# Penicillin allergy: clinical experience with a battery of skin-test reagents

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*From 1971 through August 1978, 778 patients underwent penicillin skin testing. Each patient gave a history of previous penicillin allergy. The skin-test reagents consisted of (1) fresh solutions of commercially prepared penicillin G (PEN G), ampicillin (AMP), and methicillin (METH); (2) polylysine conjugates of the major antigenic determinants of each of the three drugs; and (3) alkaline hydrolysates of each drug. A total of 108 (14%) patients showed positive reactions to one or more of the reagents. Certain patients showed reactivity to many reagents, whereas others reacted selectively to only one or two reagents. Addition of reagents of AMP and METH resulted in a greater number of positive reactors than when reagents of PEN G alone were used. Of the group whose skin tests were negative, 290 (43%) were later treated with a penicillin, twelve of these (4.1%) had allergic reactions. Eight of the group whose skin tests were positive were subsequently treated, and four of these (50%) had allergic reactions again. A group of 151 patients whose skin tests were negative and 27 patients whose skin tests were positive were treated with a cephalosporin. Only two patients had allergic reactions to the drug; both had had negative skin tests to penicillin. We conclude that the risk of subsequent allergic reactivity to penicillin is much lower if the skin tests are negative than if positive, that testing with semisynthetic penicillins increases the number of skin-test reactors, and that the incidence of allergic reactions is low in patients treated with a cephalosporin. (J ALLERGY CLIN IMMUNOL 69:238, 1982.)*

Clinical experience indicates that many patients who claim to be allergic to penicillin tolerate it without adverse effect.[1-4] The reasons for this discrepancy between the history and the incidence of a subsequent reaction include an incorrect diagnosis of penicillin allergy and a gradual decline in penicillin hypersensitivity with increasing time interval since the last exposure.[5, 6] Accordingly, these patients may be needlessly denied optimal antibiotic therapy. Accurate objective tests would be helpful in defining the patients who are at risk of serious penicillin hypersensitivity.

In this article we present our results since 1971 in skin testing patients with histories of penicillin allergy. In addition to performing tests with PEN G, its major determinant, and a minor determinant preparation, we evaluated similar derivatives of ampicillin and methicillin.

## METHODS

### Patients

From January 1971 through August 1978, 778 patients at the Mayo Clinic underwent skin testing with penicillin derivatives. In each instance the patient related a history of penicillin allergy, and in most instances the attending physician contemplated treatment with PEN G or one of the semisynthetic penicillins.* Specific details concerning penicillin allergy were obtained from each patient's clinical record. In some instances, the historical allergic reactions were clearly defined and recorded, but in others, no comment was made other than "patient allergic to penicillin," or the patient did not know the details of the reaction. In addition, the clinical records were reviewed to determine

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*PEN G and the semisynthetic penicillins will be referred to collectively throughout the article as penicillin unless specifically stated.



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*Abbreviations used*
PEN G: Penicillin G
AMP: Ampicillin
METH: Methicillin
PL: Polylysine conjugate
AH: Alkaline hydrolysate

whether the patients had histories of adverse reactions to one or more of the cephalosporin antibiotics and whether they had been treated with cephalosporin after penicillin skin testing.

From 1971 through 1973, most patients were tested with all nine reagents: the PL, AH, and unmodified forms of PEN G, AMP, and METH (Table I). During the ensuing years, however, reagents of AMP and METH were administered to fewer patients. Thus, in 1977, less than 10% of the patients were tested with METH reagents. There were a number of reasons why all patients did not receive the full battery of nine reagents. First, infants and small children were tested only with the reagents of the antibiotic of interest, usually PEN G but in some instances AMP. During the later years of this observation period, many more small children underwent testing than in the early 1970s. Second, in the latter half of the period of observation the choice of specific testing reagents depended on which antibiotic the attending physician desired to use therapeutically. For example, if PEN G were to be used, the test reagents were usually confined to derivatives of PEN G. If the semisynthetic penicillins were to be used, all nine reagents were usually tested.

