Is This Patient Allergic to Penicillin?

An Evidence-Based Analysis of the Likelihood of Penicillin Allergy

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CLINICAL SCENARIOS

Case 1

An 18-year-old male college student presents with group A streptococcal pharyngitis and you prescribe penicillin.[1] The patient informs you that he developed a rash after taking about half a penicillin prescription for a respiratory tract infection 3 years ago. The rash was bright red in color, restricted to the extremities and trunk, and resolved several days after penicillin was discontinued.

Case 2

A 26-year-old pregnant woman has syphilis. She recalls an "itchy rash" and trouble breathing after taking penicillin 4 years ago; she thinks the rash appeared about 3 days into the course of penicillin. Penicillin is the recommended antibiotic for syphilis in pregnancy, even for patients with a true penicillin allergy.[2]

Why Is It Important to Determine Whether Patients Have True Penicillin Allergy?

Penicillin, a β-lactam antibiotic, and its semisynthetic chemical derivatives (such as ampicillin and amoxicillin) and other β-lactam antibiotics (including cephalosporins, carbapenems, and monobactams) remain first-line or acceptable alternative treatments for many

Context Clinicians frequently withhold antibiotics that contain penicillin based on patients' self-reported clinical history of an adverse reaction to penicillin and the clinicians' own misunderstandings about the characteristics of a true penicillin allergy.

Objectives To determine the likelihood of true penicillin allergy with consideration of clinical history and to evaluate the diagnostic value added by appropriate skin testing.

Data Sources MEDLINE was searched for relevant English-language articles dated 1966 to October 2000. Bibliographies were searched to identify additional articles.

Study Selection We included original studies describing the precision of skin testing in diagnosis of penicillin allergy. We excluded studies that did not use both minor and major determinants, provide an explicit definition of penicillin allergy, or list the specific criteria necessary for a positive skin test result. Fourteen studies met the inclusion criteria.

Data Extraction Three authors independently reviewed and abstracted data from all articles and reached consensus about any discrepancies.

Data Synthesis Patients' self-reported history has low accuracy for diagnosis of true penicillin allergy. By evaluating studies comparing clinical history to the skin test for penicillin allergy among patients with and without a positive history for penicillin allergy, positive and negative likelihood ratios were calculated. History of penicillin allergy had a positive likelihood ratio of 1.9 (95% confidence interval [CI], 1.5-2.5), while absence of history of penicillin allergy had a negative likelihood ratio of 0.5 (95% CI, 0.4-0.6).

Conclusions Only 10% to 20% of patients reporting a history of penicillin allergy are truly allergic when assessed by skin testing. Taking a detailed history of a patient's reaction to penicillin may allow clinicians to exclude true penicillin allergy, allowing these patients to receive penicillin. Patients with a concerning history of type I penicillin allergy who have a compelling need for a drug containing penicillin should undergo skin testing. Virtually all patients with a negative skin test result can take penicillin without serious sequelae.

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infections.[3] However, the use of drugs containing penicillin is often limited by an unconfirmed or questionable history of penicillin hypersensitivity provided by the patient. Because fear of penicillin anaphylaxis is common among clinicians encountering a patient with a self-reported history of penicillin allergy, many clinicians overdiagnose penicillin allergy in patients who have

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not had a true allergic reaction to penicillin. Some clinicians may simply accept a diagnosis of penicillin allergy from a patient without obtaining a detailed history of the reaction.[4,5] Some patients, when asked, have no first-hand recall of an allergic response to penicillin, the patient perhaps having been informed of their allergy by a parent.[4,5] For example, patients reporting a penicillin allergy have described an "allergic reaction" consisting of fever and yellow spots on the tonsils, which actually related to the illness they were being treated for rather than penicillin itself.[4] Unless a detailed history and a critical evaluation of the reaction are sought, such patients may incorrectly be labeled as penicillin allergic. In fact, 80% to 90% of patients who report a penicillin allergy are not truly allergic to the drug, when assessed by skin testing.[6-9] Consequently, penicillin is withheld from many patients who could safely receive the drug or its derivatives, perhaps affecting outcomes.[10] Two studies have shown that incorrectly labeling patients as being allergic to penicillin was associated with increased health care costs.[11,12]

