Penicillin skin testing in patients with a history of β-lactam allergy

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Background: Vancomycin and fluoroquinolones are commonly used in patients with a history of penicillin allergy.

Objective: To determine the safety and utility of penicillin skin testing (PST).

Methods: Retrospective study of patients with a history of penicillin allergy between April 1, 1999, and September 30, 2004. Penicillin skin testing was performed by means of standard methods using benzylpenicilloyl-polysine, penicillin G, and histamine and saline controls.

Results: Of 596 patients studied, 25.3% were outpatients, 50.3% were inpatients, and 24.3% were intensive care unit patients. The most common antibiotics used during the time of PST were vancomycin and fluoroquinolones. Results of PST were negative in 88.4% of patients, positive in 8.2%, and indeterminate in 3.4%. One patient (0.17%) developed urticaria immediately after PST. Fifty-five percent of patients with negative PST results were changed to a β-lactam drug, more frequently in the intensive care unit vs the outpatient setting (70.3% vs 8.6%; $P < .001$) and in adults vs patients younger than 18 years (58.6% vs 8.1%; $P < .001$). A β-lactam antibiotic was used in 290 patients with negative PST results. Of the patients given β-lactam antibiotics, 5 (1.7%) had adverse reactions: 2 had hives after 16 and 20 days of therapy, 1 had a nonspecific rash after 17 days of therapy, 1 had flushing and urticaria 3 hours after a test dose of piperacillin-tazobactam, and 1 had a pruritic rash after 12 hours of therapy.

Conclusions: Patients with a history of penicillin allergy can safely use β-lactam drugs if negative PST results.

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INTRODUCTION

Adverse reactions to antibiotic drugs are common. Up to 25% of patients who require antimicrobial agents report allergic reactions to antimicrobials, and penicillin is the antibiotic most frequently reported.[1] Allergic reactions to penicillin occur in approximately 2% of patients treated with this class of antibiotics.[2] Of the possible allergic reactions noted, severe reactions such as anaphylaxis are less common but are potentially life-threatening.[2] In patients with a history of penicillin allergy the physician usually treats them with antibiotics such as vancomycin, fluoroquinolones, or third-generation cephalosporins to avoid allergic reactions. The use of these alternative antibiotics is associated with an increase in multidrug-resistant bacterial strains and, in the case of the fluoroquinolones, may be associated with outbreaks of *Clostridium difficile* diarrhea.[3–6]

Based on previous experience and the available literature,[7–9] we hypothesize that the proportion of patients labeled as being allergic to penicillin who have a true IgE-mediated reaction to a penicillin antibiotic is very low. We postulate that using penicillin skin testing (PST) in this cohort we can identify patients at high and low risk of an immediate IgE-mediated reaction. In patients with negative PST results, the likelihood of developing an immediate reaction after administration of a β-lactam drug is very low.[9] The aim of this study is to analyze the characteristics and outcomes of a large cohort of patients from a single institution evaluated in the Allergy and Immunology Section at the Cleveland Clinic for "penicillin allergy" and to determine the safety and utility of PST.

METHODS

Eight hundred forty-nine patients were identified in a search of medical records using the *International Classification of Diseases, Ninth Revision,* code for "drug allergy." This was a retrospective study of 596 patients with penicillin allergy who underwent PST between April 1, 1999, and September 30, 2004, when benzylpenicilloyl-polysine was retired from the market. In all the cases, PST was performed by the allergy and immunology team, consisting of a fellow in training and an attending physician. None of the patients in this study were included in previous studies.[7,8]

The institutional method for performing PST is consistent with the standard method described by the disease management of drug hypersensitivity practice parameter of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology.[9] In all cases, PST was performed using the following reactants: (1) benzylpenicilloyl-polysine, 6×10 mol/L^{-5} in

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Table 1. Demographic Characteristics by Site of Evaluation

Variable	Outpatient setting (n = 151)	Inpatient setting (n = 300)	ICU (n = 145)	Total (N = 596)
Patients, %	25.3	50.3	24.3	100
Female sex, %	60.2	53.6	46.2	53.5
Age				
≥18 y, %	19.7	99.2	100	79.3
<18 y, %	80.3	0.8	0	20.7
Mean ± SD, y	14.6 ± 17.2	59.4 ± 17.1	64.6 ± 13.2	49.4 ± 26

Abbreviation: ICU, intensive care unit.

0.15-mol/L sodium chloride and 0.01-mol/L phosphate (PrePen; Hollisteir-Stier LLC, Spokane, WA); (2) penicillin G, 10,000 U/mL, as a substitute for minor determinants; (3) histamine base, 1.8 mg/mL (for epicutaneous "prick") and 0.1 mg/mL (for intradermal test), as positive control; and (4) saline solution as negative control.

