

Penicillin Hypersensitivity: Value of Clinical History and Skin Testing in Daily Practice

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ABSTRACT

Penicillin often is excluded as a treatment option based on patients' self-reported history of an adverse reaction to penicillin. The objective of this prospective study was to determine the likelihood of true penicillin allergy in patients with vague and convincing histories of penicillin allergy and to evaluate the diagnostic value added by appropriate skin testing. Six hundred thirty-eight patients with prior β -lactam intake had a current indication for penicillin therapy and were referred for testing with the major (benzylpenicilloyl polylysine) and minor (minor determinant mixture) penicillin determinants from the inpatient and outpatient service of Athens University Dermatological hospital from January 2000 to December 2002. The prevalence of positive skin tests in the total group and in those patients with vague and convincing histories of penicillin allergy was determined. Positive skin tests were observed in 19/638 (3%) of the total group, 5 out of 542 (0.9%) patients without any history of penicillin allergy, 14 out of 96 (14.6%) patients with vague history (confidence interval [CI] 95% = 5.95–59.92), and 13 out of 18 (72.2%) patients with a convincing history of type I hypersensitivity reaction ($\chi^2 = 286.3$; odds ratio = 281.3; CI 95% = 62.19–1440.8). Patients with a vague history of penicillin allergy are 18 times more likely to have a positive penicillin skin test, and a convincing reaction history increases the likelihood by 281-fold compared with patients without a history of penicillin allergy. However, the fact that

5 of 18 (27.8%) patients with a convincing history were negative when skin tested points out that skin testing is helpful if the need for penicillin administration is compelling. (Allergy and Asthma Proc 25:157–160, 2004)

Penicillin is an effective and inexpensive agent that remains the antibiotic of choice for the treatment of syphilis and skin infections such as erysipelas. Agents substituted for penicillin may be potentially more toxic in 70% of cases and more costly in 55% of cases.¹ The use of alternate antibiotic therapy also has been associated with the emergence of multidrug-resistant pathogens. Penicillin is the most common cause of allergic reactions and anaphylaxis.² True anaphylaxis is rare and has an incidence of 0.05% and a mortality of 0.0002% in all patients receiving penicillin.³ Skin testing with major and minor penicillin determinants is safe and important to protect truly allergic patients from anaphylactic reactions.^{4–6}

Penicillin skin testing is performed routinely in all persons before penicillin therapy at our hospital for dermatological and sexually transmitted diseases. We reported the results of penicillin testing in 638 patients with prior β -lactam intake from January 2000 to December 2002.

MATERIALS AND METHODS

Subjects

A total of 638 patients (325 men and 313 women) had a current indication for penicillin therapy and underwent penicillin skin testing from January 2000 to December 2002. Patients were referred for testing from the inpatient and outpatient service of the "A. Syngros" hospital, which is the largest university hospital in Greece for sexually transmitted and dermatological diseases. All patients had re-

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ceived β -lactam antibiotics in the past. Patients were asked by a trained dermatologist about a prior history of allergic reactions to penicillin or other β -lactam antibiotics and those with positive history were referred to a trained allergist for a detailed evaluation that also included atopy predilection history and atopy family history. Patients were considered to have a convincing history of penicillin allergy if they reported episodes of anaphylaxis or urticarial reactions after penicillin intake. No patient reported previous Stevens–Johnson syndrome, toxic epidermal necrolysis, or serum sickness-like reactions. All patients were skin tested after informed consent was obtained, regardless of positive or negative history of reactions to antimicrobials. Patients were instructed to discontinue intake of any agents suppressing skin reactivity 10 days before skin testing. Total immunoglobulin E (IgE) was determined in all patients' sera and a radioallergosorbent test (RAST) was performed. All patients with negative skin testing received *per os* or intravenous treatment with penicillin. Outpatients were followed up by telephone 72 hours after receiving penicillin.

Skin and RAST Testing

The penicillin reagents used were benzylpenicilloyl polylysine (PPL) and minor determinant mixture (MDM; Allergopharma Joachim Ganzer KG, Reinbek, Germany) diluted in a sterile saline solution. First, skin-prick tests were performed using standard techniques with PPL at a concentration of 350 mg/mL, MDM at a concentration of 1.1 mg/mL (0.6 mg/mL of benzylpenicillin and 0.5 mg/mL of benzylpenicilloate), 1% histamine, and a negative normal saline control (ALK, Horsholm, Denmark). The wheal and flare responses of the skin were read at 20 minutes by an experienced staff physician by measuring the two largest diameters and recording the mean. A wheal diameter of >5 mm and a flare (erythema) diameter of >5 mm was considered positive. If the prick test was considered negative, intradermal tests were performed with 0.02 mL of the foregoing reagents on the skin of the upper arm and reactions were read at 20 minutes as described previously.

