

Penicillin skin testing in the evaluation and management of penicillin allergy

Stephanie Fox, MD, and Miguel A. Park, MD*

Objective: To review the role of penicillin skin testing in the evaluation and management of penicillin allergy mediated by IgE.

Data Sources: PubMed and OVID search of English-language articles regarding penicillin allergy, penicillin allergy testing, and management of penicillin allergy.

Study Selection: Articles pertinent to the subject matter were selected and reviewed.

Results: The major determinant (benzylpenicillin polylysine) detects the greatest number of penicillin allergic patients during skin testing, and the minor determinants of penicillin increase the sensitivity of penicillin skin testing. Penicillin skin testing to the major and minor determinants was found to have a negative predictive value of 97% to 99%. The incidence of systemic adverse reaction to penicillin skin testing is less than 1%.

Conclusion: A detailed history of the prior reaction to penicillin is an integral part of the evaluation, but it is not accurate in predicting a positive penicillin skin test result. A patient with a negative penicillin skin test result to the major and minor determinants is at a low risk of an immediate-type hypersensitivity reaction to penicillin. Patients with a positive skin test result should undergo desensitization to penicillin or an alternative antibiotic should be considered.

Ann Allergy Asthma Immunol. 2011;106:1–7.

Off-label disclosure: Drs Fox and Park have indicated that this article does not include the discussion of unapproved/investigative use of a commercial product/device.

Financial disclosure: Drs Fox and Park have indicated that in the last 12 months they have not had any financial relationship, affiliation, or arrangement with any corporate sponsors or commercial entities that provide financial support, education grants, honoraria, or research support or involvement as a consultant, speaker's bureau member, or major stock shareholder whose products are prominently featured either in this article or with the groups who provide general financial support for this CME program.

Instructions for CME credit

1. Read the CME review article in this issue carefully and complete the activity by answering the self-assessment examination questions on the form on page 9.
2. To receive CME credit, complete the entire form and submit it to the ACAAI office within 1 year after receipt of this issue of the *Annals*.

INTRODUCTION

Approximately 10% of hospitalized patients report an allergy to penicillin,¹ and many of these patients do not have evidence of an IgE-mediated penicillin allergy when evaluated by penicillin skin testing.^{2,3} Many physicians on hearing of a patient's penicillin allergy elect not to use penicillin or other β -lactam antimicrobials when in fact they may be the antibiotic of choice.⁴ Moreover, Sade et al⁵ have estimated that the mean antibiotic cost for patients reporting a penicillin allergy is 63% higher than for those not reporting a penicillin allergy. Consequently, patients with a history of penicillin allergy may

be unnecessarily exposed to broad-spectrum antibiotics and at a greater cost to the medical system.

Benzylpenicillin polylysine and the minor determinant mixture (MDM) have not been available since 2004. Previously, Allergopharma produced benzylpenicillin polylysine and MDM, and Hollister-Stier produced benzylpenicillin polylysine. The lack of benzylpenicillin polylysine and MDM has hampered the evaluation of patients with penicillin allergy. Recently, benzylpenicillin polylysine has been reintroduced to the United States by AllerQuest LLC (Pre-Pen) and to Spain by Diater. We review the role of penicillin skin testing for the evaluation and management of penicillin allergy.

PATIENT HISTORY IN THE EVALUATION OF PENICILLIN ALLERGY

The type and severity of reaction to penicillin in the past, as reported by the patient, are weakly associated with skin test reactivity to penicillin. In a prospective study of 638 patients with a prior history of β -lactam intake, a positive penicillin skin test result was noted in 19 of 638 patients (3%): 5 of 542

Affiliations: Mayo Clinic College of Medicine and Division of Allergic Diseases, Mayo Clinic, Rochester, Minnesota.

Received for publication January 15, 2010; Received in revised form April 19, 2010; Accepted for publication May 11, 2010.

© 2011 American College of Allergy, Asthma & Immunology.

Published by Elsevier Inc. All rights reserved.

doi:10.1016/j.anai.2010.05.010

patients (0.9%) without a history of penicillin allergy, 14 of 96 (95% confidence interval [CI], 5.95–59.92) patients (14.6%) with a vague history of penicillin allergy, and 13 of 18 (95% CI, 62.19–1440.8) patients (72.2%) with a convincing history of penicillin allergy.⁶ Salkind et al⁷ reported that a patient with a history consistent with a penicillin allergy had an increased likelihood of having a penicillin allergy (positive likelihood ratio, 1.9; 95% CI, 1.5–2.5). A negative history of penicillin allergy lowers the likelihood of a penicillin allergy as assessed by penicillin skin testing (negative likelihood ratio, 0.5; 95% CI, 0.4–0.6). The authors conclude that taking a detailed history of the patient's reaction to penicillin may exclude a penicillin allergy, but patients with a history consistent with an IgE-mediated reaction to penicillin should undergo penicillin skin testing. However, both the positive and negative likelihood ratios have a small impact on the pretest probability as assessed by the Users' Guides to the Medical Literature for Diagnosis Articles.^{8,9}

