (319)†	15 (19)	154 (221)	9 (13)	325 (412)	19 (24)

*Sum of PPL+ and PG+ may be greater than total skin test + since both skin tests were + in some patients.

†Figures in parentheses include positive and borderline skin tests.

members of the Penicillin Study Group in Phase II of this investigation (see acknowledgments). In this phase the emphasis was on the correlation of history and skin tests and the results of challenge of the subjects with penicillin when clinical circumstances require this therapy. A uniform protocol was followed and the data were reported on McBee Keysort Cards. Specific historical data included details regarding the patient's age, sex, diagnosis, and atopic state. Detailed information regarding a history of any previous penicillin therapy or allergic reaction was noted, as well as the investigators' interpretation of the validity of any history of penicillin allergy (i.e., valid, questionable, or invalid).

Two preparations were used for skin testing: (1) penicilloyl-polylysine (PPL) supplied by Kremers Urban Company, Milwaukee, Wis., as Pre-Pen; (2) benzylpenicillin (Pen G) supplied by E. R. Squibb & Sons as potassium penicillin G for injection, USP 1,000,000 U/vial, freshly diluted with saline to a concentration of 10,000 U per milliliter. For maximum safety it was recommended that tests first be done by a scratch technique. Intradermal tests were then to be done on those showing negative scratch tests. More dilute penicillin G solutions were recommended for the initial intradermal tests in cases in which the penicillin sensitivity was suspected to be of a violent character. However, tests were not to be considered negative unless negative reactions were obtained at the final concentration of 10,000 U/cc of penicillin G.

A uniform technique was recommended for the performance of the intradermal test. Only a minimal amount (0.01 to 0.03 ml) of testing reagent was to be injected, so as to make a barely discernible intradermal bleb. A control test was also applied with buffered saline for comparison purposes. The reactions were interpreted at the end of 20 minutes and a record was made of the mean diameter of the wheal of each reaction as well as any area of erythema surrounding the wheal. A Scotch tape impression was made of the outline of the original bleb and resulting wheal and erythema, and this was applied to the card for a permanent record. Reactions were to be recorded as positive if the mean diameter of the wheal was three times the control wheal or greater. Those reactions larger than the control wheal but less than three times the diameter were recorded

as borderline ($\pm$). All details regarding any penicillin therapy and/or reactions following skin testing were noted. Cards were then returned for analysis and were later coded, punched, sorted, and statistical correlations evaluated.

RESULTS

The correlation between the history of penicillin allergy and skin test results in all of the 2,947 patients is presented in Table I. These include patients in Phase I, the interim group, and Phase II. The overall incidence of positive skin tests was 19% among those patients with a history of penicillin allergy, whereas it was 7% if the history was negative ($p < 0.001$). Among the history-positive patients with a positive skin test, the reaction to PPL was positive in 79%, penicillin G in 47%, but 25% of these patients reacted to both reagents. Previous studies¹ have commented on the difficulty in assessing the relevance of the borderline reactions (reactions 1 to 3x control). These are presented separately where feasible. If such borderline responses are included as positive reactions, the incidence of skin reactivity increased to 24% in patients with a history of penicillin allergy vs 13% in those with negative history ($p < 0.001$).

Table II presents the correlation noted between specific data regarding the history of penicillin allergy vs skin tests results in the 1,276 Phase II patients only. The overall incidence of positive skin tests in history-positive patients is significantly lower ($p < 0.001$) than had been noted in Phase I. This may possibly in part be due to the more exacting definition of a positive skin test in relationship to a control test required in the protocol in Phase II. The incidence of positive skin tests was significantly higher among patients with a positive history than noted for patients with a negative history ($p < 0.001$) and especially among those patients with a positive history where: (1) the investigators' opinion was that the history was valid, (2) the history was that of anaphylaxis, an-

TABLE II. Phase II. History of penicillin allergy vs skin test results (1,276 patients)