A skin test reaction was interpreted as uninterpretable (doubtful) in the presence of (1) a wheal size between 3 and 5 mm, (2) erythema like a ring around the intradermal injection site without pruritus, and/or (3) an inappropriate reaction to the positive or negative control. In the case of doubtful reactions, repeat skin testing was performed.

Sera from all patients were investigated for total IgE levels measured by radioimmunosorbent test and allergen-specific IgE antibodies by RAST with specificity for benzylpenicilloyl and phenoxymethyl-penicilloyl using enzyme-linked immunosorbent assay (Hycor Biomedical GmbH, Kassel, Germany).

Statistical Analysis

The Mantel–Haenszel method⁷ was used to test the association between history of penicillin allergy (vague versus negative and convincing versus negative) and skin

	Erysipelas	Syphilis	Other	Total
Gender				
Male	99	182	47	328
Female	107	110	93	310
Total	206	292	140	638

test results (negative/positive) and to evaluate the corresponding odds ratio. Logistic regression analysis (backward stepwise, using Wald's criterion) was used to evaluate the predictive value of the following explanatory variables: family and personal history of atopic diseases, sex, age, and total IgE (after logarithmic transformation to the natural logarithm) on the penicillin sensitization status (skin test result as the dependent variable, positive = 1 and negative = 0). The statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS, Tokyo, Japan).

RESULTS

Population Demographics

The mean age for men was 44.5 years (range, 15–72 years) and for women was 45.1 years (range, 16–75 years). The most frequent underlying diseases were syphilis (296 patients), erysipelas (209 patients), and other skin infections (42 patients; Table I). Ninety-six patients (15%) self-reported vague history of prior reactions to penicillin. A convincing history of type I hypersensitivity reaction was established for 18 patients (2.8%) after evaluation by a trained allergist.

Results of the *In Vivo* and *In Vitro* Tests

The overall prevalence of positive skin test reactions to penicillin in our population was 3% (19/638). Of the 96 patients with a self-reported vague history of penicillin allergy 14 patients had a positive skin test (14.6%) and 82 patients (85.4%) had a negative skin test. Of the 18 out of the 96 patients for whom a convincing history of allergy could be established, 13 patients had a positive skin test (72.2%) and 5 patients had a negative skin test (27.8%). Five out of 542 patients without a history of penicillin allergy had positive skin tests (0.9%; Table II). A positive test for both PPL and MDM was seen in 14/19 patients (73.7%). In four patients (21%), PPL was reactive but MDM was negative and PPL was negative and MDM was positive in one patient (5.3%). RAST results were similar for all positive skin-tested patients. All 619 patients with negative skin tests received treatment with penicillin and only one of them reported systemic pruritus (0.16%).

TABLE II

Association and Odds Ratio Values Between History of Penicillin Allergy and Skin Test Results Using the Mantel-Haenszel Method

	History		
	Vague	Convincing	Negative
Skin tests			
Positive	14 (14.6%)	13 (72.2%)	5 (0.9%)
Negative	82 (85.4%)	5 (27.8%)	537 (99.1%)
Total	96	18	542
$p = 0.00$	$*\chi^2 = 52.5$ #Odds ratio = 18.3 CI (95% = 5.95–59.92)	$*\chi^2 = 286.3$ #Odds ratio = 281.3 CI (95% = 62.19–1440.8)	

Patients were considered to have a convincing history of penicillin allergy if they reported episodes of anaphylaxis or urticarial reactions after penicillin intake.

$*\chi^2$ Mantel-Haenszel.

#Reference category was the group of patients with negative history of penicillin allergy.

TABLE III

Logistic Regression Analysis: Distribution of Partial Coefficient B, Wald's Criterion, and Level of Significance (p)

Independent Variable	B	Wald	p
History	0.20	0.07	0.79
Family history	−0.77	1.3	0.25
Gender	−0.82	1.3	0.26
Age	0.05	6.1	0.014
Total IgE*	−0.75	6.3	0.011

Skin testing was considered the dependent variable (positive = 1; negative = 0).