## Skin-test reagents

Three skin-test reagents each were prepared from PEN G, AMP, and METH: the major determinant, an AH, and a commercially prepared antibiotic. The reagents were prepared as previously described.[7]

Briefly, the major determinant reagents (poly-L-lysine) of each antibiotic were prepared by the method of Levine.[8] Poly-L-lysine (Pilot Laboratories, Watertown, Mass.) was reacted with PEN G, AMP, or METH in aqueous solution at pH 11.5 for 90 min with 1 mole of drug per mole of epsilon amino group of lysine. The PLs were succinylated three times with a threefold excess of succinic anhydride and were then exhaustively dialyzed against an ion-exchange resin and finally against 0.15M NaCl. All conjugates were analyzed by duplicate Kjeldahl analysis. Penicilloyl analyses were performed on the conjugates by the penamaldate method. From 20% to 35% of epsilon amino groups of PL were substituted by the various penicillins when reacted as described above. The conjugates were diluted in 0.01M phosphate-buffered saline to a concentration of $1 \times 10^{-6}$M of the whole conjugate prior to skin testing. The PL reagents were stored frozen and prepared for use at 1- to 3-mo intervals. They were sterilized by passage through a 0.22-$\mu$m membrane. Solutions were cultured every month to ensure sterility. In addition, the skin reactivity of the PEN G–PL reagent was compared with that of the commercially prepared major determinant reagent of PEN G (Pre-Pen, Kremers-Urban Co., Milwaukee, Wisc.). Thirty consecutive patients were tested with both Pre-Pen and our PEN G–PL reagent. Identical skin-test responses, including both positive and negative reactors, were observed.

**TABLE I.** Annual distribution of patients* and antibiotic reagents in the test battery

| Year | Derivatives of: PEN G | AMP | METH |
|---|---|---|---|
| 1971 | 79 | 71 | 71 |
| 1972 | 70 | 60 | 60 |
| 1973 | 82 | 70 | 60 |
| 1974 | 116 | 73 | 52 |
| 1975 | 102 | 40 | 32 |
| 1976 | 123 | 48 | 36 |
| 1977 | 134 | 36 | 12 |
| 1978 (Jan.-Aug.) | 65 | 24 | 16 |
| Total | 771 | 422 | 339 |

*A total of 778 patients were tested.

One minor determinant preparation of each drug was the AH (presumably the homologous penicilloate) prepared as described by Voss et al.[9] by reacting the drug in aqueous solution with 1N NaOH at pH 11.5 for 90 min, after which the pH was adjusted to 7.4 by the addition of 1N HCl. The AH products were diluted with phosphate-buffered saline to concentrations of $1 \times 10^{-2}$M for each drug, and the volume of the entire reaction was lyophilized. Each week the AH reagents were prepared at $10^{-2}$M in phosphate-buffered saline, assuming 100% yield, and sterilized by passage through a 0.22-$\mu$m membrane.

The commercial unmodified drugs were reconstituted with phosphate-buffered saline within 1 hr of each test. PEN G was applied in a concentration of 6000 U/ml, and AMP and METH were applied in a concentration of 4 mg/ml.

## Skin-test procedures

Scratch testing was done first with each reagent. The skin of the volar surface of the forearm was abraded but not broken, and one drop of test reagent was placed on the abraded skin. Tests were read 15 min later. A positive reaction was defined as a wheal with a surrounding zone of erythema that was 3 mm or greater in diameter. Negative responders were then tested intradermally.