METHODS

We searched MEDLINE for English-language literature dated from 1966 to October 2000 using the following Medical Subject Headings and search strategy: (1) *medical history taking* or *physical examination* and *penicillin* or β-*lactam hypersensitivity* and (2) *reproducibility of results* or *observer variation* and *penicillin* or β-*lactam hypersensitivity*. A textword search was also performed using *interobserver, intraobserver, accuracy, pre-cision, reliability, sensitivity, specificity, skin testing* and *penicillin* or β-*lactam hypersensitivity* or *allergy*. The bibliographies of pertinent articles were searched to identify additional references. Included articles were original studies conducted on ambulatory or hospitalized children or adults describing the accuracy or precision of skin testing in the diagnosis of an IgE-mediated penicillin allergy. Excluded studies investigated allergy to aminopenicillins (amoxicillin and ampicillin) or cephalosporins, did not use both major and minor determinants in the skin testing procedure, or did not provide an explicit definition of penicillin allergy or of a positive skin test result. Data from patients who were reported to have had an uninterpretable or equivocal skin test result were not included in our analysis. Quality measures were applied, as used in a previous Rational Clinical Examination Series article.[13] Using study quality as a measure of the relative weight that a single study should receive was not used in our analysis, as other authors have highlighted the pitfalls of this practice.[14,15] Of the 14 studies[16-29] meeting our inclusion criteria, 4 studies[16-19] compared the clinical history with the skin test result for penicillin allergy among a group of patients with and without a positive history of penicillin allergy (**TABLE 1**). Confidence intervals (CIs) for the likelihood ratios from individual studies were computed using a previously described method.[30]

Classification of Penicillin Hypersensitivity Reactions

The frequency of all adverse reactions to penicillin in the general population ranges from 0.7% to 10%.[31] This wide variation in the frequency of adverse reactions to penicillin exists because of a number of variables, including exposure history, route of administration, duration of treatment, elapsed time between the reaction and diagnostic skin testing or reexposure, and nature of the initial reaction. Understanding the different classifications of penicillin hypersensitivity reactions aids evaluation of each individual patient's risk for an allergic reaction that would preclude administration of a drug that contains penicillin.

Gell and Coombs[32] categorized allergic reactions to penicillins by the type of reaction, immune mechanism, and clinical syndrome, while Levine[33] classified untoward reactions to penicillin by their time of onset (**TABLE 2**). Classification of penicillin allergy has been reviewed by several authors[6,34,35] and is summarized briefly below. We refer the reader to the original works for a more detailed discussion.[32,33]

Immediate Reactions. Type I, or immediate reactions, are often associated with the systemic manifestations of anaphylaxis, such as diffuse erythema, pruritus, urticaria, angioedema, bronchospasm, laryngeal edema, hyperperistalsis, hypotension, or cardiac arrhythmias, either alone or in combination (Table 2). Anaphylactic reactions occur in about 0.004% to 0.015% of penicillin courses and are most commonly seen in adults between the ages of 20 and 49 years.[31] A history of atopy does not generally place an individual at increased risk for a type I penicillin reaction.[36] However, atopic

Table 1. Studies Assessing the Skin Test for Penicillin Allergy Among Patients With and Without a History of Penicillin Allergy*

Source, y	Quality of Methods†	Setting (Sample Size, % Penicillin Allergic)	Sensitivity	Specificity	LR⁺ (95% CI)	LR⁻ (95% CI)
Adkinson et al,[16] 1971	C	Inpatient, nonconsecutive (n = 218, 11.9)	0.61	0.74	2.4 (1.6-3.5)	0.5 (0.3-0.85)
Green et al,[17] 1977	C	Multicenter study (n = 2947, 8.1)	0.79	0.45	1.4 (1.4-1.5)	0.5 (0.39-0.57)
Sogn et al,[18] 1992	C	Multicenter study, chronically ill (n = 1298, 12.6)	0.85	0.50	1.7 (1.6-1.9)	0.3 (0.21-0.44)
Gadde et al,[19] 1993	C	Sexually transmitted disease clinic (n = 5063, 2.5)	0.43	0.85	2.9 (2.4-3.7)	0.7 (0.57-0.77)
Summary					1.9 (1.5-2.5)	0.5 (0.4-0.6)