Many studies have demonstrated that clinical history and penicillin skin test results are rarely associated. Gadde et al¹⁰ reported that 17% of patients with a history of anaphylaxis to penicillin had a positive penicillin skin test result. In those who experienced urticaria to penicillin, 12% had a positive penicillin skin test result, and in those with exanthems, only 4% had a positive penicillin skin test result. In this same study, 1.7% of patients with no history of penicillin allergy had positive skin test results. Green et al¹¹ demonstrated that 19 of 258 patients (7%) with a history of a maculopapular rash to penicillin had a positive skin test result to penicillin compared with 14 of 234 patients (6%) with no history of penicillin allergy. Stember¹² also conducted a retrospective study of 319 patients who had a positive history of penicillin allergy and divided the patients into 3 groups based on the penicillin allergy history: convincing (history consistent with

an IgE-mediated reaction to penicillin), vague (plausible history of penicillin allergy), and unacceptable (either never been exposed to penicillin or an unbelievable history). Among the convincing group, 19 of 135 patients (14.1%) had a positive penicillin skin test result, 10 of 150 (6.7%) had a positive penicillin skin test result in the vague group, and 0 of 34 patients had a positive penicillin skin test result in the unacceptable group. Solensky et al,¹³ in a review of the literature, showed that 347 of 1063 patients (33%) with a history of penicillin allergy and positive penicillin skin test results had a vague history of prior reaction to penicillin. A vague history was defined as one unlikely to be IgE mediated (such as maculopapular rash, gastrointestinal symptoms, or an unknown reaction). The authors conclude that patients with a vague history should undergo penicillin skin testing because a large number of true penicillin allergies could be missed. However, in a retrospective study of 91 patients evaluated for penicillin allergy, clinical history (type of reaction, time of reaction after penicillin ingestion, or time since the last reaction) was not associated with penicillin skin test result positivity.¹⁴ Hence, although the patient's history is an important element in the evaluation of penicillin allergy, the clinical utility seems to be limited, and penicillin skin testing can be useful for many patients with a history of penicillin allergy.

COMPONENTS OF THE PENICILLIN SKIN TEST

Penicillin skin testing is performed with prick and intradermal skin tests to both the major and minor determinants of penicillin. The major determinant of penicillin skin testing is composed of benzylpenicillin polylysine. The minor determinants of penicillin that have been included in large penicillin skin test trials are benzylpenicilloate, benzylpenilloate, benzylpenicillin (penicillin G), or benzylpenicilloyl-*N*-propyla-

Table 1. Penicillin Reagents Used During Penicillin Skin Tests and Outcomes of Penicillin Challenge

Source	Positive penicillin skin test result, No. (%)	Negative penicillin skin test result, No. (%)	Patients challenged with penicillin, No. (%)	Adverse reactions to penicillin challenge, No. (%)
del Real et al ^{17b}	49/596 (8.2)	527/596 (88.4)	290	5/290 (1.7)
Jost et al ³⁰	177/921 (19)	744 (81)	NA	NA
Goldberg et al ¹⁸	73/169 (43)	96/169 (57)	94	4/94 (4.3)
Wong et al ¹⁴	16/91 (18)	75/91 (82)	72	2/72 (2.8)
Gadde et al ¹⁰	55/776 (7.1)	700/776 (90)	649	54/649 (8.3)
Cetinkaya and Cag ^{32d}	15/147 (10.2)	132/147 (89.8)	NA	NA
Sogn et al ^{26e}	146/825 (18)	656/825 (80)	566	7/566 (1.2)
Mendelson et al ²²	21/240 (9)	219 (91)	219	3/219 (1.4)
Levine et al ^{19f}	12/90 (13)	77/90 (86)	77	1/77 (1.3)

Abbreviations: MDM1, penicillin G; MDM2, penilloate, penicilloate, and penicillin G; MDM3, penicillin G and penicilloate; MDM4, penicillin G, penicilloate, and benzylpenicilloyl-*N*-propylamine; NA, not available.

^a Note that reactions were considered IgE mediated if the reaction occurred within the first 72 hours unless otherwise specified by the author.

^b Penicillin skin test result was indeterminate in 20 patients (3.4%). Patients could have been challenged with any β -lactams, but most patients were given penicillins.

^c Includes history-positive and history-negative patients.

^d Study tested children without a history of penicillin allergy.

^e Twenty-three patients (3%) had a penicillin skin test result that was uninterpretable.