Intradermal tests were performed over the deltoid area of the upper arm. Approximately 0.005 to 0.05 ml of solution was injected so that the initial bleb was 2 to 4 mm in diameter. A positive reaction, measured at 15 min, was a wheal with a surrounding zone of erythema that was at least 1 to 2 mm greater (in two perpendicular diameters) than either the initial bleb or the bleb at the site injected with phosphate-buffered saline. If the wheal at 15 min was the same size as the initial bleb, the test result was considered to be negative. A wheal that increased by 1 to 2 mm but had no associated

**TABLE II.** Correlation of reactivity with antibiotic tested

| Reactivity | No. of patients* PEN G (n = 107) | AMP (n = 75) | METH (n = 73) |
|---|---|---|---|
| All three reagents positive† | 15 | 5 | 5 |
| All three reagents negative | 18 (17%) | 42 (56%) | 46 (63%) |
| One reagent positive | | | |
| Unmodified drug | 22 | 13 | 7 |
| PL (major determinant) | 14 | 5 | 2 |
| AH | 11 | 3 | 6 |
| Two reagents positive | | | |
| Unmodified drug and major determinant | 5 | 0 | 0 |
| Unmodified drug and AH | 14 | 5 | 6 |
| Major determinant and AH | 8 | 2 | 1 |

*Refers only to the select group of 108 patients who had at least one positive skin test.

†The three reagents are the unmodified drug, major determinant, and AH of the individual antibiotic.

erythema, or a wheal that had erythema without a measurable increase in size, was considered a negative reaction.

## RESULTS

Of the 778 patients in this study, 108 (14%) had positive skin reactions; 290 patients who had negative skin tests were treated with a penicillin, and 12 (4.1%) had reactions. A total of 151 patients with negative skin tests were treated with a cephalosporin, and two (1.5%) had reactions. Of those with positive skin tests, only eight were treated with a penicillin drug, and four had reactions. Twenty-seven patients with positive skin tests were treated with a cephalosporin drug, and none of these patients had reactions. Thus, a large majority of patients with histories of penicillin allergy can subsequently be treated safely with penicillin and cephalosporin drugs.

The incidence of skin reactivity with the specific reagents tested in the 108 patients with positive skin tests is shown in Table II. All patients but one in this group were tested with derivatives of PEN G, whereas 75 and 73, were also tested with reagents of AMP or METH, respectively (or both). Eighteen (17%) of the 107 patients tested with PEN G derivatives had positive reactions to at least one of the reagents of AMP or METH but had negative reactions to all derivatives of PEN G. However, 42 (56%) and 46 (63%), respectively, of the patients tested with AMP and METH reagents showed no reactivity to them but were positive to at least one of the PEN G reagents. With each antibiotic group, some patients reacted only to PL, AH, or unmodified drug, whereas others reacted to two or all three of the reagents. In addition, some patients reacted only to all PL reagents of the three antibiotics, others reacted only to AH preparations, and still others reacted to a combination of reagents (for example, one patient reacted only to PL of PEN G and AH of AMP). In many instances, it was impossible to determine from the clinical records which penicillin compound had caused the allergic reaction in the individual patient. Thus no attempt was made to determine whether the patients showed skin reactivity to the same antibiotic that allegedly caused the historical reaction.

**TABLE III.** Correlation of positive reactions with commercially available reagents

| Antigen(s) tested | Patients with positive reactions No. | % | With positive tests (%) |
|---|---|---|---|
| PEN G only | 55 | 7.1 | 50.9 |
| PEN G + PEN G–PL | 79 | 10.2 | 73 |
| PEN G, AMP, METH, and PEN G–PL | 90 | 11.6 | 83 |
| Full reagent battery | 108 | 13.9 | 100 |

In clinical practice, the reagents available for penicillin allergy testing are the unmodified antibiotics themselves and Pre-Pen (the PL reagent for PEN G). Table III depicts the skin-test reactivity in the entire group of patients according to the current availability of testing reagents. If PEN G alone had been used for testing, the positive reaction rate would have been about half that obtained from using the full battery of reagents in the study. The addition of PEN G–PL (comparable to testing with Pre-Pen) increased the reactivity of 10.2% of all the patients tested. Testing unmodified semisynthetic penicillins increased the overall rate of positive reactivity to 11.6%. The application of the PL reagents of AMP and METH and the AH preparations of all three antibiotics therefore resulted in the detection of 18 more patients with positive skin tests, bringing the overall positive reactivity rate to 13.9%.

