JAMA The Journal of the American Medical Association
Issue: Volume 270(20), 24 Nov 1993, pp 2456-2463

Publication Type: [Original Contributions]
ISSN: 0098-7484
Accession: 00005407-199311240-00028

[Original Contributions] « Previous Article | Table of Contents | Next Article »

Clinical Experience With Penicillin Skin Testing in a Large Inner-City STD Clinic.

Gadde, Jyothi; Spence, Michael; Wheeler, Barbara; Adkinson, N. Franklin Jr.

Author Information

From the Division of Allergy and Clinical Immunology, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Md. At the time of the study, Dr Spence was affiliated with the Baltimore City (Md) Eastern Health District Clinic for Sexually Transmitted Disease. He is now with the Department of Obstetrics and Gynecology, Hahnemann Hospital, Philadelphia, Pa.
Reprint requests to The Johns Hopkins Asthma and Allergy Center, 5501 Hopkins Bayview Cir, Baltimore, MD 21224 (Dr Adkinson).
This study was supported by grant AI 11936 from the National Institutes of Health, Bethesda, Md.

Abstract

Objective: To establish (1) the prevalence of positive penicillin skin tests among outpatients with well-defined but variable history of penicillin allergy and (2) the reproducibility, safety, and negative predictive value of skin testing with benzylpenicilloyl polylysine (PPL) and a minor-determinant mixture (MDM).

Design: Serial consenting outpatients with current indications for penicillin therapy were skin-tested in duplicate with PPL and MDM. Subjects with negative skin tests (93% of those positive by history and 95% of those negative by history) received therapeutic courses of benzylpenicillin (81%) or ampicillin (19%). Negative predictive value of skin testing was established by 72-hour follow-up for adverse reactions to drug.

Setting/Patients-A total of 5063 consecutive, qualifying outpatients in a Baltimore, Md, sexually transmitted disease (STD) clinic. The study group was young (73% between 20 and 40 years old), 66% male, and 90% black; 25% had history of atopy. Follow-up was 94% complete.

Results: Positive skin tests were observed in 7.1% of 776 individuals with previous history of penicillin allergy and in 1.7% of 4287 subjects negative by history (P<<.001). Previous history of anaphylaxis or urticaria was associated with significantly higher rates of positive skin tests of 17.3% and 12.4%, respectively (P<<.001). Only 4% with history of exanthem had positive skin tests (P=.03). The coefficient of variation for duplicate skin tests was 11%. Time intervals since last penicillin treatment did not influence the rate of positive skin tests. Adverse reactions to skin tests occurred in 13 (1.2% of patients positive by history; 9.4% of those with positive skin tests). A mild anaphylactic reaction occurred in one individual whose preliminary scratch testing was inadvertently omitted; systemic pruritus or urticaria occurred in 11 subjects; one had a large local reaction. After penicillin administration to individuals with negative skin tests, acute allergic reactions occurred in 0.5% of subjects negative by history compared with 2.9% of subjects positive by history (chi squared (chi^2) =33.3; P=.0001). Reactions were generally mild and self-limited; only two cases of mild anaphylactic reaction occurred, both in patients with history of severe IgE-mediated reaction.

Conclusions: Skin testing with both major and minor penicillin determinants is safe using current recommendations, and both reagents are necessary for maximizing the identification of sensitized subjects. Routine penicillin skin testing can facilitate the safe use of penicillin in 90% of individuals with a previous history of penicillin allergy.

Outline

Abstract
MATERIALS AND METHODS
Subjects
Reagents
Skin-Testing Procedure
Treatment With Penicillinand Follow-up
Statistical Methods
RESULTS
Population Demographics
Rates of Positive Skin Tests Among Groups Positive and Negativeby History
Skin-Test Patterns
Prevalence of Positive PenicillinSkin Tests With Various Historiesof Penicillin Reactions
Distribution of Intensity of Skin-Test Responses
Equivocal Skin Tests
Adverse Reactions to Skin Testing

(JAMA. 1993;270:2456-2463).

A history of penicillin allergy can be elicited in up to 10% of various medical populations [1]. A previous history of hypersensitivity to penicillin has been the principal limiting factor in the use of this efficacious, and otherwise relatively safe, group of drugs. If the patients with continuing risk of acute allergic reactions could be identified, penicillin could be used in many patients who are currently deprived of its benefits. For this purpose, skin testing with two reagents, benzylpenicilloyl polylysine (PPL) and a minor-determinant mixture (MDM), has been widely used. Sensitivity to one or both reagents has been noted in 8.8% to 91% of subjects with prior penicillin allergy in various studies [2]; such individuals are at substantial risk of IgE-mediated hypersensitivity reactions, which can be life threatening [2,3,4,5,6,7,8,9,10]. Conversely, those patients with negative penicillin skin tests are at acceptably low risk for acute reactions, despite prior penicillin reactivity [1,3,4,5,11,12,13,14,15,16,17,18].