The first step was to perform the prick or epicutaneous method using a bifurcated needle applied to the volar aspect of the forearm or, if not possible in this anatomical location, to the anterior aspect of the arm. Test results were interpreted after 15 minutes of application. Positive results were considered if the penicillin G or PrePen sites had a wheal larger than 3 mm compared with the negative saline control. In those cases patients were considered to be allergic to penicillin, and no further testing was performed. If negative results were found after the prick testing then further testing was performed using the same reactants by means of intradermal injection. Again, intradermal skin test results were reevaluated after 15 minutes. If positive results were found the patient was considered to be penicillin allergic; if negative results were found the patient was considered not to be penicillin allergic. Test-dose challenges and desensitization were performed at the discretion of the allergist and were based on the published literature.[2] The institutional review board at the Cleveland Clinic approved this study.

Summaries of categorical data are given as frequencies and percentages. Quantitative data are summarized using mean ± SD. Subgroup comparisons of categorical and quantitative data were performed using χ^2 and Wilcoxon rank sum tests, respectively. All analyses were performed using R version 1.9.0.[10]

RESULTS

Five hundred ninety-six patients were evaluated by means of PST. The demographic characteristics are given in Table 1. Most of the patients were hospitalized. Eighty-two percent (n = 492) remembered the time since the initial reaction, and the mean ± SD time was 20.4 ± 17.9 years. Of 45 patients (7.5%) who reported reexposure to a β-lactam drug, 18 (40.0%) developed an immunologically mediated adverse reaction, such as urticaria (6 patients), unspecified rash (6 patients), or angioedema (4 patients).

Five hundred sixty-four patients (94.6%) had documented in their medical record the drug that caused the allergic reaction. The most common drug mentioned was penicillin (409 patients), followed by amoxicillin or amoxicillin-clavulanate in 117 patients and cephalosporins in 26 patients. The most common reactions were urticaria, unspecified rash, and anaphylaxis (Table 2).

The PST result was negative in 527 patients (88.4%), positive in 49 (8.2%), and indeterminate in 20 (3.4%) (Fig 1). Patients with a positive PST result reacted more commonly to PrePen intradermal injection (Table 3). Thirty-five patients reacted to a single reagent (5 to PrePen prick, 1 to penicillin G prick, 24 to PrePen intradermal, and 5 to penicillin G intradermal). One patient (0.17%) developed urticaria immediately after administration of the intradermal PST. Of the 49 patients with a positive PST result, 4 received a cephalosporin (3 were given a third-generation cephalosporin before and after the PST result and 1 received cefazolin after PST). All the patients tolerated the cephalosporins well. The other 45 patients with a positive PST result did not have any changes in antibiotics.

Patients admitted to the intensive care unit (ICU) were less likely to be positive (3.4%) vs patients tested in the outpatient setting (16.4%) ($P < .001$). Adult patients were less likely as well to be positive to PST (6.0%) vs patients younger than 18 years (16.1%) ($P < .001$). Sixty-eight patients with a negative PST result underwent an oral (31 patients) or intravenous (37 patients) challenge with a β-lactam antibiotic as indicated by the allergist. Seven patients with indeterminate PST results underwent desensitization. The challenges and desensitizations were well tolerated, and no patient developed a reaction.

Fourteen percent of the adults and 95% of the pediatric patients were not receiving antibiotics at the time of PST. The

Table 2. History of Reactions in 496 Patients*

Reaction	Patients, No. (%)
Urticaria	201 (40.5)
Unspecified rash	190 (38.3)
Anaphylaxis	148 (29.8)
Pruritus	87 (17.5)
Angioedema of the mouth and throat	77 (15.5)
Shortness of breath	43 (8.7)
Local angioedema	26 (5.2)

* Patients could report more than 1 type of reaction.

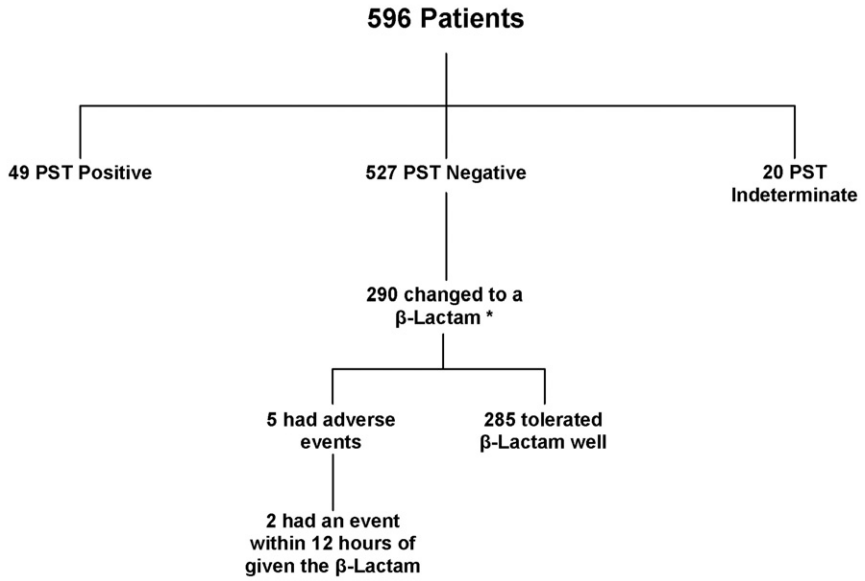

Figure 1. Flowchart of the 596 patients who underwent penicillin skin testing (PST). *This number includes 68 patients who underwent challenge and 7 who underwent desensitization.