*LR indicates likelihood ratio; CI, confidence interval. A positive LR indicates the likelihood that a patient with a history of penicillin allergy will have a positive penicillin skin test result; a negative LR indicates the likelihood that a patient without a history of penicillin allergy will have a positive penicillin skin test result.
†Quality of methods was based on published criteria. Grade C: independent, blind comparison of sign or symptom, with a gold standard of diagnosis among nonconsecutive patients suspected of having the target condition plus, perhaps, individuals without the target condition; or nonindependent comparison of sign or symptom with a standard of uncertain validity.[13] Of the included studies, not all patients received penicillin challenge.

patients may have a higher frequency of severe anaphylactic reactions.[36]

Type I reactions result when penicillin or its reactive metabolites covalently bind to serum proteins and then crosslink with preformed penicillin-specific IgE antibodies bound to tissue mast cells, circulating basophils, or both. When the bound IgE antibodies are crosslinked by allergen, mast cells are activated to release their mediators. A patient using β-adrenergic antagonists may be at increased risk of death if anaphylaxis occurs.[37]

Some reactions to penicillin occurring from 1 to 72 hours after administration may also be IgE mediated. These reactions, termed "accelerated reactions," can be manifested by urticaria, angioedema, laryngeal edema, and wheezing . However, urticaria and angioedema can occur at any time after administration of penicillin. Life-threatening reactions occurring beyond 1 hour of penicillin administration are rare. The patient described in case 1 had none of the features of a serious IgE-mediated penicillin allergy. In contrast, the patient described in case 2 had features that suggest an IgE-mediated accelerated reaction.

Late Reactions. Late penicillin hypersensitivity reactions are those that occur after 72 hours of drug administration. These responses have been classified as types II, III, or IV depending on the immune mechanism underlying the response (Table 2). Because none of these reactions are IgE dependent, skin testing has no role in the evaluation of a patient with type II, III, IV, or idiopathic responses to penicillin.

Some reactions to penicillin are not included in the Gell and Coombs[32] classification and have been termed "idiopathic." Although various immune-mediated responses have been postulated, the exact immunological mechanisms underlying these responses are not known. The most common idiopathic reaction to drugs containing penicillin is a maculopapular or morbilliform rash. The combined frequency of all rashes occurring in patients taking penicillin is estimated at 1% to 4%.[38,39] These eruptions are usually symmetric, often confluent erythematous macules and papules that generally spare the palm and soles. They may originate on the extremities of ambulatory patients or overlie pressure areas of bedridden patients.[9] Rashes associated with ampicillin administration occur in 5.2% to 9.5% of treatment courses.[38-40] Patients with Epstein-Barr virus or cytomegalovirus infections, or with acute or chronic lymphocytic leukemia, are reported to have a higher incidence of ampicillin-associated rash.[6] The reason for the increased incidence of rash caused by ampicillin remains unknown.

In experimental settings, individuals with histories of prior type I hypersensitivity reactions to aminopenicillins (ampicillin, amoxicillin, bacampacillin) demonstrate cross-reactivity to penicillin when assessed by skin testing.[41] Although some of these individuals fail to react to penicillin skin testing and react only to skin testing with aminopenicillins, these occurrences appear less commonly, yet are well documented.[42,43] In contrast, individuals reporting a history of a nonimmediate reaction are less likely to react to penicillin skin test determinants.[42] In light of the above, it is prudent to perform a skin test for penicillin in those individuals with a history of an urticarial reaction to aminopenicillin derivatives and administer a drug containing penicillin only in patients with negative skin test results.[44] Patients without urticarial rashes to aminopenicillins are unlikely to manifest a serious reaction and can generally receive a drug containing penicillin without further testing.[44]