*Total IgE values were transformed to the natural logarithm to obtain Gaussian distribution.

A history of atopy has been designated as a possible predilection factor for penicillin sensitization. We used a logistic regression model with the skin tests as the dependent variable and history of atopy, family history of atopy, gender, age, and total IgE as independent variable. Results indicated that in the population studied, history, family history of atopy, and gender did not predispose to penicillin sensitization. On the contrary, we confirmed the well-known negative association between skin test reactivity and age and the positive association between positive skin tests and total IgE values ($p = 0.014$ and $p = 0.011$, respectively; Table III).

DISCUSSION

Between 10 and 20% of patients admitted to a hospital report histories of allergic reaction to penicillin.^{8–9} The higher estimates are from venereal clinic populations.^{3,10} In our population of patients with both venereal

and skin diseases the incidence of self-reported antibiotic allergy also was high (15%; 96/638).

Skin testing with the major and minor penicillin determinant is a well-established method used to identify those patients at risk of an IgE-mediated, immediate, anaphylactic reaction if challenged with penicillin.³ A negative skin test is rarely followed by an allergic reaction on challenge.^{2–4} Only one of the patients with negative skin tests in this study who was treated with the drug on the ward or outpatient clinic had an immediate hypersensitivity reaction (0.16%). Elective penicillin skin testing before acute antibiotic administration has been shown to decrease the cost of antibiotics used.^{11,12}

Clearly, differences in patient selection can greatly influence penicillin skin test results. In most studies, between 10 and 20% of patients with a history of allergy to penicillin had positive skin tests.^{10,13–15} It would be expected that a high percentage of positive skin tests would be found if only patients with a convincing history of allergy were skin tested. In fact, studies in which only patients with convincing histories were skin tested consistently have found skin test-positive rates of >60%.¹⁶ The overall prevalence of positive skin test reactions to penicillin in our population was 3%; 0.9% of patients with no history of prior adverse reactions to penicillin or related drugs were found to have a positive test compared with 14.6% of the patients with vague history and 72.2% of the patients with convincing history of penicillin allergy. These results indicate that patients with even a vague history of penicillin allergy are 18 times more likely to have a positive penicillin skin test, and a convincing reaction history increases the likelihood by 281-fold compared with patients without a history of penicillin allergy (Table II).

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 fre-

quent among individuals with positive and negative skin tests. This confirms results in other studies and suggests that atopy may affect the expression of allergic disease but not the rate of drug sensitization.¹⁷ We also observed a positive correlation between total IgE levels and incidence of positive skin tests in accordance with results reported in previous studies¹⁸ (Table III).

In addition, age may be a risk factor for drug allergy and allergic drug reactions are thought to be less common in the very young and the very old¹⁹ but severe reactions can affect all ages.¹⁹ We did find a negative association between age and the frequency of positive skin tests (Table III).

Many different degradation products of penicillin are implicated in immediate hypersensitivity. Most antibodies recognize the major determinant that is the PPL group.^{2-4,20} In our patients, 18/19 skin test-positive patients reacted to the major determinant (PPL). Reactions to the minor determinants (MDM) have been associated with more severe anaphylactic reactions.^{20,21}

Other methods that are used to study hypersensitivity to penicillin are *in vitro* IgE assays that measure specific anti-penicillin IgE antibodies,²² *in vitro* lymphocyte proliferation tests (lymphocyte transformation test),²³ and the flow assay stimulation test that uses flow cytometry to determine the percentage of basophils that express CD63 as an activation marker after *in vitro* stimulation with allergen.²⁴ Serum-specific IgE is not as consistently reliable as skin tests, although they are useful for some authors. The lymphocyte proliferation test and the flow assay stimulation test are not widely available. The presence of positive skin tests, specific serum IgE antibodies lymphocyte or basophils responses demonstrates sensitization; however, a definite diagnosis of penicillin allergy can be made only with drug challenge.