Between 1979 and 1984, we established a surveillance program for penicillin allergies in a large public sexually transmitted disease clinic facility in Baltimore, Md. We report herein our experience with penicillin skin testing in 5063 subjects, including 776 who had a previous history of penicillin allergy. We determined the reproducibility and safety of a reliable skin-test method, the prevalence of positive skin tests in patients with previous history of prior reactivity, the frequency of equivocal tests, the pattern of skin-test reactivity to major and minor determinants, and the relationship of time interval since last penicillin treatment to current skin reactivity. We found that penicillin skin testing can be safely performed and reliably interpreted in a high-volume outpatient setting. Penicillin was administered to subjects with negative skin tests. Although a higher rate of adverse reactions was observed in subjects positive by history, the majority of these reactions were mild and self-limited.

Back to Top

MATERIALS AND METHODS

Back to Top

Subjects

A total of 9313 consecutive qualifying subjects from the Baltimore City Eastern Health District Clinic for Sexually Transmitted Disease were evaluated between 1979 and 1984. All had a current indication for penicillin therapy. Previous penicillin use and type of adverse reactions, if any, time elapsed since last penicillin dosage, and personal and family history of atopy (early-onset asthma, seasonal rhinitis, atopic dermatitis) were documented for all subjects. Histories of prior adverse reactions to penicillin were categorized into five groups based on clinical description: (1) anaphylaxis, (2) generalized urticaria, (3) exanthematous rashes, (4) other, and (5) those who were uncertain. All subjects positive by history were skin-tested. Subjects negative by history were invited to participate in a randomized controlled study of the value of routine penicillin skin testing (results to be reported elsewhere). All individuals with negative skin tests in both groups were treated with penicillin. The protocol was approved by the Johns Hopkins Committee on Clinical Investigation, and written informed consent was obtained from all subjects.

Back to Top

Reagents

Benzylpenicilloyl polylysine (Pre-Pen, Schwarz Pharma, Milwaukee, Wis) is a conjugate of benzylpenicillin with poly-L-lysine at a concentration of $6x10^{-5}$ mEq penicilloyl moieties in a sterile phosphate-buffered saline solution. The individual constituents of the penicillin MDM (crystalline benzylpenicillin, benzylpenicilloate, and benzylpenilloate) were prepared and standardized by Schwarz Pharma. The MDM was constituted monthly from lyophilized materials to consist of 10 mmol/L of each of the three constituents in sterile phosphate-buffered solution, pH 7.4, and stored frozen at -20 degrees C until the day of use. The MDM was prepared and used under physician-sponsored Investigational New Drug number 1358.

Back to Top

Skin-Testing Procedure

Interval Since Last Penicillin Treatment and Current Skin-Test Reactivity
Treatment With Penicillin in Patients With Negative Skin Tests
COMMENT
REFERENCES
IMAGE GALLERY

Intradermal skin testing was used for the definitive evaluation of all subjects. All skin tests were performed in duplicate except for diluent control. Sufficient volume of each reagent was injected intradermally, using a 25- to 27-gauge needle and tuberculin syringe to raise a 2- to 3-mm wheal (approximately 0.02 to 0.03 mL). The wheal sizes were marked with a fine-tip ballpoint pen immediately after injection and 20 minutes later, and a permanent record of the wheals was obtained by transferring the outline with transparent tape. Wheal sizes of 5 mm or greater at 20 minutes were considered positive. Erythema was difficult to read in most of the dark-skinned subjects (90% were black), so this parameter was not measured. Preliminary scratch tests with PPL and MDM were performed in patients with previous histories of penicillin allergy. If a large wheal-and-flare response or systemic reaction to a scratch test was observed, subsequent intradermal tests were performed with the corresponding reagent diluted 10 (^{2}) -fold to 10^4 -fold. Subjects who were positive to the MDM were also skin-tested with individual constituents (data to be reported elsewhere). Tests were considered equivocal if only one of the duplicate tests was positive, erythema occurred without wheal formation, the scratch test was positive but intradermal tests were negative, or the subject did not react to at least one of the constituents when the MDM was positive.

Back to Top

Treatment With Penicillinand Follow-up

Skin-test-negative subjects received treatment with penicillin. Subjects with equivocal skin-test results were not treated with beta-lactam antibiotics. Since all of these subjects required treatment for sexually transmitted diseases, appropriate penicillin dosages were given. The majority received high-dose parenteral penicillin (penicillin G procaine, 73%; penicillin G benzathine, 8%) with probenecid. Oral therapy consisting of 3.5 g of ampicillin and probenecid was given to 19%. All patients were followed up by telephone or postcard 72 hours after receiving penicillin. Subjects with previous histories of adverse reactions to penicillin were followed up again at 10 days. Often postcards from patients detailed adverse reactions but did not include any treatment taken. Adverse reactions were classified as clinically similar to IgE-mediated reactions (anaphylaxis, urticaria, and angioedema); cutaneous (nonurticarial rash and/or systemic pruritus); atypical (temporally related but with atypical or undescribed side effects); other possibly immunologic reactions such as fever, chills, and joint swelling; and procaine related (dizziness, light-headedness, nausea, or apprehension occurring within 10 minutes of administration of penicillin G procaine without any other associated symptoms).