The 290 treated patients were placed into two categories: (1) those considered to have valid indications of penicillin allergy (for example, urticaria, angioedema, asthma, or anaphylaxis) and (2) those in whom the history was either unknown or believed to be a nonallergic one (that is, those with equivocal

**TABLE IV.** Analysis of reactions to penicillin in patients whose skin tests were negative

| Patient | Antibiotic causing previous reactions | Previous reactions | Reagents tested | Antibiotic used in treatment | Type of reaction | Onset of reaction after challenge |
|---|---|---|---|---|---|---|
| 1 | PEN G | "Drug fever" | PEN G<br>AMP<br>METH | PEN G | "Drug fever" | >24 hr |
| 2 | PEN G | Rash | PEN G<br>METH | AMP | Generalized rash | 3-4 days |
| 3 | PEN G | Urticaria | PEN G<br>AMP | PEN G | Urticaria | <30 min |
| 4 | PEN G | Urticaria | PEN G | Carbenicillin | Urticaria | >24 hr |
| 5 | PEN G | Urticaria | PEN G<br>AMP | AMP | "Adverse reaction" | 12-24 hr |
| 6 | AMP | Rash (?) | PEN G<br>AMP<br>METH | AMP | Urticaria | 4 days* |
| 7 | AMP | Diarrhea | PEN G | PEN G | Urticaria | 12-24 hr |
| 8 | PEN G | Local erythema | PEN G<br>AMP<br>METH | AMP | Urticaria | 6 days |
| 9 | AMP | Unknown | PEN G<br>AMP | AMP | Generalized rash | >24 hr |
| 10 | PEN G | Blisters on hands | PEN G<br>AMP | AMP | Rash on hands | 8 days |
| 11 | METH | Maculopapular rash and blisters | PEN G<br>AMP<br>METH | METH | Maculopapular rash | 3 days |
| 12 | PEN G | Rash | PEN G<br>AMP<br>METH | PEN G<br>+<br>Nafcillin | Generalized maculopapular rash | 7 days |

*Patient tolerated three courses of AMP between 1973 and 1977; in December 1977 a "rash" developed during AMP treatment.

histories). Of the 169 patients considered to have valid histories, seven (4.1%) subsequently had reactions to penicillin treatment. Of the remaining 121 patients with equivocal histories, five (4.1%) also had reactions. Thus, in patients with negative skin tests, regardless of whether the histories of prior reactions were considered valid or equivocal, the incidence of allergic responses to subsequent penicillin treatment was similar.

A synopsis of the patients with negative skin tests who reacted to penicillin therapy is found in Table IV. Six of the 12 patients were given the same antibiotic as that which allegedly caused their previous allergic response. With the exception of one patient (No. 3), none of this group had an allergic reaction immediate in onset. Indeed, patient 3 displayed marked dermographism; each of her test reagents and the phosphate-buffered saline control showed wheals of 3 to 4 mm, with flares of 12 to 20 mm, and the histamine control showed a wheal of 7 mm and a flare of 25 mm. Hence, the dermographic response may have masked positive skin reactivity. In general, the patients responded to the penicillin "challenge" with the same type of clinical reaction as that described historically. Each of these subsequent allergic responses was mild and readily reversible. Five of the patients had urticaria. The other six patients had reactions that were not likely to have been IgE mediated. However, none of these 12 treated patients gave a history of a previous life-threatening reaction to penicillin.