History	No. of patients	PPL+		Pen G+		Skin test+*	
		No.	%	No.	%	No.	%
<i>A. Total group</i>	1,276	122	10	67	5	161	13
		(167)†	(13)	(109)	(9)	(224)	(18)
History (-)	234	10	4	5	2	14	6
		(14)	(6)	(8)	(3)	(21)	(9)
History (+)	1,042	112	11	62	6	147	14
		(153)	(15)	(103)	(10)	(203)	(20)
<i>B. Interpretation of history</i>							
Valid	437	71	16	37	8	91	21
		(96)†	(22)	(54)	(12)	(119)	(27)
Questionable	498	38	8	24	5	52	10
		(53)	(11)	(44)	(9)	(77)	(16)
Invalid	107	3	3	1	1	4	4
		(4)	(4)	(3)	(3)	(7)	(7)
<i>C. Type of prior reaction</i>							
Anaphylactic	26	9	35	5	19	12	46
		(9)†	(35)	(8)	(31)	(12)	(46)
Other systemic	120	13	11	5	4	16	13
		(17)	(14)	(13)	(11)	(25)	(21)
Angioedema	116	15	13	9	8	21	18
		(19)	(16)	(12)	(11)	(27)	(23)
Urticaria	366	46	13	24	7	59	16
		(66)	(18)	(38)	(10)	(83)	(23)
Maculopapular	258	13	5	12	5	19	7
		(21)	(8)	(23)	(9)	(32)	(12)
Other skin	156	16	10	7	4	20	13
		(21)	(13)	(9)	(6)	(24)	(15)
<i>D. Time since prior reaction before testing</i>							
<1 yr	286	46	16	24	8	61	21
		(56)†	(20)	(37)	(13)	(74)	(26)
1-5 yr	234	23	10	12	5	28	12
		(31)	(13)	(17)	(7)	(39)	(17)
>5 yr	422	35	8	23	5	48	11
		(53)	(13)	(42)	(10)	(76)	(18)
? Time	100	8	8	3	3	10	10
		(13)	(13)	(7)	(7)	(14)	(14)
<i>E. Onset of prior reaction after penicillin</i>							
<30"	93	19	23	13	14	26	28
		(23)†	(25)	(20)	(28)	(32)	(34)
30" - 24'	276	30	11	16	6	41	15
		(42)	(15)	(28)	(10)	(59)	(21)
>24'	517	52	10	28	5	66	13
		(69)	(13)	(40)	(8)	(88)	(17)
? Time	156	11	7	5	3	14	9
		(17)	(11)	(14)	(9)	(24)	(15)

*Sum of PPL+ and PG+ may be greater than total skin test + since both skin tests were + in some patients.

†Figures in parentheses include positive and borderline skin tests.

gioedema, or urticaria, (3) the reaction occurred less than one year prior to testing, or (4) the reaction occurred less than 24 hr after the previous penicillin administration. It is also of interest that patients with a history of a maculopapular reaction do not have

significantly higher incidence of positive skin tests than those with a negative history.

Table III relates the occurrence of adverse reactions to penicillin challenge to any history of penicillin allergy. Although the incidence of reactions to chal-

TABLE III. Reaction to challenge vs history of penicillin allergy

History	No. of patients	No. challenged	No. reaction	% reaction
A. Total group	1,276	379	20	5
History (-)	234	96	2	2
History (+)	1,042	283	18	6
B. Interpretation of history				
Valid	437	113	12	11
Questionable	498	145	6	4
Invalid	107	25	0	—
C. Type of prior reaction				
Anaphylactic	26	6	1	17
Other systemic	120	27	1	4
Angioedema	116	25	2	8
Urticaria	366	94	8	9
Maculopapular	258	85	3	4
Other skin	156	46	3	7
D. Time since prior reaction before testing				
<1 yr	286	56	3	5
1-5 yr	234	62	4	7
<5 yr	422	131	10	8
? Time	100	34	1	3
E. Onset of prior reaction after penicillin				
<30"	93	26	2	8
30"-24'	276	75	3	4
>1 day	517	124	10	8
? Time	156	58	3	5

challenge was higher (6% vs 2%) in those patients with a history of penicillin allergy, the difference is not highly significant ($p < 0.20$). Patients with a negative history of penicillin allergy had a significantly lower incidence of reactions to challenge only when compared to those patients with a valid history of penicillin allergy ($p = 0.03$). One must be mindful of the fact that patients were skin-tested before challenge and hence the low incidence of reactions in both history-negative and history-positive groups may not be representative of a non-skin-tested population.

The correlation of reactions to penicillin challenge compared to the results of prospective skin testing is presented in Table IV. Here a highly significant difference is noted between incidence of adverse reactions to challenge and the results of the prospective skin tests. Although few patients with a positive skin test were challenged with penicillin (9 of 161), the high (67%) incidence of adverse reactions is statistically significant ($p < 0.001$) when compared to a 3% incidence of reactions in 346 of 1,092 skin test-negative patients challenged with penicillin. It is also of importance to note that 253 of these skin test-

TABLE IV. Phase II. Reaction to challenge vs skin test result prior to challenge

result	No. of patients	No. challenged	No. reaction	% reaction
Total Group	1,276	379	20	5%
Skin test -	1,052	346	12	3%
Skin test +	161	9	6	67%
PPL +	122	6	4	67%
PG +	67	3	2	67%
Skin test ±	63	24	2	8%
PPL ±	45	16	1	7%
PG ±	42	12	1	8%

negative challenged patients had a positive history of penicillin allergy.