Drug-independent rashes are common in patients with viral infections, especially those caused by the human immunodeficiency virus, hepatitis B, mumps, Echovirus,[11] and Coxsackie virus.[45] Infections with numerous bacteria can also be associated with a rash.[45] Therefore, patients with some infections who develop a rash while taking penicillin derivatives or penicillin itself should not be automatically labeled as penicillin allergic. Moreover,

Table 2. Classification of Penicillin Reactions

Classification	Time of Onset, h	Mediator(s)	Clinical Signs	Skin Testing Useful	Comments
Immediate (type I reaction)	<1 h	Penicillin-specific IgE antibodies	Anaphylaxis and/or hypotension, laryngeal edema, wheezing, angioedema, urticaria	Yes	Much more likely with parenteral administration than oral administration; fatal outcome in 1 per 50 000 to 1 per 100 000 treatment courses; some reactions occurring between 1-72 h of exposure may be IgE mediated (see text for details)
Late reactions	>72 after exposure				
Type II		IgG, complement	Increased clearance of red blood cells, platelets by lymphoreticular system	No	IgE not involved
Type III		IgG, IgM immune complexes	Serum sickness, tissue injury	No	Tissue lodging of immune complexes; drug fever
Type IV			Contact dermatitis	No	
Other (idiopathic)	Usually > 72 after exposure		Maculopapular or morbilliform rashes	No	1% to 4% of all patients receiving penicillin

Box. Taking a History of Penicillin Allergy: What to Ask

- What was the patient's age at the time of the reaction?
- Does the patient recall the reaction? If not, who informed them of it?
- How long after beginning penicillin did the reaction begin?
- What were the characteristics of the reaction?
- What was the route of administration?
- Why was the patient taking penicillin?
- What other medications was the patient taking? Why and when were they prescribed?
- What happened when the penicillin was discontinued?
- Has the patient taken antibiotics similar to penicillin (for example, amoxicillin, ampicillin, cephalosporins) before or after the reaction? If yes, what was the result?

many patients taking penicillin may also be taking other medications, including other antibiotics, that can cause rashes that are independent of β-lactam compounds.[9] Maculopapular eruptions caused by drugs containing penicillin may subside spontaneously despite continued use of the drug and may not recur on reexposure.[9,40] The frequency of a penicillin-associated maculopapular eruption on reexposure to the drug is not known because many clinicians withhold drugs that contain penicillin in this patient population. Green et al[17] reported that 3 (3.5%) of 85 patients with a maculopapular rash associated with penicillin administration had adverse reactions to oral challenge with penicillin. The nature of the oral challenge reaction was not specified, but none were classified as type I reactions. Six (4.5%) of 134 patients with negative penicillin skin test results and a history of a penicillin-associated cutaneous reaction had an adverse response to penicillin readministration. The nature of the response was not described.[19] An-

other 3 patients with negative penicillin skin test results and a history of rash caused by penicillin developed a type I reaction to penicillin administration,[19] likely indicating the inaccuracy of the historical information. If a detailed history of a patient's reaction to penicillin indicates that the rash was strictly maculopapular, with no signs of a type I reaction, then it appears to be safe to readminister an antibiotic that contains penicillin.[20,35]

Penicillin (or any medication) that is clearly associated with the development of exfoliative dermatitis or the Stevens-Johnson syndrome should be discontinued immediately and not readministered to the patient.[9] Patients with a history of Stevens-Johnson syndrome or exfoliative dermatitis attributable to β-lactam drugs should not undergo a skin test[9] and should wear a Medic Alert bracelet indicating a severe reaction to the drug.