Back to Top

Statistical Methods

Categorical frequency data were compared by the chi squared (chi^2) test (df=1 except where noted) or by Fisher's Exact Test. Differences between means were evaluated by Student's t tests, using paired analysis when appropriate. Pearson's product-moment coefficient was calculated to estimate association between continuous variables. All reported P values represent two-tailed tests of the null hypothesis, with values of .05 or less considered statistically significant.

Back to Top

RESULTS

Back to Top

Population Demographics

A total of 9313 subjects were included. The mean age of subjects was 25 years (range, 20 to 80 years); 73% were between 20 and 40 years of age. Women constituted 34% of the population. A personal history of atopy was elicited in 24.9%. Ninety percent of the subjects were black, 9% were white, and the remainder were in other racial groups. Of the study population, 776 (8.3%) reported a previous adverse reaction to penicillin or another beta-lactam antibiotic. Of these, 52 had history of anaphylaxis, 274 had experienced urticaria, 166 had exanthematous rashes, and 227 reported other atypical adverse reactions. Fifty-seven subjects were uncertain about their history or could not recall the particular symptoms experienced. The remaining 8537 (91.7%) denied previous difficulties with penicillin; of these, only 4287 subjects were skin-tested as part of randomized controlled study of routine penicillin skin testing among subjects negative by history (data to be reported elsewhere). A significantly higher percentage of women than men reported previous adverse reactions to penicillin (11.1% vs 6.9%, respectively; chi squared (chi^2) =47.6; P<<.001). A history of atopy (rhinitis, eczema, or asthma) was obtained significantly more frequently among individuals with previous adverse reactions than in those without adverse reactions (34% vs 23%, respectively; chi squared (chi^2) =27.6; P<<.001). Of the 326 patients with histories of anaphylaxis and/or urticaria, 34.4% were atopic by history. A history of rhinitis occurred in 27.4% of subjects positive by history, with 11.9% having asthma and 6.8% demonstrating eczema. In the subjects negative by history, the incidence was lower, with 15.5% having rhinitis, while 8.6% exhibited asthma symptoms and only 2.6% had eczema.

Back to Top

Rates of Positive Skin Tests Among Groups Positive and Negativeby History

A total of 776 individuals with prior histories of adverse reactions to penicillin or other beta-lactam drugs were evaluated by skin testing Table 1. Of these, 55 subjects (7.1%) reacted to either MDM or PPL or both. Another 21 subjects (2.7%) had equivocal skin responses to one or both reagents. Of the 4287 subjects with no previous history of penicillin sensitivity, 73 (1.7%) had positive skin tests. An additional 13 (0.3%) demonstrated equivocal tests. The rate of positive skin tests was significantly higher (chi squared (chi^2) =68.0; P<<.001) in the group positive by history than in the group negative by history (7.1% vs 1.7%, respectively). The rate of equivocal tests was also significantly higher in the group positive by history (2.7% vs 0.3%) (chi squared (chi^2) =57.0; P<<.001). The frequency of atopic background was similar in groups with positive (25%) and negative (25%) skin tests (P=.96), unlike the case with history of prior reactions. Likewise, the prevalence of atopy was not significantly different in skin-test-positive (21%) and skin-test-negative (36%) groups (chi squared (chi^2) =3.3; P=.06) among those with previous histories of anaphylaxis and/or urticaria.


Table 1

Back to Top

Skin-Test Patterns

Of subjects with positive skin tests, 75% reacted to PPL alone, 10.2% to the MDM alone, and 14.8% to both PPL and MDM Table 2. There was no difference in the distribution of skin-test patterns between groups that were positive and negative by history.


Table 2

Back to Top

Prevalence of Positive PenicillinSkin Tests With Various Historiesof Penicillin Reactions

Types of previous reactions and observed skin-sensitivity patterns to the reagents are summarized in Table 3. A history of penicillin anaphylaxis was given by 52 subjects, of whom nine (17.3%) had a positive skin test. Of the 274 subjects with urticarial reactions in the past, 12.4% demonstrated current skin reactivity. Only 4% of those with history of exanthematous rash had a positive skin test. A history of adverse effects other than these three categories was given by 227 individuals, of whom only 1.8% were positive when skin-tested. Among 57 subjects who were uncertain about previous type of reaction, 1.7% demonstrated sensitivity. A previous history of urticaria and/or anaphylaxis is associated with a significantly increased rate of skin-test sensitivity compared with subjects negative by history (chi squared (chi^2) =30.0; P<<.001). Subjects reporting only exanthematous reactions also had a significantly higher rate of reactivity compared with subjects negative by history (chi squared (chi^2) =4.3; P=.03). Other rates of adverse reactions were indistinguishable from those of subjects negative by history (P>=.5, by Fisher's Exact Test). When compared with subjects negative by history, those with anaphylaxis and urticaria had a 10 and seven times greater probability of having positive skin tests, respectively. History of exanthem was associated with a relative risk of 2.4. Subjects whose reactions were categorized as other or uncertain were indistinguishable from the subjects who were negative by history.