Table V gives pertinent details regarding the 20 patients in Phase II of the study who had an adverse reaction to penicillin challenge. Among the six skin test-positive challenged patients, 3 had an immediate or early systemic reaction following the skin tests. All responded to therapy, but it is quite likely that these individuals would have had a much more serious reaction if a therapeutic dose of penicillin had been administered rather than a skin test. A fourth patient who was skin test-positive to PPL had delayed urticaria. Patient 5 had erythema to a small dose of penicillin administered in a "rapid desensitization" procedure, but died 10 minutes following therapeutic administration of penicillin from an intracerebral hemorrhage. The 2 patients with equivocal skin tests had reactions probably not IgE-mediated.

Only 3 of the 12 patients with negative skin tests had early reactions thought to be mediated by IgE. Patient 9's reaction occurred during general anesthesia where other drugs were simultaneously being administered, and the tenth patient received tetanus toxoid at the same time as penicillin. Patient 11 had hypotension and generalized pruritus and was skin test-negative to PPL but had not been tested to penicillin G. An additional 5 patients had typical maculopapular reactions, and the remaining 4 had reactions not thought to be IgE-mediated.

A comment should also be made regarding the patients with positive or equivocal skin tests who were challenged with penicillin but who did not have a reaction. Three of the 9 patients with positive skin tests tolerated challenge. One was a 67-yr-old patient with subacute bacterial endocarditis and a positive skin test to PPL who tolerated intravenous penicillin while on treatment with prednisone, 40 mg daily. The second was a 3-yr-old girl with a positive skin test to PPL and ampicillin but negative tests to penicillin.

TABLE V. Phase II. Reactions to challenge—case histories

Case No.	Skin test		History of penicillin allergy	Years ago	Challenge dose	Reaction	Onset after challenge
	PPL	Pen G					
1	—	+	Urticaria	22	Pen G 200 U ID	Gen. urticaria	Imm.
2	—	+	Urticaria	2	Pen G 200 U ID	Anaphylaxis	Imm.
3	+	—	Serum sickness	4	PPL ID	Urticaria and angioedema	6 hr
4	+	—	Urticaria	1/20	Pen G 10 ⁶ U IV	Urticaria	36 days
5	+	—	Angioedema	2	Pen G 30,000 U IV	Local erythema died (IC hem)	10 min.
6	+	—	Sore tongue	2	Pen V 250 QID p.o.	Sore tongue	2 wk
7	±	—	Urticaria	5	Carb. 30 gm IV	Mac Pap rash	2 days
8	—	±	Mac Pap	15	Meth 12 gm IV	Fever	6 days
9	—	—	Injection site	1	Prostaphlin 2 gm IV	Hypotension Urticaria (under anesthesia)	10 min
10	—	—	Urticaria	10	Pen G IM and tetanus toxoid	Hives	24 hr
11	—	N.D.	Rash Gen.	1/4	Pen G 800,000 U p.o.	Gen. pruritus, Hypotension	24 hr
12	—	—	Mac Pap	1/20	Pen G IV	Mac Pap pruritus	24 hr
13	—	—	Urticaria	10	Pen G 400,000 U p.o.	Mac Pap pruritus	12 hr
14	—	—	Mac Pap	16	Pen G IV	Mac Pap generalized	6 days
15	—	—	0	—	Ampicillin p.o.	Mac Pap generalized	4 days
16	—	—	0	—	Pen G IM	Mac Pap, groin	3 days
17	—	—	Anaphylaxis?	11	Pen G IV	Petechiae, fever, arthralgia	4 days
18	—	—	Urticaria	20	Carb. 40 gm IV	Fever, leukopenia	12 days
19	—	—	Urticaria	30	Meth IV	Fever	1 day
20	—	—	Mac Pap	14	Pen G, Meth IV	Coombs + hemolytic anemia	4 days

Abbreviations used: Mac Pap: maculopapular rash; Carb: carbenicillin; Pen G or V: penicillin G or V; Meth: methicillin; ND: not done; ID: intradermally; IV: intravenously; QID: 4 times daily; p.o.: orally; IM: intramuscularly.

This patient tolerated a single oral test dose of penicillin V without adverse reaction. The third patient was noted to have a wheal to PPL but also to the control and was challenged without reaction. An additional 22 patients with equivocal reactions tolerated penicillin therapy without difficulty.

DISCUSSION

These data collected in a clinical setting by a number of investigators are useful in placing the problem of penicillin hypersensitivity in perspective. Good judgment requires avoiding the use of penicillin type drugs if there is a history of penicillin allergy and an alternative therapy is available without added risk to the patient. However, when clinical judgment suggests that using nonpenicillin therapy presents an added risk from the infectious disease itself, skin testing with penicillin G and PPL can give valuable in-

formation that then can be balanced clinically against the risk entailed in using nonpenicillin therapy. Hence, many patients with a false history of penicillin allergy or who have lost their hypersensitivity to the antibiotic need not be denied optimal therapy for serious illnesses.