^f Penicillin skin test result was uninterpretable in 1 patient.

mine. An MDM is not commercially available in the United States but is available in Spain (Diater).³ In areas where the MDM is not available, many clinicians make their own benzylpenicilloate. In addition, testing with amoxicillin has been recommended by the European Network for Drug Allergy because of the recognition that side-chain structures can act as antigenic determinants.³

The recommended doses of benzylpenicillin polylysine, MDM, penicillin G, and amoxicillin are 5×10^{-5} mmol/L, 2×10^{-2} mmol/L, 10,000 IU/mL, and 20 mg/mL, respectively.³ In the United States amoxicillin has been used at a concentration of 10^{-2} M.¹⁵

PREDICTIVE VALUE OF PENICILLIN SKIN TESTING WITH DIFFERENT PENICILLIN DERIVATIVES

Approximately 50% of patients with a positive penicillin skin test result will have an immediate-type hypersensitivity reaction when rechallenged with penicillin.^{2,16} However, because of the possible risk of an adverse reaction to penicillin, the precise positive predictive value is unknown. Patients with a history of an IgE-mediated penicillin allergy and a negative penicillin skin test result to the benzylpenicillin polylysine and MDM (penicillin G, benzylpenicilloate, benzylpenilloate, penicillin G, benzylpenicilloate, and benzylpenicilloyl-*N*-propylamine) are at low risk of developing an immediate adverse drug reaction to penicillin.² Adverse drug reaction rates to penicillin drugs after history of a negative penicillin skin test result range from 0% to 11.4%, depending on the penicillin skin test reagents.^{10,11,14,17–29} Specifically, IgE-mediated reactions, such as urticaria or angioedema, occurred in 0% to 4.3% of patients with a history of negative penicillin skin test results on challenge with a penicillin drug.^{10,14,17–19,22,26}

The literature has used the term *MDM* to include many different combinations of minor determinants of penicillin (benzylpenicilloate, benzylpenilloate, penicillin G, and/or benzylpenicilloyl-*N*-propylamine) (Table 1). Although it is widely accepted that the major determinant should be included in skin testing, it is unclear which minor determinants would be most predictive of an IgE-mediated reaction to penicillin.³ To aid clinicians in making an informed decision on the evaluation of penicillin allergy with penicillin skin test, a summary of selected studies have been included in this article that describe the sensitivities of the different components of the penicillin skin test (benzylpenicillin polylysine and MDM).

Benzylpenicillin Polylysine Alone on Skin Testing

The utility of benzylpenicillin polylysine in the penicillin skin test has been well established.^{2,3,10,26} Sogn et al²⁶ demonstrated that among 167 patients with a positive penicillin skin test result, 140 of the patients (84%) were skin test positive to the benzylpenicillin polylysine.²⁶ Gadde et al¹⁰ reported that 115 of 128 patients (89.8%) with a positive penicillin test result tested positive to benzylpenicillin polylysine. However, several recent studies have shown a less robust detection of penicillin allergy by benzylpenicillin polylysine (64%–69%).^{3,14,18,30} The differences in the response to benzylpenicillin polylysine may be due to different patient populations.³ Therefore, benzylpenicillin polylysine is still an important component of penicillin skin testing and essential in the evaluation of patients with a history of penicillin allergy.

Benzylpenicillin Polylysine and Penicillin G on Skin Testing

In a study of patients with a history of penicillin allergy evaluated with benzylpenicillin polylysine and penicillin G, del Real et al¹⁷ reported that 527 of 596 patients (88.4%) had

IgE-mediated reactions to penicillin challenge, No. (%) ^a	Benzylpenicillin polylysine, No. (%)	MDM1, No. (%)	MDM2, No. (%)	MDM3, No. (%)	MDM4, No. (%)	Amoxicillin, No. (%)
2/290 (0.7)	44/49 (90)	21/49 (43)	NA	NA	NA	NA
NA	116/177 (66)	NA	NA	61/177(34)	NA	NA
4/94 (4.3)	47/73 (64)	NA	NA	56/73 (73)	NA	37/73 (51)
0/72	11/16 (69)	NA	NA	2/16 (12.5)	NA	NA
17/649 (2.6)	115/128 (89.8) ^c	NA	32/128 (25)	NA	NA	NA
NA	12/15 (80)	NA	NA	3/15 (20)	NA	NA
7/566 (1.2)	140/167 (84) ^e	NA	NA	NA	27/167 (16%)	NA
0/219	18/21 (86)	NA	11/21 (52)	NA	NA	NA
0/77	9/12 (75)	NA	NA	N/A	8/12 (67)	NA

negative skin test results, 49 patients (8.2%) tested positive to 1 or both benzylpenicillin polylysine and/or penicillin G, and 20 (3.4%) had indeterminate results. Among the 49 patients with a positive penicillin skin test result, 44 (90%) tested positive to benzylpenicillin polylysine and 21 (43%) to penicillin G (some patients tested positive to both). Two hundred ninety of the patients were administered β -lactam antibiotics, with 189 patients receiving a penicillin antibiotic (122 piperacillin-tazobactam, 36 ampicillin or ampicillin-sulbactam, and 31 oxacillin). Some patients may have received multiple β -lactam antibiotics. Five (3%) of the 189 patients who had a negative penicillin skin test result and received β -lactam antibiotics had adverse drug reactions; however, only 2 (1%) patients were assumed to have IgE-mediated reactions. One of the 2 immediate adverse drug reactions was to piperacillin-tazobactam.