Only 14.6% of the patients reporting a vague history of penicillin allergy in our population were truly allergic when assessed by skin testing. The prevalence was raised to 72.2% among patients with a convincing history of immediate reactions to penicillin established by detailed evaluation. However, the fact that 27.8% of the patients with convincing histories were negative when skin tested points out that history alone can not predict who is or is not allergic. Consequently, both detailed history and skin testing are helpful to all patients when penicillin administration is required. Virtually all patients with a negative skin test result can take penicillin without serious sequelae.²⁵

REFERENCES

- Forrest DM, Schellenberg RR, Thien VV, et al. Introduction of a practical guideline for penicillin skin testing improves the appropriateness of antibiotic therapy. *Clin Infect Dis* 32:1685-1690, 2001.
- DeShazo RD, and Kemp SF. Allergic reactions to drugs and biologic agents. *JAMA* 278:1895-1900, 1997.
- Lin RY. A perspective on penicillin allergy. *Arch Intern Med* 152:930-937, 1992.
- Sogn DD, 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* 152:1025-1032, 1992.
- Pichichero ME, and Pichichero DM. Diagnosis of penicillin, amoxicillin, and cephalosporin allergy: Reliability of examination assessed by skin tests and oral challenge. *J Pediatr* 132:137-143, 1998.
- Li JT. Allergy testing. *Am Fam Physician* 66:621-624, 2002.
- Mantel N, and Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 22:719-748, 1959.
- Mendelson LM. Adverse reactions to β -lactam antibiotics. *Immunol Allergy Clin North Am* 18:745-756, 1998.
- Nicklas RA, Bernstein IL, Li JT, et al. β -lactam antibiotics: The diagnosis and management of anaphylaxis. *J Allergy Clin Immunol* 101:S498-S501, 1999.
- Walker T, Jung EG, and Bayerl C. Penicillin allergy as a diagnostic problem. Overview and personal studies. *Hautarzt* 51:838-845, 2000.
- Macy E. Elective penicillin skin testing and amoxicillin challenge: Effect on outpatient antibiotic use, cost, and clinical outcomes. *J Allergy Clin Immunol* 102:281-285, 1998.
- Harris AD, Sauberman L, Kabbasha L, et al. Penicillin skin testing: A way to optimize antibiotic utilization. *Am J Med* 107:166-168, 1999.
- Arroliga ME, Wagner W, Bobek MB, et al. A pilot study of penicillin skin testing in patients with a history of penicillin allergy admitted to a medical ICU. *Chest* 118:1106-1108, 2000.
- Salkind AR, Cuddy PG, and Foxworth JW. The rational clinical examination. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. *JAMA* 285:2498-2505, 2001.
- Romano A, Quarantino D, Papa G, et al. Aminopenicillin allergy. *Arch Dis Child* 76:513-517, 1997.
- Solensky R, Earl HS, and Gruchalla RS. Penicillin allergy: Prevalence of vague history in skin test positive patients. *Ann Allergy Asthma Immunol* 85:195-199, 2000.
- Gadde J, Spence M, Wheeler B, et al. Clinical experience with penicillin skin testing in a large inner city STD clinic. *JAMA* 270:2456-2463, 1993.
- Kraft D, Roth A, Mischer P, et al. Specific and total serum IgE measurements in the diagnosis of penicillin allergy. A long term follow-up study. *Clin Allergy* 7:21-28, 1977.
- Adkinson NF. Risk factors for drug allergy. *J Allergy Clin Immunol* 74:567-572, 1984.
- Adkinson NF. Drug allergy. In *Allergy: Principles and Practice*, 5th ed. Middleton E, Reed C, Ellis E, Adkinson NF, Unginger J, and Busse W. (Eds). St. Louis, MO: Mosby, 1212-1224, 1998.
- Torres MJ, Mayorga C, Pamies R, et al. Immunological response to different determinants of benzylpenicillin, amoxicillin, and ampicillin. Comparison between urticaria and anaphylactic shock. *Allergy* 54:936-943, 1999.
- Moreno F, Blanca M, Mayorga C, et al. Studies of the specificities of IgE antibodies found in the sera from subjects with allergic reactions to penicillins. *Int Arch Allergy Immunol* 108:74-81, 1995.
- Nyfeler B, and Picher WJ. The lymphocyte transformation test for the diagnosis of drug allergy: Sensitivity and specificity. *Clin Exp Allergy* 27:175-181, 1997.
- Sanz ML, Gamboa PM, Antepara I, et al. Flow cytometric basophil activation test by detection of CD63 expression in patients with immediate type reactions to beta-lactam antibiotics. *Clin Exp Allergy* 32:277-286, 2002.
- Macy E, Mangat R, and Burchette RJ. Penicillin skin testing in advance of need: Multiyear follow-up of 568 test result-negative subjects exposed to oral penicillins. *J Allergy Clin Immunol* 111:1111-1115, 2003. □

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