Of the 108 patients with at least one positive skin test, eight were treated subsequently with penicillin. In each, penicillin was given in small amounts initially and gradually increased to full therapeutic doses. Four of these eight patients (50%) developed an allergic response during the penicillin therapy (Table V). None of the reactions was immediate in onset, possibly because of the "desensitization" procedure. Of the four patients who reacted to subsequent penicillin treatment, two received antibiotics that were not tested: carbenicillin in one and nafcillin in the other. The third patient had a positive skin test to METH and reacted to the drug. The fourth had a mild

**TABLE V.** Analysis of penicillin treatment in patients whose skin tests were positive

| Patient | Antibiotic causing previous reaction | Previous reaction | Skin test reactivity* | | Antibiotic used in treatment | Type of reaction | Onset of reaction after challenge |
|---|---|---|---|---|---|---|---|
| | | | Reagents | Grade | | | |
| 1 | PEN G | Urticaria | PEN G | 3+ | Carbenicillin | Mild urticaria | 12-24 hr |
| 2 | PEN G | Urticaria | METH | 2+ | METH | Morbilliform rash and interstitial nephritis | 2 wk |
| 3 | PEN G | Urticaria | PEN G–AH | 3+ | Nafcillin | Urticaria | 24-48 hr |
| | | | AMP–AH | 2+ | | | |
| | | | METH–AH | 2+ | | | |
| | | | PEN G | 3+ | | | |
| | | | AMP | 2+ | | | |
| | | | METH | 2+ | | | |
| 4 | PEN G | Angioedema | METH–AH | 1+ | PEN G | Urticaria | 6 days |
| 5 | PEN G (?) | Unknown | PEN G–PL | 2+ | Carbenicillin | None | — |
| 6 | PEN G | Rash | PEN G–AH | 2+ | Carbenicillin | None | — |
| 7 | PEN G | Morbilliform rash | METH | 2+ | PEN G | None | — |
| 8 | METH | Hypotension | METH–AH | 2+ | METH | None | — |
| | | | METH | 1+ | Oxacillin | | |

*Grading of skin-test positivity to individual reagents; measurement of the average of two perpendicular diameters of the wheal at 15 min in excess of the average diameter of the initial wheal: 1+ = 1 to 2 mm; 2+ = 3 to 4 mm; 3+ = 5 to 8 mm; 4+ = >8 mm.

reaction to METH on skin testing and not to PEN G derivatives. He tolerated PEN G treatment for 6 days before developing mild urticaria. Of the four patients who tolerated penicillin treatment without a reaction, two were treated with an antibiotic not included in the battery of test reagents (carbenicillin). The third patient in this subgroup had a positive skin test only to METH and subsequently tolerated PEN G treatment. The remaining patient, who had previously developed hypotension while receiving an intravenous injection of METH, had positive skin reactivity to the drug yet had no allergic response to treatment that included METH and oxacillin. None of the patients had reactions to the skin-test procedure.

## DISCUSSION

The results presented here confirm the experience of others[1–4, 10] that most patients with previous histories of allergic reactions to penicillin and negative penicillin skin tests tolerate subsequent treatment with penicillin without a further allergic response. The low reactivity rate to subsequent penicillin treatment among patients whose skin tests were negative (4.1%) is in sharp contrast to that of patients whose skin tests were positive. Although only eight patients with positive skin tests were given penicillin, a substantial number (50%) of these reacted again. This also has been found by others.[1, 2]

In this study, the incidence of allergic reactions to the cephalosporin antibiotics was very low; only two of the 178 patients who received cephalosporin had reactions. This incidence (1.1%) is virtually identical to that of patients without histories of penicillin allergy, reported by Petz[11] as 1.7%. It may not accurately reflect the incidence of reactions to cephalosporin because many patients at our institution who have histories of penicillin allergy may have received cephalosporin without having had penicillin skin tests. Nevertheless, the study indicates that most patients with histories of penicillin allergy can safely tolerate cephalosporin.