Table 3

Back to Top

Distribution of Intensity of Skin-Test Responses

Intensity of skin-test responses was measured as mean orthogonal diameters of the wheals. Duplicate skin tests were in good agreement with a mean coefficient of variation of 9.9% for diameters in the 5- to 9-mm range and 11% for those with 10- to 15-mm diameters. Somewhat higher coefficients of variation of 14.3% and 17.9% were observed in the ranges of 16 to 20 mm and 21 to 24 mm, respectively. Figure 1shows the frequency distribution of mean diameters for PPL and MDM skin tests observed in 128 subjects. The PPL skin tests averaged 13.9+- .4 mm (mean+- SEM), whereas mean diameter of MDM skin tests was 10.7+- .5 mm (P<.001; Table 4. Mean wheal diameters for various skin-test patterns are shown in Table 4. The MDM wheal size was greater in those reacting to both PPL and MDM (P=.008), but this was not observed for PPL skin tests (P=.5). For the 19 subjects reacting to both PPL and MDM, no correlation was observed between the PPL and MDM diameters (r=.25; P>.5) Figure 2.


Table 4


Figure 1


Figure 2

Back to Top

Equivocal Skin Tests

In 21 (2.7%) of 776 subjects positive by history and 13 (0.3%) of 4287 subjects negative by history, skin-testing results were questionable Table 1. Tests were considered equivocal if only one of the duplicate tests was positive (eight subjects), erythema occurred without any wheal formation (five subjects), the scratch test was positive but intradermal tests were negative (five subjects), and all minor-determinant constituents were negative despite positive tests with the mixture (16 subjects). Eighty-two percent of these subjects were retested later (mean interval+- SEM, 52+- 8 days), and all repeat tests were found to be completely negative.

Back to Top

Adverse Reactions to Skin Testing


Table 5

Adverse reactions to skin testing occurred in 13 of 128 subjects with positive skin tests. Patients with a past history of allergic reactions had a higher risk of an adverse reaction to skin testing when compared with the group that was negative by history (10 of 55 vs three of 73; chi squared (chi^2) =4.2; P=.04). The types of reactions, previous history, and current skin-test pattern are shown in Table 5. An anaphylactic reaction occurred in one subject (case 1), in whom scratch testing was inadvertently omitted. In this case, systemic urticaria developed immediately after the intradermal skin test and the patient complained of generalized pruritus, nausea, and dizziness. Mild hypotension was observed and wheezing was heard on auscultation. The patient was treated with epinephrine and diphenhydramine hydrochloride and responded immediately. This patient had had an urticarial reaction to penicillin 17 years previously. She failed to react to PPL but was strongly positive to MDM. Unfortunately, we failed to measure the wheal size during the treatment of her acute reaction.

In three subjects, urticarial reactions occurred after skin tests. One was generalized, another was localized to the shoulders, face, and neck, and in the third, urticarial lesions were limited to the forearm that was skin-tested. Generalized pruritus without any skin lesions was experienced by six subjects, while pruritus of the periorbital area occurred in one and itching limited to the face, arms, and neck was seen in another. All reactions occurred 5 to 25 minutes after skin testing. Diphenhydramine was administered intramuscularly to four patients and oral diphenhydramine was given to five patients. All reactions subsided promptly, and except for case 1, none required emergency attention (noted above).


Table 6

The distribution of intervals since last penicillin exposure Table 6 was the same for subjects with adverse reactions to skin tests (all of whom were skin-test positive) as for skin-test-positive subjects who had no reactions to the skin testing. Mean intervals since last penicillin treatment also did not differ (39+- 29 months vs 48+- 5.1 months; P>=.2).

Back to Top

Interval Since Last Penicillin Treatment and Current Skin-Test Reactivity

Of the 776 individuals positive by history, 748 (96.3%) were able to estimate an interval since last penicillin treatment. This interval was similar in subjects with positive and negative skin tests (65+- 10 months vs 81+- 3.2 months; P>=.1). Of the 4287 subjects negative by history, 3383 (78.9%) recalled an approximate interval since last penicillin treatment, and this interval was similar in skin-test-positive and skin-test-negative subjects (25+- 7.3 months vs 31+- .7 months; P>=.2).

As seen in Table 6, 52% of subjects negative by history had received penicillin within the past year compared with 25% of the subjects positive by history. Skin-test positivity was independent of the interval since last penicillin dose in the subjects negative by history (chi squared (chi^2) =0.02, df=7; P=.9). A higher rate of positive skin tests occurred in individuals positive by history at all intervals when compared with subjects negative by history. In the group positive by history, sensitivity appeared to decline with time, but differences in interval rates did not reach statistical significance. Subjects with previous history of anaphylaxis had significantly higher rates of positive skin tests at all intervals than subjects with other histories.

Back to Top

Treatment With Penicillin in Patients With Negative Skin Tests


Table 7


Table 8


Table 9

Only 649 (92.7%) of the subjects who were positive by history and skin-testnegative elected to receive penicillin treatment Table 7. Of these, 91.8% were followed up for 72 hours; and 54 (9.1%) reported adverse reactions, in 34 of whom these reactions were probably immunologic in origin. However, probable IgE-mediated reactions occurred in only 17 (2.9%). Of these, nine (1.4%) had immediate reactions (within 1 hour), while eight (1.2%) had accelerated reactions (between 1 and 72 hours) Table 8. Delayed reactions (after 72 hours) in only eight of 649 treated patients who were positive by history generally consisted of cutaneous nonurticarial rash or pruritus Table 9.