Another study using benzylpenicillin polylysine as the major determinant and penicillin G as the only minor determinant was sponsored by the American Academy of Allergy. Three hundred twenty-five patients of 1,718 history-positive patients (19%) had positive penicillin skin test results. Two hundred fifty-three of 325 history-positive patients (78%) tested positive to benzylpenicillin polylysine, and 154 of 325 (47%) tested positive to penicillin G, but 25% tested positive to both. In this study, 346 patients found to have a negative skin test result were challenged with penicillin (patients with and without a history penicillin allergy). A total of 12 of 346 patients (3.5%) had adverse drug reactions to penicillin, with only 3 of these thought to be IgE mediated (1% of the total patients).¹¹

Romano et al³¹ demonstrated that 8 of 300 patients (2.7%) with a history of immediate adverse drug reaction to penicillin tested positive only to penicillin G. In a large study by Sogn et al,²⁶ 7 of 167 patients (4%) with a positive penicillin skin test result (benzylpenicillin polylysine and/or MDM) tested positive only to penicillin G. Wong et al,¹⁴ in a small study, revealed that 4 of 16 patients (25%) with a positive penicillin skin test result tested positive to penicillin G only, and Mendelson et al²² reported that 0 of 23 patients with a positive penicillin skin test result tested positive to penicillin G only. A total of 7% to 17% of patients with a positive skin test result to penicillin will be positive to another minor determinant other than penicillin G.² If one considers the largest studies in which enough information is provided to determine how many patients tested positive only to penicillin G on skin testing, 2.7% to 4% of additional patients would be identified by adding penicillin G to the penicillin skin test reagents. Therefore, adding penicillin G to the penicillin skin test panel is valuable.

Benzylpenicillin Polylysine, Penicillin G, and Benzylpenicilloate on Skin Testing

Several studies have been performed using benzylpenicillin polylysine, penicillin G, and benzylpenicilloate as the reagents tested. Jost et al³⁰ performed a retrospective and a prospective study on 921 children. This study found that 177

children (19%) tested positive on penicillin skin testing. Within this group, 46 (26%) tested positive to the major determinant alone, whereas 70 (40%) tested positive to both the major and minor determinants. In the group that tested positive only to the minor determinant, 29 (16.4%) had positive results to both penicillin G and benzylpenicilloate and 15 (8.5%) had positive results to penicilloate alone.

Wong et al¹⁴ examined 91 patients who reported a penicillin allergy. Sixteen (18%) of these patients had at least 1 positive result on skin testing with benzylpenicillin polylysine, penicillin G, and benzylpenicilloate. Twelve of the 16 patients with a positive result tested positive to 1 reagent only. Seven patients (44%) were positive to the major determinant alone, 4 (25%) were positive to penicillin G, and 1 (6.25%) was positive to penicilloate. Two of 72 patients (2.8%) with a negative skin test result had an adverse drug reaction to penicillin on challenge.

Cetinkaya and Cag³² performed skin tests on 147 children with a negative penicillin allergy history. Overall, they found 15 patients (10.2%) to have positive penicillin skin test results. Twelve of the 15 children (80%) tested positive to the major determinant. Three of the 15 children (20%) tested negative for the major determinant but positive for penicillin G and penicilloate.

Bousquet et al³³ enrolled 1,218 patients with a history of penicillin allergy. A total of 854 of 1,218 patients underwent skin testing with benzylpenicillin polylysine and MDM (penicillin G and benzylpenicilloate). A total of 802 of the 854 patients (94%) had negative penicillin skin test results, and 52 of 854 patients (6%) had positive results. However, 144 of 802 (18%) had positive skin test or oral challenge results to other β -lactams (amoxicillin, ampicillin, other penicillins, and cephalosporins). The authors conclude that if the skin test result to benzylpenicillin polylysine and MDM (penicillin G and benzylpenicilloate) is negative, these patients should also undergo skin testing to other determinants and/or provocation testing. However, benzylpenicilloate or benzylpenicilloyl-*N*-propylamine was not included in the MDM, which may have detected some of the 144 patients who had negative skin test results to benzylpenicillin polylysine, penicillin G, and benzylpenicilloate. Hence, including benzylpenicilloate in penicillin skin testing may detect an additional 6% to 8.5% patients with a history of penicillin skin testing.