Cross-Reactivity With Other β-Lactam Antibiotics

Cephalosporins (like penicillins) contain a β-lactam ring.[3] The frequency of allergic reactions within 24 hours of cephalosporin administration to patients with a history of penicillin allergy and positive skin test results was 5.6% vs 1.7% for patients with a history of penicillin allergy and negative skin test results.[35] Earlier reports suggested that the cross-reaction rate may be higher for first-generation cephalosporins than for subsequent cephalosporins.[46] Complicating interpretation of these data was the finding that some early first-generation cephalosporins contained trace amounts of penicillin.[46]

One group of investigators challenged 19 patients with well-documented histories of a type I allergy to penicillin with cephalosporins containing side chain structures expected to lead to cross-reaction.[47] Seventeen patients tolerated the challenge doses and subsequent courses of the cephalosporin. Both of the patients who had allergic reactions had positive penicillin skin test results to benzylpenicillin only; how-

ever, another patient with the same skin test pattern tolerated cephalosporin challenge without incident. Because this study did not contain a control group without penicillin allergy, the relative significance of the penicillin allergy cannot be determined.[47] In another study, 1 (1.6%) of 62 patients with positive skin test results to penicillin who were challenged with a cephalosporin on the same day as the skin testing, developed mild urticaria plus bronchospasm within 24 hours.[7] Solley et al[22] described 27 patients with positive penicillin skin test results, all of whom were treated with cephalosporins without a reaction; whereas 2 (1.5%) of 151 patients with a positive history of penicillin allergy and negative penicillin skin test results had an allergic reaction to cephalosporins. Forty-three treatment courses with cephalosporins were administered to children who had positive skin test results or positive oral challenge to penicillin. Forty-one (95%) of the cephalosporin courses were well tolerated. Two children experienced a mild IgE type–mediated reaction.[26]

In summary, neither the history nor the penicillin skin test result reliably predict the probability of allergic reactions to cephalosporins in patients with positive histories of penicillin allergy. Available data suggest that the vast majority of patients who are allergic to penicillin tolerate cephalosporins without significant reaction. Our approach to a patient with a history of penicillin allergy requiring a cephalosporin is to first determine the likelihood that the patient requiring a cephalosporin had a type I allergic reaction to penicillin (BOX). If a detailed history does not suggest a true penicillin allergy, we administer the cephalosporin. When the history is concerning for penicillin allergy, we recommend penicillin skin testing. For patients with negative skin test results, the cephalosporin can be administered. When the penicillin skin test result is positive and an alternate drug cannot be used, cephalosporin desensitization by an experienced practitioner should be considered.[44]

Some investigators have called for broader use of cephalosporin skin testing in patients who are allergic to penicillin and require a cephalosporin.[26,47] However, protocols for skin testing with cephalosporin compounds are not well standardized, and the negative predictive value of cephalosporin skin testing is not known.[7,44,46]

Carbapenems and monobactams are β-lactam antibiotics of which imipenem and aztreonam are respective prototypes. Patients who have positive skin test results to penicillin have also shown a high degree of reactivity to imipenem determinants.[7] Therefore, carbapenems should not be administered to patients with positive penicillin skin test results or a concerning history of a type I allergic response to penicillin.[7] Available information indicates that aztreonam may be safely administered to most, if not all, patients with a type I allergic response to penicillin.[7]

PRECISION AND ACCURACY
Why Is Taking a Detailed Clinical History for Penicillin Allergy Important?

The overwhelming majority of patients with a history of penicillin allergy have no concurrent physical examination findings related to the adverse response to penicillin. Thus, initial determination of the probability of a true penicillin allergy relies almost solely on a detailed history (Box). For example, a patient receiving penicillin who developed a rash on day 5 of treatment for an upper respiratory tract infection who has since taken multiple courses of drugs containing penicillin without an untoward reaction does not have a true penicillin allergy. In contrast, if a patient described new-onset wheezing 1 hour after a penicillin injection, it is highly probable that this patient had an immediate type hypersensitivity reaction to the drug.

When assessing a patient for penicillin allergy, all medications that the patient is (or was) taking should be evaluated for their propensity to cause a reaction similar to the one being attributed to penicillin. For example, a patient receiving penicillin for 4 days without untoward effects who then begins taking an angiotensin-converting enzyme inhibitor and develops angioedema on the third day of administration (day 7 of penicillin therapy) should not be automatically labeled as penicillin allergic.[9]

Serious allergic and fatal reactions to antibiotics that contain penicillin can occur in individuals who have never had a prior allergic reaction to penicillin or who deny any medical exposure to drugs that contain penicillin.[6] The clinical history, no matter how carefully considered, cannot prevent these rare reactions.