Anaphylaxis occurred in two subjects. Urticaria, angioedema, and difficulty breathing occurred in both, but no cardiovascular compromise was observed. Both patients responded to epinephrine promptly. Both had received parenteral penicillin G procaine. One of these subjects remained skin-test negative 42 and 132 days later, while the other was positive to MDM on day 18 and to both skin tests at day 128. Twelve of the 15 others were retested Table 8, and three demonstrated positive skin tests.

All of the skin-test-negative subjects who were negative by history received penicillin Table 7. A complete 72-hour follow-up was obtained in 95.1%. Adverse reactions within 72 hours of treatment occurred in 74 patients (1.9%), in 40 (1%) of whom these reactions were judged probably immunopathological in origin (types 1, 2, and 4; Table 7. Possible IgE-mediated reactions occurred in only 0.5%, or 18 subjects. Of these, only three (0.08%) had immediate reactions, while 15 others had accelerated reactions. None had an anaphylactic reaction. Most reactions subsided within 48 hours, with only four subjects having persistent urticaria for longer periods. Repeat skin tests were done in nine of the 18 subjects. Only one of three subjects with an immediate reaction had a skin test that was positive to PPL when repeated on days 33 and 125, but this subject continued to be negative to MDM.

Back to Top

COMMENT

The present study reports our penicillin skin-testing experience in a group of 5063 outpatients from a single center evaluated in a prospective fashion by the same three-person technical team. Since the subjects were recruited from a sexually transmitted disease clinic, they are likely to have received penicillin more frequently and perhaps more recently than an age- and sex-matched sample of the general population. This predominantly young, healthy, male study group may not, therefore, be typical of general outpatient populations with regard to the frequency of sensitization or reactions to beta-lactam antibiotics. However, we would expect the data on skin-testing patterns and their relation to history and time from last exposure to be representative.

The rate of 7.1% for positive skin tests found in our 776 subjects positive by history is lower than the 8% to 40% range of incidences noted in similar outpatient studies [4,11,16]. We also observed positive skin tests in 1.7% of patients negative by history, which is somewhat lower than the rates of 4% to 7% reported in earlier outpatient studies [1,14,15,16,17]. Patient selection [4,11,16], differences in the skin-testing technique [1,14,15,16,17], and criteria used for considering a test positive [14,16] may account for some of the variation in frequency seen. Other possible explanations of our lower prevalence of positive skin tests include a significant decline in the incidence of IgE sensitization from the past decades because of increasing purity and declining use of parenteral repository preparations. Reported rates of positive skin tests have generally been higher among inpatients than outpatients [5,7,19], among subjects with acute allergic reactions to penicillin [4,17,20,21,22], and when skin tests are done within 6 months of a penicillin reaction [4,11,20,21].

Although a history of atopy was observed more frequently in our study in subjects with previous histories of adverse reactions, an atopic background was equally frequent among individuals with positive and negative skin tests. This confirms results in another large outpatient study [19,23] and suggests that atopy may affect the expression of allergic disease but not the rate of drug sensitization.

While 90% of skin-test-positive subjects demonstrated major-determinant sensitivity, a significant minority (10%) reacted to minor determinants alone. These results are in agreement with previous studies in which one or more of the minor penicillin determinants were used [4,5,7,11,12,20,24]. Since IgE antibodies for minor determinants are clinically associated with acute systemic reactions including anaphylaxis [5,8,9,10,25], the use of an MDM is crucial for maximizing the negative predictive value of penicillin skin testing. The association between minor-determinant IgE and anaphylaxis is further demonstrated in the current study by the single subject (case 1, Table 5 who experienced a mild anaphylactic response to skin testing; her skin test was positive to MDM but negative to PPL. Therefore, both PPL and MDM skin tests have to be performed to identify patients at risk of anaphylaxis.

We report herein the distribution of reactions (as manifested by wheal size) to penicillin skin tests for the first time. Mean wheal size for MDM was 18% smaller than for PPL (P=.02). Thus, the penicilloyl response was "major" both in terms of frequency and intensity of reaction. The lack of correlation between PPL and MDM wheal diameters suggests that the minor-determinant response is predominantly to nonpenicilloyl determinants [24,26]. The somewhat weaker skin responses to the minor determinants in part may be due to the unconjugated simple haptenic form currently used in MDM testing.

Duplicate skin tests allowed us to demonstrate that reproducibility of positive skin tests is acceptable. The coefficients of variation ranged from 10% to 18%, and as expected, variation was higher for wheal sizes greater than 15 mm. Eight of 5063 skin-tested subjects tested positive to only one of the duplicate tests; when immediately retested in duplicate, all were negative, indicating some potential for false-positive results. In addition, an indeterminant number of discordant duplicate skin tests produced clearly positive results when repeated. Equivocal tests occurred in others due to erythema without any wheal formation (n=5), a positive scratch test with no reaction to the intradermal test (n=5), and a positive reaction to the MDM without sensitivity to any of its constituents (n=16). Thus, we believe that duplicate skin testing is an important routine for drug-allergy skin testing to minimize erroneous results.