*Benzylpenicillin Polylysine, Penicillin G, Benzylpenicilloate, and Benzylpenicilloyl-*N*-Propylamine on Skin Testing*

A study sponsored by the National Institute of Allergy and Infectious Disease used penicillin G, benzylpenicilloate, and benzylpenicilloyl-*N*-propylamine as skin testing reagents.²⁶ This study tested 1,539 patients of whom 825 had a history of penicillin allergy, 104 were unsure of a previous reaction, and 610 had a negative history of penicillin allergy. Among the 825 patients with a history of penicillin allergy, 146 patients (18%) had a positive penicillin skin test result. Twenty-five of 610 patients (4%) with no history of penicillin allergy were found to have a positive penicillin skin test result to at least

1 of the determinants tested. Specifically, they found that 140 of 167 patients (84%) with positive skin test results who completed their protocol tested positive to at least the major determinant, with or without the minor determinant. Twenty-seven of 167 patients (16%) with a positive penicillin skin test result tested positive to the MDM only. Twenty-four of the 27 patients with positive results to the MDM only were tested for the individual components of the MDM. Seven of the 167 patients (4%) tested positive only to penicillin G, and 5 (3%) reacted to penicillin G and either benzylpenicilloate or benzylpenicilloyl-*N*-propylamine. Twelve of 167 patients (7%) reacted only to either benzylpenicilloate or benzylpenicilloyl-*N*-propylamine.²⁶ Seven of 566 patients (1.2%) with a negative skin test result had an adverse drug reaction to penicillin on challenge. Therefore, the addition of penicillin G, benzylpenicilloate, and benzylpenicilloyl-*N*-propylamine to penicillin skin testing increases the number of positive penicillin skin test results by 16%. A negative penicillin skin test result that includes benzylpenicillin polylysine, penicillin G, benzylpenicilloate, and benzylpenicilloyl-*N*-propylamine predicts a low (1.2%) adverse reaction to penicillin.

Benzylpenicillin Polylysine, Penicillin G, Benzylpenicilloate, and Benzylpenilloate on Skin Testing

Gadde et al¹⁰ studied a total of 5,063 outpatients with and without a history of penicillin allergy. Among the patients with a history of penicillin allergy, 700 of 776 patients had a negative penicillin skin test result, 21 (2.7%) had an equivocal penicillin skin test result, and 55 (7.1%) had a positive penicillin skin test. Among patients with a negative history of penicillin allergy, 4,201 of 4,287 patients had a negative penicillin skin test result, 13 (0.3%) had an equivocal penicillin skin test, and 73 (1.7%) had a positive penicillin skin test result. The components of the skin test result that were positive among patients with or without penicillin allergy did not differ significantly. Among those with a history of penicillin allergy, 38 of 55 patients (69%) tested positive to benzylpenicillin polylysine only, 5 (9%) tested positive to MDM only, and 12 (22%) tested positive to both. In those without a history of penicillin allergy, 58 of 73 patients (79.5%) were positive to benzylpenicillin polylysine only, 8 (11%) were positive to MDM only, and 13 (10.2%) were positive to both. When patients with a history of penicillin allergy and a negative penicillin skin test result were challenged with penicillin, 54 of 649 patients (8.3%) had an adverse drug reaction. Of these, 17 of 596 patients (2.9%), who completed the 72-hour follow-up after penicillin challenge, had IgE-mediated reactions.

Mendelson et al²² tested 240 children and found 21 patients (8.75%) to have positive skin test results. Of the positive reactors, 3 (14%) tested positive to the MDM alone. No patients demonstrated positivity to penicillin G alone. Two of the 3 patients who tested positive to the MDM alone were tested to benzylpenicilloate only, and 1 child was found to have a positive test result to this reagent alone. The other child had a positive skin test result to benzylpenilloate.

Among the 219 patients with a negative penicillin skin test result who were challenged with penicillin, 3 (1.4%) had an adverse drug reaction to penicillin. Hence, penicillin skin testing with penicillin G, benzylpenicilloate, benzylpenilloate, and benzylpenicillin polylysine predicts a low risk of an adverse drug reaction to penicillin.

Amoxicillin on Skin Testing

Several studies have included amoxicillin skin testing when evaluating penicillin allergy. Park et al¹⁵ showed that 9 of 64 patients (14%) tested positive solely to amoxicillin (10^{-2} M) among patients with a positive penicillin skin test result. Silviu-Dan et al³⁴ evaluated 38 patients with a history of adverse drug reaction to amoxicillin in whom 16 were skin tested with ampicillin and 22 with amoxicillin. Two of the 22 patients (9.1%) tested with amoxicillin (10^{-2} M) had positive results. Several European studies have found much higher rates of skin test result positivity to amoxicillin. Torres et al³⁵ showed that 64.8% of 290 patients with a history of penicillin had a positive skin test result to amoxicillin (20 mg/mL). Ponvert et al²⁵ found that 42% of children with a history of penicillin allergy tested positive to amoxicillin (25 mg/mL). The differences between the North American studies and the European studies may be due to the different concentrations of amoxicillin used for skin testing and/or different patient populations. Hence, the addition of amoxicillin skin test may detect additional penicillin allergic patients; however, the concentration of amoxicillin needs further study.