The incidence of positive skin-test reactivity in patients with penicillin allergy varies according to the population studied. If the tests are performed within 3 mo of the reaction,[3, 5, 12, 13] the rate can be as high as 70% to 100% in patients who have had anaphylactic reactions. However, the incidence has been reported in the range of 10% to 15% in patients in whom the alleged allergic reactions included assorted rashes, local reactions at injection sites, dizziness, and authenticated anaphylactic reactions.[4, 14] These studies include a heterogeneous group of patients both in terms of the types of allergic responses and in the time intervals between testing and the allergic reaction. The resulting low incidence of positive skin-test reactivity (14%) in our group of patients is consistent with

that seen in patients with the spectrum of problems seen in clinical practice. A similar incidence also has been found by others.[1, 4, 14]

Analysis of the patterns of skin-test reactivity revealed considerable variety. Some patients were extremely selective in the antigens to which they reacted; for example, two patients had reactions only to the AH preparation of METH and another only to AMP-PL. However, 14 patients reacted to at least one reagent of each of the three parent antibiotic agents, indicating broad antigenic cross-reactivity. In an earlier study from our institution on a different patient population, Van Dellen et al.[7] observed similar patterns of skin-test responses; some patients exhibited reactivity to only selected antigens, whereas others had reactivity to a wide variety of antigens.

We found that testing with reagents for METH and AMP in addition to PEN G increased the number of patients with positive skin tests (see Table III). Recently, Warrington et al.[4] found that testing with minor determinants to several penicillins in addition to PEN G did not increase the number of patients with positive skin tests. They did not test with a major determinant or PL determinant for any drug other than PEN G. No definite statement can be made as to the significance of the increased number of patients with positive skin tests detected by testing with reagents to AMP and METH in addition to PEN G. Among those 12 patients who had negative skin tests and subsequently had reactions to the administration of a PEN drug, six were not tested with all reagents.

Only a few patients with positive skin tests were treated with a penicillin. This is true also for other studies of penicillin skin-test reagents.[1-3] Of those treated, a high percentage (50% in our study) had subsequent reactions to the penicillin used. No specific pattern was apparent in analyzing those eight patients who were treated.

Unexpectedly, for the patients with negative skin tests the incidence of further allergic reactivity to subsequent treatment with penicillin was identical to the incidence for patients with equivocal or unknown reactions and for patients with valid histories of penicillin allergy. This suggests that the less definite or equivocal history may be as valid as the more definite history.

In our experience, penicillin skin testing is a safe procedure. Although the procedure has proved fatal in at least one reported instance,[15] no serious reaction occurred in any of our 778 patients. In each of our studies, scratch tests were performed initially, and if extreme hypersensitivity was suspected clinically, 100-fold dilutions of the test reagents were given. In some cases, the reagents should be diluted even more. In addition, resuscitation equipment and epinephrine should be easily accessible whenever the tests are performed.

We tested with three reagents for each drug. The unmodified drug was freshly prepared just prior to testing. The only commercially available reagent is the major determinant for PEN G, available as a lyophilized powder in a single-dose vial (Pre-Pen). The AH is not available and its stability is unknown. Arbitrarily, we prepared this weekly on Monday morning. Possibly some patients tested later in the week who were negative to the AH reagent were negative because the reagent had deteriorated. Some of the 12 patients, for example, who were skin-test negative and who had reactions to treatment might have had a positive skin test to the AH reagents were they freshly prepared. Eleven of 90 patients with positive skin tests to the PEN G reagents were positive to the AH and negative to the unmodified drug and the major determinant for an incidence of 12.2%. Sullivan et al.,[16] who prepared their AH daily, found 7.2% of patients who reacted to this agent singly. Thus their findings are little different from our results. Ideally, this reagent should be available lyophilized in single-dose vials so it could be prepared freshly for each test.

Penicillin skin tests are helpful in the management of patients with histories of penicillin allergy who need treatment with a penicillin drug. All histories of penicillin allergy should be taken seriously, whether or not the physician thinks they are valid. If the skin tests are negative, the likelihood of the patient having a reaction to penicillin treatment, from our results, is 4%, which is similar to that found by others.[1, 2] The patients should be fully advised of what is being done, and their consent should be obtained. The patients with negative skin tests are given a small test dose, and if no reaction occurs after 1 hr, the full therapeutic dose is administered, with the patients being closely monitored.

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