Adverse reactions including anaphylaxis have occurred following penicillin skin testing [16,20,22,27,28]. Among the 128 patients with positive skin tests, 12 (9.4%) experienced some systemic responses to testing. Nine of the 12 had previous histories of IgE-mediated (type 1, Table 7 reactions. The interval since last penicillin treatment was not significantly different among those who reacted to skin tests than among those who did not react to skin tests Table 6. Two thirds of these reactions involved systemic pruritus without other signs and symptoms. Three patients (2.3%) had urticaria, and one of these received therapeutic intervention with oral antihistamines. Only one patient had anaphylaxis. A 31-year-old woman with a history of penicillin-induced urticaria was skin-tested intradermally without preliminary scratch tests. This accidental deviation from our usual procedure reinforces our belief in the importance of preliminary scratch testing in subjects positive by history. Intradermal testing may not be necessary after strongly positive scratch tests and may evoke systemic reactions in highly sensitive patients. However, because scratch tests are notorious for false-positive results (five cases in this series), we recommend that weakly positive scratch testing be followed by intradermal testing, but beginning with a 1:100 dilution of the standard reagent concentrations.

Subjects with histories suggesting IgE-mediated reactions such as anaphylaxis and urticaria clearly have a higher prevalence of positive skin tests (17.3% and 12.4%, respectively) compared with those with histories suggesting non-IgE-mediated reactions (1.7% to 4%) [4,13,20,21,22]. Of interest is that skin-test rates among those with histories of exanthem are significantly higher than for subjects negative by history (4% vs 1.5%; chi squared (chi^2) =4.3; P=.03), suggesting that some of these reactions were probably IgE-mediated, which indicates the lack of precision of historical information. The lower rates of positive skin tests seen in our subjects with anaphylaxis and/or urticaria compared with other studies (42% to 83%) [4,13,20,21,22] may reflect longer intervals since last treatment (77% who had an adverse reaction to penicillin had their last treatment more than 1 year earlier).

Penicillin hypersensitivity declines with time [4,11,20,21]. The interval since last penicillin treatment did not significantly influence the rate of current skin-test reactivity in individuals negative by history, although about half had received penicillin within the past year. Among those with previous adverse reactions, a trend of decreasing reactivity was noted over time, although this was not statistically significant. Others have reported a significant decline [4,11,20,21]. The lower overall reactivity rates in our study and the fact that 77% with anaphylaxis and/or urticaria had last received penicillin over a year earlier might explain our inability to demonstrate any significant loss of sensitivity with time. Our findings suggest that approximately 80% of individuals with IgE-mediated reactions could safely be treated with penicillin within 1 year from their adverse reaction with the aid of skin testing.

Adverse reactions to therapeutic doses of penicillin in subjects with skin tests negative to PPL and MDM have been reported to occur in 0.1% to 7% of treated cases [1,3,4,11,12,13,14,15,16,17,18,29,30]. We observed a similarly low incidence of possibly IgE-mediated reactions. Although 9.1% of subjects who were positive by history experienced adverse effects, less than one third of these reactions, or 2.9% of those treated, were probably IgE-mediated. This is comparable with the 1.2% rate of immediate reactions reported by the National Institute of Allergy and Infectious Diseases collaborative trial [30]. Mild anaphylaxis occurred in two of our subjects, both of whom had a previous history of severe IgE-mediated reactions, and both received penicillin G procaine intramuscularly. All of our subjects received a bolus of parenteral or high-dose oral penicillin, which might account for the increased rate of overall adverse reactions. Either subthreshold sensitivity to the skin-testing reagent concentrations used or misinterpretation of the original skin tests (unlikely, with duplication) could account for positive results when skin tests were repeated at a later date in some of the individuals reacting to penicillin treatment.

On the other hand, the vast majority (over 97%) of patients with previous penicillin allergy were able to tolerate full-dose therapy after negative penicillin skin tests. This finding, coupled with the high prevalence of negative skin tests in subjects positive by history, suggests that penicillin skin testing can be a valuable tool to permit beta-lactam therapy to be used safely in most patients who are now stigmatized with the label of penicillin allergy. This conclusion is supported by numerous studies with similar findings [1,3,4,5,11,12,13,14,15,16,17,18], but has recently been challenged. Redelmeier and Sox [31], using a decision-analysis approach with a meta-analysis of published data, concluded that skin testing is unnecessary in patients with "convincing histories of severe allergic reactions to penicillin." This study has been criticized for its unvalidated assumptions and uncritical pooling of studies with and without minor-determinant testing [32]. Their principal conclusion hinges on an estimate of a pretest probability of .5 for severe allergic reactions among patients with "very strong" histories of penicillin allergy. Clearly, this is a gross overestimate since in the current study only 17% of patients with convincing histories of anaphylaxis had positive skin tests, and the risk of treatment with penicillin in skin-test-positive patients who are positive by history has been estimated at 0.5 to 0.7 [2,3,4,5,6,7,8,9,10].