ADVERSE REACTIONS TO PENICILLIN SKIN TESTING

Penicillin skin testing has generally been considered to be safe, with a low incidence of systemic reactions. The incidence of systemic reactions is considered to be less than 1% in patients who undergo stepwise prick or intradermal penicillin skin testing.^{18,23–25,32,36–38} Valyasevi and Van Dellen³⁶ reported on 1,710 patients who underwent skin testing and found that 0.12% of patients had a systemic reaction rate, 2.3% in patients testing positive. No fatalities were reported. Gadde et al¹⁰ report that of 128 patients with a positive penicillin skin test result, 12 patients (9.4%) had a systemic response to testing. Eight of these 12 patients had a history of an IgE-mediated reaction to penicillin previously. They report that 1 individual had an anaphylactic reaction; however, skin prick testing had been inadvertently omitted during the individual's testing. Sogn et al²⁶ reported no adverse reactions to penicillin skin testing. Macy et al²¹ stated that 4 of 101 patients (4%) with a positive penicillin skin test result had an adverse reaction to skin testing. Three patients noted itching or hives distant from the penicillin skin test sites and 1 had a systemic reaction. Among patients with a negative penicillin skin test result, 16 of 980 patients (1.6%) had an adverse reaction to penicillin skin testing (8 faintness, 2 nausea, 1 anxiety, 1 cough, 1 vertigo, 1 headache, 1 hives, and 1 itching).

Fatalities have been reported with penicillin skin testing.³⁹ From 1973 to 1983, 1 death after penicillin skin testing was

reported in a survey of practicing allergists sponsored by the American Academy of Allergy and Immunology. The patient had undergone intradermal testing with penicillin without performing skin prick testing. The fatality may have been avoided if the skin prick test had been performed first. Therefore, if proper reagents and correct technique are used, penicillin skin testing is considered relatively safe.

RESENSITIZATION AFTER NEGATIVE PENICILLIN SKIN TEST RESULT AND A COURSE OF PENICILLIN

The rate of resensitization in patients given multiple courses of penicillin drugs after a negative skin test result has been reported to be low by several studies. Mendelson et al²² report that 0.9% of children who had safely tolerated an oral penicillin course after a negative skin test results had a positive skin test result on retesting. Solensky et al²⁷ studied 46 patients with negative penicillin skin test results. These patients were given 3 courses of penicillin, and none were found to have a positive skin test result after the third course was completed. Hershkovich et al⁴⁰ report that in a group of 98 children who had negative skin test and oral challenge results, only 2 had positive skin test results on additional testing. Another child developed a rash after the fifth exposure to amoxicillin. They report the resensitization rate to be 3%. Parker et al⁴¹ showed a 16% rate of resensitization in 18 patients. In the group that became skin test positive after rechallenge, all had received intravenous penicillins before the subsequent skin test. In summary, the resensitization rate appears to be low after challenge with penicillin drugs in patients who previously have had negative skin test results to penicillin.

DIAGNOSTIC EVALUATION OF A PATIENT WITH A HISTORY OF PENICILLIN ALLERGY

In the evaluation of a patient with a history of penicillin allergy, it is useful to classify adverse drug reactions to penicillin into IgE-mediated and non-IgE-mediated adverse drug reactions.³ Immediate-type reactions, IgE mediated, usually appear within 1 hour after exposure to the medication but can occur up to 72 hours later. The symptoms of immediate-type reactions can consist of urticaria, angioedema, bronchospasm, and/or anaphylaxis.³ Non-IgE-mediated reactions commonly occur more than 72 hours after drug administration and consist of interstitial nephritis, thrombocytopenia, serum sickness, drug fever, erythema multiforme minor, Stevens-Johnson syndrome, toxic epidermal necrolysis, and others.^{16,42} The results of penicillin skin testing can only predict for IgE-mediated reactions to penicillins. If a patient's history is consistent with an IgE-mediated reaction to penicillin or there is no evidence of Stevens-Johnson syndrome, toxic epidermal necrolysis, serum sickness, or other life-threatening reaction to penicillin that is not IgE mediated, then penicillin skin testing with benzylpenicillin polylysine and MDM (penicillin G, benzylpenicilloate, and benzylpenicilloate) is recommended. If the penicillin skin test result is

negative, the patient is at low risk of an immediate-type hypersensitivity reaction to penicillin. If the penicillin skin test result is positive, an alternative antibiotic is recommended or penicillin desensitization.²

Most clinicians do not have access to MDM in the United States. Benzylpenicillin polylysine and penicillin G skin testing can be an alternative to penicillin skin testing with benzylpenicillin polylysine and the MDM as shown by Green et al¹¹ and del Real et al.¹⁷ However, because some patients with a history of penicillin allergy can be missed by testing only benzylpenicillin polylysine and penicillin G, an oral challenge under medical supervision may be prudent to exclude an IgE-mediated penicillin allergy in patients with a negative skin test result to these 2 reagents.