A prior study² has indicated that the majority of patients with a history of penicillin allergy will tolerate penicillin without reaction. This may relate to either an incorrect initial diagnosis or to the evanescent nature of penicillin hypersensitivity. Serious anaphylactic reactions are uncommon even in history-positive patients. This study provides further evidence to the earlier information³⁻⁴ regarding the usefulness of skin testing to evaluate the real status of a patient's current penicillin hypersensitivity. A positive test indicates that IgE antibodies are present to penicillin or its major antigenic degradation product

(penicilloyl) and that an allergic reaction is likely if penicillin is administered. A negative test to both materials is strong evidence that previous penicillin hypersensitivity has diminished or has ceased to exist.

PPL is now available for clinical use in a single dose ampule. Penicillin G is readily available. The technique of skin testing is well known to physicians. Generally, for reasons of safety, a scratch test should first be performed, followed by an intradermal test if the scratch test is negative. Although more dilute solutions may be used initially, a final test with penicillin G in a concentration of 10,000 U/cc should be used before the test is considered negative. This study and others³⁻⁵ indicate that both PPL and penicillin G should be used to pick up the maximum number of reactors and provide maximum safety.

Although concern regarding the sensitizing potential of penicillin G (PPL is nonsensitizing)⁶ can be raised if skin tests are employed for routine screening, no such concern is justified when testing a patient who is about to receive penicillin therapeutically. Similarly, the risk of an allergic reaction to the skin test can easily be justified if one is testing a patient where serious consideration of administering therapeutic doses of penicillin is planned.

Several problems with regard to penicillin allergy remain unanswered by this study. The role of the "minor determinants" other than penicillin G was not investigated in this study. Although penicillin G itself is the most important minor determinant, cases have been described in which the sensitivity was specific for other metabolites.⁵ A majority of patients with potential immediate or anaphylactic sensitivity to penicillin will be identified by skin testing with penicillin G and PPL, but a small number of patients whose hypersensitivity involves antibody specificity to other penicillin metabolites may remain undetected. An attempt to produce stabilized preparations of sodium benzyl-penicilloate and sodium benzyl-penilloate for skin testing would help reduce this risk further. However, it is unlikely that we can ever predict with 100% certainty that we have identified all potential penicillin reactors. Hence, whenever penicillin hypersensitivity is highly suspected, good judgment requires the careful administration of graded doses of penicillin² under close supervision (experienced M.D. or allergist) in those circumstances in which the drug is needed for serious indications.

Cross-sensitivity between patients allergic to penicillin G and its semisynthetic analogs and the cephalosporin antibiotics also remains incompletely studied. The semisynthetic penicillins all contain the

6 amino-penicillanic acid nucleus which is responsible for their reactivity with body proteins to produce antigenic conjugates.⁷ Exceptions may occur, but all patients with a history of allergy to penicillin G should be presumed to be allergic to the semisynthetic analogs of penicillin.

The cephalosporins contain the 7 amino cephalosporanic acid nucleus and hence are not chemically penicillins, but they do share the common highly reactive beta lactam ring structure. Immunologic studies⁸ have demonstrated cross reactions between the cephalosporins and the penicillins. One clinical study⁹ indicated that patients with a history of penicillin allergy had four times as many allergic reactions to cephalosporin therapy as did patients with no history of penicillin allergy. This was noted to be close to the 6-fold increase in reactions that had previously been found among bacterial endocarditis patients² who had been treated with penicillin itself despite a history of allergic reactions to it. Furthermore, the incidence of allergic reactions to the cephalosporins approached 50% in those few patients with a history of penicillin allergy and a positive PPL skin test who were challenged with these antibiotics.

The role of skin testing in history-negative patients is imprecisely defined. Extrapolation of these and similar data¹⁰ would suggest that it would be useful in screening for the occasional immediate reactor with a negative history. However, no history-negative, skin test-positive patients were challenged in this study, and few have been reported. The time and cost of routine skin testing prior to penicillin administration needs to be balanced against the benefit of detecting those patients with a negative history but a positive skin test. Most investigators would be very reluctant to administer penicillin to a history-negative patient with a positive skin test unless grave indications existed and then adequate precautions would be needed.

This study clearly indicates that skin testing with penicillin G and penicilloyl-polylysine adds valuable data to the management of patients with a history of penicillin allergy who may need penicillin therapeutically. If the tests are negative, the risk of using non-penicillin therapy may far outweigh the relatively small risk of an immediate allergic reaction in this large group of patients. However, if the tests are positive, we can then balance the relatively high risk of an allergic reaction against the seriousness of the therapeutic problem. If penicillin or related drugs must still be used, we should administer the drug with adequate precautions and be prepared to treat anaphylaxis if it should occur.

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