Whether these remaining results are generalizable to patients whose mast-cell function may be impaired by intensive chemotherapy or immunodeficiency is currently unknown. However, over the past 10 years, we have proceeded in such patients with extra caution and have not experienced difficulties. We conclude that skin testing with major and minor determinants of penicillin is safe when intradermal testing is preceded by puncture or scratch tests. Skin testing with the major-determinant PPL alone will identify the majority of sensitized subjects. However, about 10% of allergic individuals will be missed if minor-determinant reagents are not included. Only 7.1% of subjects with a previous history of penicillin allergy have IgE-mediated sensitivity as measured by skin testing. A previous history of anaphylaxis or urticaria is more likely to be accompanied by positive skin tests than a history of exanthem or other reaction types. Sensitivity clearly declines with time. Re-treatment with penicillin was well tolerated by the vast majority of skin-test-negative patients who were positive by history. Therefore, skin testing with both reagents should permit the use of this otherwise safe and efficacious group of antibiotics in over 90% of individuals with previous histories of reactions.

We gratefully acknowledge the helpful assistance of the Baltimore City Health Department and the staff of its Eastern Health Division Clinic for Sexually Transmitted Disease, Baltimore, Md.

Back to Top

REFERENCES

1. Lentz JW, Nichol L. Penicilloyl-polylysine intradermal testing for penicillin hypersensitivity. Br J Venereal Dis. 1970;46:457-460. [Context Link]

2. Weiss ME. Immediate hypersensitivity reaction to penicillin and related antibiotics. Clin Allergy. 1988;18:515-540. LinkSource | Bibliographic Links | [Context Link]

3. Chandre RK, Joylekan SA, Tomes E. Penicillin allergy: antipenicillin IgE antibodies and immediate hypersensitivity skin reactions employing major and minor determinants of penicillin. Arch Dis Child. 1980;55:857-860. LinkSource | [Context Link]

4. Green GR, Rosenblum AH, Sweet LC. Evaluation of penicillin hypersensitivity: value of clinical history and skin testing with penicilloyl-polylysine and penicillin G. J Allergy Clin Immunol. 1977;60:339-345. LinkSource | Bibliographic Links | [Context Link]

5. Levine BB, Zolov DM. Prediction of penicillin allergy by immunologic tests. J Allergy. 1969;43:231-244. [Context Link]

6. Graybill Jr, Sande MA, Reinarz JA, Shapiro SR. Controlled penicillin anaphylaxis leading to desensitization. South Med J. 1974;67:62-64. MGH Ovid Full Text | Bibliographic Links | [Context Link]

7. Adkinson NF, Thomspon W, Lichtenstein LM. Routine use of penicillin skin testing on an inpatient service. N Engl J Med. 1971;285:22-24. LinkSource | Bibliographic Links | [Context Link]

8. Gorevic PD, Levine BB. Desensitization of anaphylactic hypersensitivity specific for the penicilloate minor determinant of penicillin and carbenicillin. J Allergy Clin Immunol. 1981;68:267-272. LinkSource | Bibliographic Links | [Context Link]

9. Brown LA, Goldberg ND, Shearer WT. Long-term ticarcillin desensitization by the continuous oral administration of penicillin. J Allergy Clin Immunol. 1982;69:51-54. LinkSource | Bibliographic Links | [Context Link]

10. Naclerio RM, Mizrahi E, Adkinson NF III. Desensitization and maintenance of clinical tolerance to penicillin in an exquisitely allergic subject. J Allergy Clin Immunol. 1982;69:139. Abstract. [Context Link]

11. Mendelson LM, Ressler C, Rosen JP, Selcow JE. Routine elective penicillin allergy skin testing in children and adolescents: study of sensitization. J Allergy Clin Immunol. 1984;73:76-81. LinkSource | Bibliographic Links | [Context Link]

12. Solley GO, Gleich GJ, Van Dellen RG. Penicillin allergy: clinical experience with a battery of skin test reagents. J Allergy Clin Immunol. 1982;69:238-244. LinkSource | Bibliographic Links | [Context Link]

13. Warrington RJ, Simons FER, Holt W, Gorski BA. Diagnosis of penicillin allergy by skin testing: the Manitoba experience. Can Med Assoc J. 1978;11:787. LinkSource | Bibliographic Links | [Context Link]

14. Rytel MW, Klion FM, Arlander TR, Miller LF. Detection of penicillin hypersensitivity with penicilloyl-polylysine. JAMA. 1963;186:894-898. LinkSource | Bibliographic Links | [Context Link]

15. Parker JW, Shapiro J, Kern M, Eisen HN. Hypersensitivity to penicillin acid derivative in human beings with penicillin allergy. J Exp Med. 1962;115:821-838. LinkSource | Bibliographic Links | [Context Link]

16. Brown BC, Price EV, Moore MB. Penicilloyl polylysine as an intradermal test of penicillin sensitivity. JAMA. 1964;189:599-604. LinkSource | Bibliographic Links | [Context Link]

17. Budd MA, Parker CW, Norden CW. Evaluation of intradermal skin tests in penicillin hypersensitivity. JAMA. 1964;190:115-117. LinkSource | [Context Link]