CONCLUSION

A detailed history of the prior reaction to penicillin is an integral part of the evaluation, but it is not accurate in predicting a positive penicillin skin test result. Therefore, patients with a history of prior reaction should undergo penicillin skin testing. Skin testing with the major determinant alone may only detect 70% of patients; therefore, skin testing should be performed with the major and minor determinants consisting of penicillin G and benzylpenicilloate plus either benzylpenicilloate or benzylpenicilloyl-*N*-propylamine. A patient with a negative penicillin skin test result to the major and minor determinants has a 1% to 3% chance of having an IgE-mediated reaction on challenge with a penicillin drug. If the minor determinants are not available, penicillin G and/or amoxicillin skin testing can identify additional patients with a history of penicillin allergy at risk of an IgE-mediated adverse drug reaction to penicillin. Moreover, the patient would benefit by undergoing an oral challenge in the clinician's office to exclude an IgE-mediated reaction to penicillin. Patients with a positive skin test result should undergo desensitization to penicillin or an alternative antibiotic should be considered.

REFERENCES

1. Apter AJ, Schelleman H, Walker A, Addya K, Rebbeck T. Clinical and genetic risk factors of self-reported penicillin allergy. *J Allergy Clin Immunol*. 2008;122:152–158.
2. Joint Task Force on Practice Parameters, the American Academy of Allergy, Asthma and Immunology, the American Academy of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. Executive summary of disease management of drug hypersensitivity: a practice parameter. *Ann Allergy Asthma Immunol*. 1999;83:665–700.
3. Blanca M, Romano A, Torres MJ, et al. Update on the evaluation of hypersensitivity reactions to betalactams. *Allergy*. 2009;64:183–193.
4. Kerr JR. Penicillin allergy: a study of incidence as reported by patients. *Br J Clin Pract*. 1994;48:5–7.
5. Sade K, Holtzer I, Levo Y, Kivity S. The economic burden of antibiotic treatment of penicillin-allergic patients in internal medicine wards of a general tertiary care hospital. *Clin Exp Allergy*. 2003;33:501–506.
6. Kalogeromitros D, Rigopoulos D, Gregoriou S, Papaioannou D, Mousatou V, Katsarou-Katsari A. Penicillin hypersensitivity: value of clinical history and skin testing in daily practice. *Allergy Asthma Proc*. 2004;25:157–60.

