A Pilot Study of Penicillin Skin Testing in Patients With a History of Penicillin Allergy Admitted to a Medical ICU*

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Background: **Penicillin skin testing is an accurate method to determine whether a person with a history of penicillin allergy is at risk of having an immediate reaction to penicillin. A patient with a negative reaction to a skin test may be able to use a penicillin compound safely, which could reduce the use of broad-spectrum antibiotics in this patient population.**
Methods: **We prospectively studied all patients with histories of penicillin allergy who were admitted to a medical ICU during a 3-month period and who received antibiotics. Skin testing was performed with benzylpenicilloyl polylysine and penicillin G. We determined the incidence of true allergy, the percentage of patients in whom antibiotic coverage was modified, and the safety of the test.**
Results: **Two hundred fifty-seven patients were admitted to the medical ICU of The Cleveland Clinic Foundation during the study period. Twenty-four patients (9%), labeled as penicillin allergic and receiving antibiotics, were enrolled. Three patients (13%, 3 of 21) gave histories of type I reaction to penicillin and were not skin tested. Twenty patients (95%, 20 of 21) had negative skin test reactions to penicillin and positive skin test reactions to histamine control. One patient (4%, 1 of 21) with negative skin test reactions to both penicillin and histamine control had a test dose challenge with piperacillin that was well tolerated. There were no adverse events. Antibiotic coverage was changed in 10 patients (48%) as a result of skin testing.**
Conclusion: **Most patients with histories of allergy to penicillin have negative reactions to skin tests and may receive penicillin safely. Penicillin skin testing can be utilized as a safe and effective strategy to reduce the use of broad-spectrum antibiotics.** ***(CHEST 2000; 118:1106–1108)***

Key words: anaphylaxis; antibiotic resistance; antibiotic therapy; ICU; penicillin allergy; skin test

Abbreviation: BPP = benzylpenicilloyl polylysine

A history of penicillin allergy is unreliable in predicting immediate allergic reactions on subsequent administration of the drug.[1] Many patients do not remember the type of reaction they developed to penicillin.[2] Furthermore, patients with allergy to penicillin lose their sensitivity with time, as demonstrated by a negative penicillin skin test.[2] Between 10% and 20% of patients admitted to a hospital have histories of allergic reaction to penicillin.[2–4] The majority of patients with histories of penicillin allergy will be placed on regimens of alternative antibiotic therapy, such as vancomycin or fluoroquinolones, to try to avoid the risk of severe reaction to penicillin. The use of some of these antibiotics has been associated with the emergence of multidrug-resistant pathogens.[5] Infections caused by multidrug-resistant pathogens are associated with increased morbidity and mortality rates.

Penicillin skin testing in a person with a history of allergy to penicillin is a safe and reliable method for determining whether a person is at risk of an immediate systemic allergic reaction. Penicillin skin testing has a reaction rate between 0.3% and 1.2%, with no serious reactions if performed properly.[6,7] A person with history of penicillin allergy and a negative reaction to a skin test may be able to use a penicillin compound, which could reduce the use of

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certain antibiotics and decrease the emergence of resistant microorganisms.[5,8]

We report our initial experience with the use of penicillin skin testing to determine whether patients with a history of penicillin allergy, who were admitted to a medical ICU, could take penicillin safely.

Materials and Methods

We prospectively studied all patients with a history of penicillin allergy, as documented in the patient's chart, who were receiving antibiotics and who were admitted to the 18-bed Medical ICU of The Cleveland Clinic Foundation during the period from April 1 to June 30, 1999. This group represents those patients in whom the demonstration of true penicillin allergy may be clinically important.

Skin Test Material, Procedure, and Interpretation

Skin testing was performed and interpreted by Allergy fellows under the supervision of a physician who is board certified in allergy and immunology. Two penicillin skin testing reagents were used for prick and intradermal tests: benzylpenicilloyl polylysine (BPP) at concentration of 6.0×10^{-5} mol/L in 0.15 mol/L sodium chloride and 0.01 mol/L phosphate (Prepen; Schwarz Pharma; Milwaukee, WI) and penicillin G at a concentration of 10,000 U/mL as has been suggested.[9] Histamine base at 1.8 mg/mL and at 0.1 mg/mL was used as a positive control in prick and intradermal tests, respectively. Saline solution was used as a negative control.

All patients first underwent full-strength prick test with BPP, penicillin G, and positive and negative controls. If the test results were negative, full-strength intradermal tests were performed using the antigens and controls. The site for testing was the volar area of the forearm or the lateral aspect of the upper arm, depending on which site was available. For prick test, drops of the antigens and control solution to be tested were applied sequentially to premarked skin sites. A bifurcated needle (Allergy Labs of Ohio; Columbus, OH) was used through the drop of the test material to accomplish a slight lifting of the skin. Intradermal skin testing consisted of intradermal injection of approximately 0.02 mL of the antigens and control solutions into sequential, premarked skin sites. Each of the tests, prick and intradermal, was read 15 min after application. The test results were considered positive if a wheal and flare reaction larger than that of the negative control was present during prick or intradermal testing either for BPP or penicillin G. The total time required to perform the test is approximately 30 min. Patients who were receiving histamine-2 blockers had the medication held at least 4 h before the skin test.