Accuracy of the Clinical History for Penicillin Allergy

Four studies[16-19] compared the clinical history of penicillin allergy to the skin test result and included patients who had positive histories of penicillin allergy and those who did not. We pooled the results of these studies (Table 1). The presence of a clinical history suggesting penicillin allergy increases the likelihood that the patient will be allergic to penicillin as assessed by skin testing (summary positive likelihood ratio, 1.9; 95% CI, 1.5-2.5). The absence of a clinical history suggesting penicillin allergy decreases the likelihood of a positive skin test result by slightly more than half (summary negative likelihood ratio, 0.5; 95% CI, 0.4-0.6).

The percentages of positive skin test results for patients with a history of anaphylaxis, urticaria, or a maculopapular rash ranged from 17% to 46%, 12% to 16%, and 4% to 7%, respectively, in 2 studies.[17,19] One study[17] also reported that 18% of patients with a history of angioedema had a positive penicillin skin test result. Limited data are available about the rate of skin test reactivity when the patient's allergic status to penicillin is unknown. Sogn et al[18] found that the proportion of positive skin test results among patients with an unknown history of penicillin allergy was 3% (3/96). In another study of 57 patients with an uncertain allergy to penicillin, 1.7% had a positive skin test reaction.[19] Although the clinical history does help separate those more likely from those less likely to have a penicillin allergy as demonstrated by skin testing, the history is not precise. The studies[16-19] evaluating the skin test in patients with and without a history of penicillin allergy had higher positive predictive values for the clinical history than all but one of the studies that included only patients with positive histories of penicillin allergy (summary positive predictive value, 19% [95% CI, 18%-21%]). After excluding the outlier study,[21] the positive predictive value for the clinical history of penicillin allergy is 14% (95% CI, 12%-18%). Thus, a clinician would need to perform skin tests on 7 patients with a history suggesting penicillin allergy to find 1 positive reaction.

Penicillin Skin Testing

Blackley introduced the skin test in 1865 when he scarified a portion of his forearm, sprinkled it with pollen, and noted the development of itching and swelling surrounded by erythema. It is now known that IgE antibodies mediate such reactions.[48]

The penicillin skin test has no place in the management of patients without a clinical history of a type I penicillin allergy. It would also be unnecessary in the face of a bonafide history of a life-threatening type I reaction, when equally efficacious antibiotics are available, or if the clinician would still withhold penicillin therapy regardless of skin test results. Some,[11,20,26] but not all,[6,7] investigators have suggested elective skin testing for penicillin allergy. Elective skin testing for penicillin allergy may be useful in children because of the frequent outpatient need for antibiotics that contain penicillin. In addition, elective skin testing of adults with positive histories of penicillin allergy might be considered in certain situations. An example of this would be a cancer patient who has a positive history of penicillin allergy who is likely to develop chemotherapy-induced neutropenia and requires a drug containing penicillin promptly for an infection.[44] Recommendations regarding the general

use of elective penicillin skin testing await further study.

However, when the history of type I hypersensitivity is concerning and penicillin therapy is warranted, skin testing is helpful and should be considered. For example, a patient who has a positive history of penicillin allergy and has *Staphylococcus aureus* endocarditis susceptible to an antistaphylococcal penicillin (such as nafcillin or oxacillin) would be an appropriate candidate for skin testing[49] because vancomycin, an antibiotic often used in patients allergic to penicillin with serious *S aureus* infections, is less effective and more expensive than nafcillin.[50]

Another factor influencing the decision to perform a skin test relates to the ability to do the test in an efficient manner using appropriate reagents and with appropriate interpretation. A recent study of hospitalized patients showed that the time for skin testing averaged 40 minutes, and the cost for the skin test reagents and equipment was $17 per patient.[12]