7. Salkind AR, Cuddy PG, Foxworth JW. The rational clinical examination: is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. *JAMA*. 2001;285:2498–505.
8. Jaeschke R, Guyatt G, Sackett DL. Users' guides to the medical literature, III: how to use an article about a diagnostic test, A: are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA*. 1994;271:389–391.
9. Jaeschke R, Guyatt GH, Sackett DL; The Evidence-Based Medicine Working Group. Users' guides to the medical literature, III: how to use an article about a diagnostic test, B: what are the results and will they help me in caring for my patients? *JAMA*. 1994;271:703–707.
10. Gadde J, Spence M, Wheeler B, Adkinson NF Jr. Clinical experience with penicillin skin testing in a large inner-city STD clinic. *JAMA*. 1993;270:2456–2463.
11. Green GR, Rosenblum AH, Sweet LC. 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. *J Allergy Clin Immunol*. 1977;60:339–345.
12. Sember RH. Prevalence of skin test reactivity in patients with convincing, vague, and unacceptable histories of penicillin allergy. *Allergy Asthma Proc*. 2005;26:59–64.
13. Solensky R, Earl HS, Gruchalla RS. Penicillin allergy: prevalence of vague history in skin test-positive patients. *Ann Allergy Asthma Immunol*. 2000;85:195–199.
14. Wong BB, Keith PK, Wasserman S. Clinical history as a predictor of penicillin skin test outcome. *Ann Allergy Asthma Immunol*. 2006;97:169–174.
15. Park MA, Matesic D, Markus PJ, Li JT. Female sex as a risk factor for penicillin allergy. *Ann Allergy Asthma Immunol*. 2007;99:54–58.
16. Park MA, Li JT. Diagnosis and management of penicillin allergy. *Mayo Clin Proc*. 2005;80:405–410.
17. del Real GA, Rose ME, Ramirez-Atamoros MT, et al. Penicillin skin testing in patients with a history of beta-lactam allergy. *Ann Allergy Asthma Immunol*. 2007;98:355–359.
18. Goldberg A, Confino-Cohen R. Skin testing and oral penicillin challenge in patients with a history of remote penicillin allergy. *Ann Allergy Asthma Immunol*. 2008;100:37–43.
19. Levine BB, Zolov DM. Prediction of penicillin allergy by immunological tests. *J Allergy*. 1969;43:231–244.
20. Macy E, Burchette RJ. Oral antibiotic adverse reactions after penicillin skin testing: multi-year follow-up. *Allergy*. 2002;57:1151–1158.
21. Macy E, Mangat R, Burchette RJ. Penicillin skin testing in advance of need: multiyear follow-up in 568 test result-negative subjects exposed to oral penicillins. *J Allergy Clin Immunol*. 2003;111:1111–1115.
22. 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.
23. Nadarajah K, Green GR, Naglak M. Clinical outcomes of penicillin skin testing. *Ann Allergy Asthma Immunol*. 2005;95:541–545.
24. Pichichero ME, Pichichero DM. Diagnosis of penicillin, amoxicillin, and cephalosporin allergy: reliability of examination assessed by skin testing and oral challenge. *J Pediatr*. 1998;132:137–143.
25. Ponvert C, Le Clainche L, de Blic J, Le Bourgeois M, Scheinmann P, Paupe J. Allergy to beta-lactam antibiotics in children. *Pediatrics*. 1999;104:e45.
26. Sogn DD, Evans R, 3rd, 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;152:1025–1032.
27. Solensky R, Earl HS, Gruchalla RS. Lack of penicillin resensitization in patients with a history of penicillin allergy after receiving repeated penicillin courses. *Arch Intern Med*. 2002;162:822–826.
28. 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.
29. Warrington RJ, Simons FE, Ho HW, Gorski BA. Diagnosis of penicillin allergy by skin testing: the Manitoba experience. *Can Med Assoc J*. 1978;118:787–791.
30. Jost BC, Wedner HJ, Bloomberg GR. Elective penicillin skin testing in a pediatric outpatient setting. *Ann Allergy Asthma Immunol*. 2006;97:807–812.
31. Romano A, Bousquet-Rouanet L, Viola M, Gaeta F, Demoly P, Bousquet PJ. Benzylpenicillin skin testing is still important in diagnosing immediate hypersensitivity reactions to penicillins. *Allergy*. 2009;64:249–253.
32. Cetinkaya F, Cag Y. Penicillin sensitivity among children without a positive history for penicillin allergy. *Pediatr Allergy Immunol*. 2004;15:278–280.
33. Bousquet PJ, Pipet A, Bousquet-Rouanet L, Demoly P. Oral challenges are needed in the diagnosis of beta-lactam hypersensitivity. *Clin Exp Allergy*. 2008;38:185–190.
34. Silviu-Dan F, McPhillips S, Warrington RJ. The frequency of skin test reactions to side-chain penicillin determinants. *J Allergy Clin Immunol*. 1993;91:694–701.
35. Torres MJ, Romano A, Mayorga C, et al. Diagnostic evaluation of a large group of patients with immediate allergy to penicillins: the role of skin testing. *Allergy*. 2001;56:850–856.
36. Valyasevi MA, Van Dellen RG. Frequency of systematic reactions to penicillin skin tests. *Ann Allergy Asthma Immunol*. 2000;85:363–365.
37. Brown BC, Price EV, Moore MB Jr. Penicilloyl-polylysine as an intradermal test of penicillin sensitivity. *JAMA*. 1964;189:599–604.
38. Raja AS, Lindsell CJ, Bernstein JA, Codispoti CD, Moellman JJ. The use of penicillin skin testing to assess the prevalence of penicillin allergy in an emergency department setting. *Ann Emerg Med*. 2009;54:72–77.
39. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol*. 1987;79:660–677.
40. Hershkovich J, Broides A, Kirjner L, Smith H, Gorodischer R. Beta lactam allergy and resensitization in children with suspected beta lactam allergy. *Clin Exp Allergy*. 2009;39:726–730.
41. Parker PJ, Parrinello JT, Condemni JJ, Rosenfeld SI. Penicillin resensitization among hospitalized patients. *J Allergy Clin Immunol*. 1991;88:213–217.
42. Greenberger PA. Part B: allergic reactions to individual drugs: low molecular weight. In: Grammer LC, Greenberger PA, eds. *Patterson's Allergic Diseases*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002:335–359.

Requests for reprints should be addressed to:

Miguel A. Park, MD
 Division of Allergic Diseases
 Mayo Clinic
 200 First St SW
 Rochester, MN 55905
 E-mail: park.miguel@mayo.edu