The Institutional Review Board approved the study. Informed consent was waived because penicillin skin test is usual practice in patients with a history of penicillin allergy requiring treatment with β-lactam antibiotics.

Analysis of the data was limited to descriptive statistics.

Results

Two hundred fifty-seven patients were admitted to the medical ICU during the study period. Twenty-four patients (9%) labeled as penicillin allergic were enrolled in the study. The characteristics and diagnoses at the time of ICU admission are listed in Table 1. Three patients had had recent episodes of immediate reaction to penicillin, including anaphylaxis.

The characteristics of penicillin allergy were unknown in 11 (46%) of the 21 patients who had the skin test done. Six patients (25%) had had skin rash, and four patients (16%) had developed urticaria when given penicillin 30 years ago. In 20 patients (95%, 20 of 21), the skin test results for penicillin were negative (for BPP and penicillin G), with a positive histamine control. In one patient (4%), the skin test could not be read because of lack of skin reactivity to histamine. The patient received a test dose challenge with piperacillin that was well tolerated. No adverse reaction was noted during the skin test procedure. The three patients (13%; 3 of 24) with recent episodes of immediate reaction to penicillin were not tested.

Treatment with penicillin antibiotic was started in 10 of the 21 patients (48%) as a result of the negative skin test results. No side effects were reported. The antibiotics that the patients were given before the skin test were ciprofloxacin (five patients), clindamycin (two patients), imipenem (two patients), and erythromycin (one patient).

Discussion

The major finding of this study is that the majority of patients (20 of 21, 95% of the patients tested) admitted to a medical ICU with a history of penicillin allergy and no clear history of recent type I reaction had negative reactions to penicillin skin test and

Table 1—*Characteristics and Diagnosis at the Time of ICU Admission (n = 24)*

Characteristics	Data
Mean age, yr (range)	64.6 (41–87)
Gender, No. (%)	
Female	13 (54)
Male	11 (46)
APACHE* III score (range)	83 (37–160)
Diagnosis, No.	
Pneumonia	4
Upper-airway obstruction	3
ARDS	2
Alveolar hemorrhage	2
COPD	1
Pleural effusion	1
Sepsis	6
Pancreatitis	2
Metabolic acidosis	1
Heart failure	1
Gastric bleeding	1

*Acute physiology and chronic health evaluation.

were able to receive a penicillin compound. In one patient, the penicillin skin test was nondiagnostic, and the patient had a test dose challenge with piperacillin without any adverse effect. We did not perform penicillin skin tests on three patients because they had clear histories of recent immediate reactions to penicillin. The incidence of reported allergy to penicillin, as documented in the charts of patients, was 9% and is similar to the 10 to 20% reported in patients admitted to general wards.[2,3] Like patients described by other authors,[2] a significant portion (46%) of our patients or their families did not remember the type of reaction developed.

In spite of the elimination of several contaminants that were implicated in allergic reactions to penicillin in the 1970s,[10] it has been estimated that penicillin compounds are responsible for the majority of all drug-mediated anaphylactic deaths in the United States.[9] Skin testing is helpful to identify patients with penicillin-specific IgE antibodies who may be at risk of an immediate reaction if a penicillin compound is used.[9]

Up to 90% of penicillin breakdown products are in the form of a penicilloyl hapten moiety conjugated to endogenous proteins; the penicilloyl hapten moiety is a metabolite that is referred to as major determinant.[7] Most antibodies formed in patients with penicillin allergy are specific for the penicilloyl group. A small amount of penicillin metabolized by other pathways results in metabolites known as minor determinants. Skin testing is the most reliable method for the evaluation of IgE-mediated penicillin allergy.[9] We performed the skin tests with a commercially available preparation of benzyl penicilloyl and with penicillin G to test for major and minor determinants, respectively.[9] When both the prick and intradermal tests were negative for BPP and penicillin G, the skin test was read as negative. When a skin test is performed by personnel skilled in performing and interpreting the test, 97% of patients with negative reactions to the skin test will tolerate a penicillin compound.[9] In 48% of our patients, the physician started treatment with a penicillin antibiotic after results for the skin test for penicillin allergy were negative. There were no significant side effects after the administration of the β-lactam antibiotic.

Penicillin skin testing can be a safe and effective strategy to reduce the use of broad-spectrum antibiotics and can be a useful strategy to modify antibiotic use. To manage antimicrobial resistance, decreases of the use of antibiotics such as third-generation cephalosporins, imipenem, the quinolones, and vancomycin, and increases of the use of extended-spectrum penicillins have been suggested.[8] Patients with histories of penicillin allergy receiving alternative antibiotics like vancomycin or quinolones should be referred for skin testing; if the skin test results are negative, the patients should be able to receive penicillin safely. This practice could reduce the spread of antibiotic resistance and improve quality of care.

The most important limitation of this study is the small sample size. However, this preliminary experience suggests that penicillin skin testing in patients with a history of penicillin allergy can have a significant role in a strategy to modify antibiotic use in the ICU. Similarly, this strategy can be extended to the general wards and outpatient areas.

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