The positive predictive value of skin testing to assess risk for an allergic reaction to penicillin is unclear because patients providing a convincing history of a type I reaction to penicillin who subsequently react to skin testing are unlikely to undergo oral penicillin challenge. However, a limited number of patients with positive skin test results have been treated with penicillin. The risk of a type I allergic reaction ranges from about 9% in subjects with negative histories to 50% to 70% in subjects with positive histories.[6] Despite the observation that some patients with positive skin test results are able to tolerate penicillin, it is inadvisable to administer penicillin to these patients because of an unfavorable risk-benefit ratio. Patients with positive skin test results who need penicillin should undergo desensitization.[6]

Many studies have used penicillin challenge in subjects with positive histories of penicillin allergy and negative skin test results, and the experiences have been very consistent: the vast majority of subjects tolerated the challenge and those who did not experienced only urticaria

or other mild cutaneous reaction. When 6739 patients with positive histories of penicillin allergy and negative skin test results were given penicillin, only 101 (1.49%) developed an IgE-mediated reaction, while 43 (0.63%) developed a delayed reaction.[16-29] Penicillin anaphylaxis was not reported in subjects with negative skin test results who received a penicillin challenge. Patients with positive histories of penicillin allergy who have negative skin test results may receive a medically supervised oral penicillin challenge. If there is no reaction to the oral challenge, patients can then generally be treated with an oral or parenteral penicillin. When the skin test is properly performed, almost all patients with negative penicillin skin test results can safely receive the drug. Thus, even when the history of a previous type I reaction is concerning and penicillin is the clear drug of choice, skin testing should be considered because the vast majority of those patients will have a negative skin test result, and 98% of patients with a negative result will tolerate penicillin without any serious sequelae.[6,7]

If skin testing seems appropriate after obtaining a detailed history of the patient's reaction to penicillin, both the major determinant (benzyl penicilloyl; commercially available as PrePen, Kremers-Urban, Milwaukee, Wis), and the minor determinant composed of freshly diluted aqueous penicillin G should be used.[44] A minor determinant mixture (MDM) is not commercially available in the United States. The use of the major determinant reagent alone would detect between 75% to 90% of all potential positive reactions. Including fresh penicillin G as the sole MDM reagent improves identification of patients who may potentially have reactions to the skin test by 5% to 10%.[6] However, the addition of other minor determinants to the testing protocol may increase identification of patients allergic to penicillin by skin testing to about 99%.[16,23] The absence of a commercially available MDM solution has hampered the general use of the penicillin skin test. The steps for performing a penicillin skin test are described in detail elsewhere.[44,51]

Limitations of Skin Testing Compared With Other Diagnostic Techniques

A recent review identified the essential criteria that any diagnostic test must satisfy; studies evaluating penicillin skin testing fail to meet several of these criteria.[52] An independent, blind comparison of a reference standard—oral penicillin challenge—has never been uniformly applied to all patients who have undergone skin testing. Moreover, few studies have actually subjected all subjects with positive histories of penicillin allergy and negative skin test results to oral challenge. It is clear that in most studies the skin test results influenced the decision to perform the penicillin challenge, thus introducing a built-in bias. These limitations undermine attempts to generate reliable estimates of sensitivity and specificity for penicillin skin testing compared with oral penicillin challenge used as the gold standard. This problem, labeled "reverse workup bias," can result in biased test estimates since it is likely that patients who do not undergo skin testing differ in important ways from patients in whom testing is undertaken.[53]

Redelmeier and Sox[53] used expert opinion to estimate the probability of severe allergic reactions in 100 patients with a convincing penicillin allergy history who were to receive the drug without prior skin testing. Respondents estimated that 5 to 90 (median, 50) patients would experience a severe reaction to penicillin.[53] Accordingly, these authors concluded that skin testing for patients with a "very strong" history of penicillin allergy is not recommended, based on their estimated pretest probability of 0.5 (50%) of a severe allergic reaction to penicillin in a patient with a positive history of penicillin allergy. They reasoned that clinicians would be unwilling to risk a potential serious reaction in these patients even if they had negative skin test results.[53] However, at least 50% of patients with a history of an IgE-mediated reaction will have a negative skin test result.[17,19] Since the experi-

ence is that patients with negative skin test results tolerate penicillin well, patients with histories of a type I reaction should undergo skin testing with the expectation that at least 50% of these patients will be identified as candidates for penicillin therapy (when the indication for penicillin is very strong). Still, if the clinician's treatment threshold is so high that he or she is unwilling to administer penicillin regardless of the clinical situation (given a prior history of a type I reaction), skin testing clearly has no value.