18. Sullivan TJ, Wedner HJ, Shatz GS, Yecies LD, Parker CW. Skin testing to detect penicillin allergy. J Allergy Clin Immunol. 1981;68:171-180. LinkSource | Bibliographic Links | [Context Link]

19. Sogn DD. Penicillin allergy. J Allergy Clin Immunol. 1984;74:589-593. LinkSource | Bibliographic Links | [Context Link]

20. Sullivan TJ. Pathogenesis and management of allergic reaction to penicillin and other beta-lactam antibiotics. Pediatr Infect Dis. 1982;1:344-350. MGH Ovid Full Text | Bibliographic Links | [Context Link]

21. Finke S, Greico M, Connell J. Results of comparative skin tests with penicilloyl-polylysine and penicillin patients with penicillin allergy. Am J Med. 1965;38:71-82. [Context Link]

22. Tuchinda M, Chaleg Y. Evaluation of skin testing in children with penicillin hypersensitivity. J Med Assoc Thai. 1980;63:143-147. LinkSource | Bibliographic Links | [Context Link]

23. Sogn DD. Prevention of allergic reactions to penicillin. J Allergy Clin Immunol. 1987;78:1051-1052. LinkSource | Bibliographic Links | [Context Link]

24. Voss HW, Redmond AP, Levine BB. Clinical detection of the potential allergic reactor to penicillin by immunologic tests. JAMA. 1966;196:679-683. LinkSource | [Context Link]

25. Seigel BB, Levine BB. Antigenic specificities of skin sensitizing antibodies in sera from patients with immediate systemic allergic reactions to penicillin. J Allergy. 1964;35:488-498. LinkSource | Bibliographic Links | [Context Link]

26. Levine BB, Redmond HF, Fellner MJ. Penicillin allergy and the heterogeneous immune response of man to benzyl penicillin. J Clin Invest. 1966;45:1895-1906. [Context Link]

27. Rose B. Allergic reactions to penicillin. J Allergy. 1953;24:383. LinkSource | [Context Link]

28. Dogliotti M. An instance of fatal reaction to the penicillin scratch test. Dermatologica. 1968;136:489. LinkSource | Bibliographic Links | [Context Link]

29. Sogn DD, Casale TB, Condemi JJ, et al. Interim results of the NIAID collaborative clinical trial of skin testing with major and minor penicillin derivatives in hospitalized adults. J Allergy Clin Immunol. 1983;71:147. Abstract. [Context Link]

30. Sogn DC, Evans R III, Shepherd GM, et al. Results of the National Institute of Allergy and Infectious Diseases collaborative clinical trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. Arch Intern Med. 1992;152:1023-1032. LinkSource | [Context Link]

31. Redelmeier DA, Sox HC Jr. The role of skin testing for penicillin allergy. Arch Intern Med. 1990;150:1939-1945. LinkSource | Bibliographic Links | [Context Link]

32. Shepherd G, Mendelson L. The role of skin testing for penicillin allergy. Arch Intern Med. 1992;152:2505. LinkSource | Bibliographic Links | [Context Link]

IMAGE GALLERY

Select All

Export Selected to PowerPoint

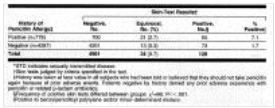

Table 1

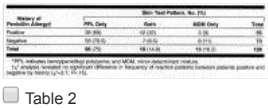

Table 2

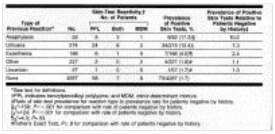

Table 3

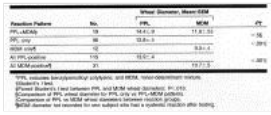

Table 4

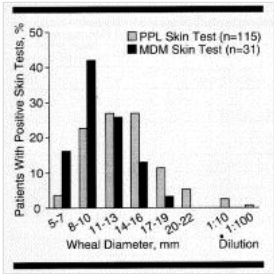

Figure 1

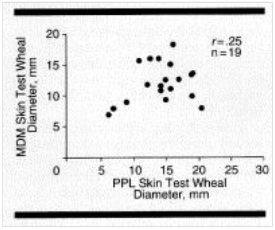

Figure 2

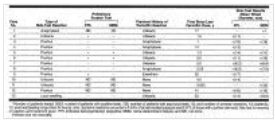

Table 5

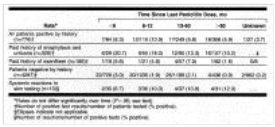

Table 6

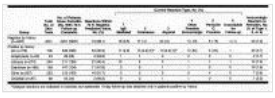

Table 7

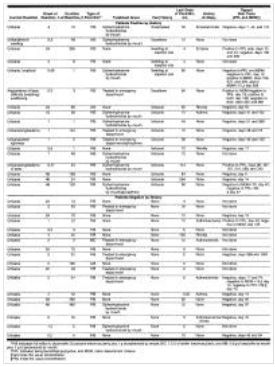

Table 8

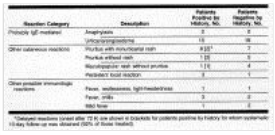

Table 9

Back to Top

« Previous Article | Table of Contents | Next Article »

About Us Contact Us Privacy Policy Terms of Use