SCENARIO RESOLUTION

In case 1, the patient reported a maculopapular rash halfway through a course of penicillin. The pretest probability that this represents a true reaction to penicillin would be 10%, using a conservative estimate for the frequency of any adverse reaction to penicillin.[31] After a careful history is taken from the patient, one might conclude that his experience is inconsistent with a type I reaction. Using a negative likelihood ratio of 0.5 for a negative history, the probability that this patient will experience any adverse reaction to penicillin can be revised to 5.2%, a percentage that is similar to the frequency of any adverse reaction to penicillin in the general population.[31] In this patient, skin testing should not be performed and the patient should receive penicillin. Careful history taking should have increased confidence about the safety of administering penicillin to this patient.

The patient described in case 2 reported, and a detailed history confirmed, an urticarial rash within 72 hours of taking penicillin. Again, using 10% as the pretest probability of any adverse reaction to penicillin,[31] a 17% posttest probability that this patient has a true penicillin allergy is arrived at by using the positive likelihood ratio of 1.9. We would perform skin testing on this patient since a negative skin test result virtually excludes a significant reaction to penicillin, while a positive skin test result in this patient with a strong indication for penicillin would mandate desensitization.[6]

COMMENT

We identified only 4 studies meeting our inclusion criteria that used penicillin skin testing in patients with and without positive histories of penicillin allergy (Table 1). Two of these studies provided no data on the frequency of positive skin test results in patients based on their previous reaction to penicillin.[16,17] Moreover, none of the studies included in our analysis were independent, blind comparisons of signs or symptoms of penicillin allergy compared with the gold standard, oral penicillin challenge. These methodological flaws have tempered the quality of the published database for this common clinical problem, leaving us with a pervasive lack of guidelines for determining penicillin allergy.

Nonetheless, encountering patients with a stated penicillin allergy remains an everyday problem for many clinicians, and some clinicians simply prescribe an alternate antibiotic for these patients. However, some alternative antibiotics are more expensive, less effective, or associated with more adverse effects than penicillin, and there is the risk of increasing antimicrobial resistance. Other clinicians turn to the literature hoping to find a rich evidence-based database to help guide their decision-making process. Regrettably, the methods of diagnosing true penicillin allergy have been inadequately studied, leaving the busy clinician to make the most informed decision possible while recognizing the limitations in the available data.

We provide an approach to the patient with a stated penicillin allergy based on a critical analysis of an admittedly limited database: by systematically documenting signs and symptoms associated with the patient's adverse reaction to penicillin (Box), the clinician should be able to determine with a higher degree of certainty whether the patient has a true penicillin allergy. Using a more structured approach should allow the clinician to assess the likelihood that the patient had a true penicillin allergy, thereby allowing a more rational decision-making

process in consideration of penicillin usage, as illustrated by the resolution of the clinical scenarios.

THE BOTTOM LINE

• Many patients recalling a reaction to penicillin are unsure of specific details, and even when evidence supporting true penicillin allergy is absent, are nevertheless labeled as penicillin allergic by many clinicians.

• A detailed history of the patient's drug reaction can help the clinician determine whether or not the patient's self-reported history is compatible with a true penicillin allergy, permitting penicillin administration to those patients who are unlikely to have true penicillin allergy.

• Eighty percent to 90% of all patients reporting a penicillin allergy are negative for penicillin allergy when assessed by skin testing, meaning that penicillin is withheld from many patients who could safely receive the drug.

• Patients who develop a rash while taking penicillins should not be automatically labeled as penicillin allergic without considering other possibilities, such as a rash caused by the infection being treated or by other drugs the patient is taking.

• For patients with a concerning history of penicillin allergy who have a compelling need for penicillin, skin testing should be performed.

• At least 98% of patients with positive histories of penicillin allergy and negative skin test results can tolerate penicillin without any sequelae.

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