Table 3. Penicillin Skin Test in 49 Patients With Positive Results*

Variable	Patients, No. (%)
PrePen prick	8 (16.3)
Penicillin G prick	3 (6.1)
PrePen intradermal	36 (73.5)
Penicillin G intradermal	18 (36.7)

* Patients could have been positive to 1 or 2 reagents.

most commonly used antibiotics at the time of PST were vancomycin and fluoroquinolones (Table 4), and the mean ± SD number of antibiotics used was 1.5 ± 1.3. Two hundred ninety patients (48.7% of the 596 patients who underwent PST) were changed to a β-lactam drug (Fig 1). The antibiotic drug changes in hospitalized patients were performed within 48 hours after PST. Patients evaluated in the ICU were more likely to be changed (70.3%) vs patients tested in the outpatient setting (8.6%) ($P < .001$). Patients tested in the hospital but not in the ICU were changed to a β-lactam antibiotic 57.4% of the time. Adult patients were more likely to be changed compared with patients younger than 18 years (58.6% vs 8.1%; $P < .001$). The most common antibiotic used after a negative PST result was a β-lactam antibiotic in 74.7% of the patients. The mean ± SD duration of treatment with a β-lactam antibiotic was 8.4 ± 12.6 days. Of the 290 patients given β-lactam antibiotics, 5 (1.7%) had adverse reactions: 2 had hives after 16 and 20 days of therapy, 1 had a nonspecific rash after 17 days of therapy, 1 had flushing and urticaria 3 hours after a test dose of piperacillin-tazobactam, and 1 had a pruritic rash after 12 hours of therapy. Assuming that only reactions starting within the first 24 hours could be IgE mediated, the negative predictive value of PST for IgE-mediated events was 99.3% (284/286 patients). The results of PST helped to modify the antibiotic drug coverage. Tables 5

Table 4. Antibiotic Drug Use Before Penicillin Skin Testing*

Antibiotic	Patients, %			
	Outpatient (n = 151)	Inpatient (n = 300)	ICU (n = 145)	Overall (N = 596)
None	95.3	8.3	9	30.5
Vancomycin	0.7	44.3	57.2	36.5
Fluoroquinolones	0.7	40.3	61.4	35.5
Third-generation cephalosporins	0.7	7.5	6.8	8
Clindamycin	0.7	19.3	21.4	15.2
Metronidazole	0	15.1	15.9	11.5
Gentamycin	0	11.8	19.3	10.7

Abbreviation: ICU, intensive care unit.
* Patients could have been taking multiple antibiotics.

Table 5. Antibiotics Administered Before and After Penicillin Skin Testing (PST)*

Antibiotic used before PST	Patients, No. (%)		
	No. of patients	Continued after PST	Stopped after PST
Fluoroquinolones	213	76 (35.7)	137 (64.3)
Vancomycin	219	98 (44.7)	121 (55.2)
Clindamycin	91	28 (30.8)	63 (69.2)
Metronidazole	69	32 (46.4)	37 (53.6)
Third-generation cephalosporins	48	13 (27.1)	35 (72.9)
Gentamycin	64	31 (48.4)	33 (51.6)

* Patients could have been taking multiple antibiotic agents.

Table 6. Patients in Whom Antibiotics Were Given After Penicillin Skin Testing (PST)*

Antibiotic	Patients, No.	
	Taking antibiotic before PST	Taking antibiotic after PST
Piperacillin-tazobactam	3	122
Ampicillin or ampicillin-sulbactam	0	36
Oxacillin	0	31
First- and second-generation cephalosporins	6	22
Third-generation cephalosporins	48	39
Other β-lactams†	0	27

* Patients could have been taking multiple antibiotics.
† Other β-lactams include amoxicillin and amoxicillin-clavulanate, dicloxacillin, and penicillin G.

and 6 display the reduction in the use of antibiotics such as fluoroquinolones, vancomycin, and clindamycin and the increase in the use of β-lactam antibiotics.

DISCUSSION

The most important findings from this large study are as follows: (1) the most common β-lactam antibiotics reported to cause an allergic reaction were penicillin and amoxicillin, and the most common reactions were urticaria, rash, and angioedema; (2) only 1 patient had a reaction to PST; (3) PST results were negative in 88.4% of patients, positive in 8.2%, and indeterminate in 3.4%; (4) in hospitalized patients, the most commonly used antibiotics were vancomycin in 36.5% and fluoroquinolones in 35.5%; and (5) after PST, 57.4% of inpatients were changed to β-lactam antibiotics, with a negative predictive value for an IgE-mediated event of 99.3%, and the percentage of patients in the ICU who were changed was even higher (70.3%).

The results of this study show that the strategy of using PST helps the physician modify the antibiotics used in patients with a history of "penicillin allergy." In this study, the most common antibiotics used were vancomycin in 36.5% and fluoroquinolones in 35.5%. The use of these antibiotics has been associated with the emergence of multidrug-resistant organisms and increased mortality.[3,4,11] The reduction in the use of antibiotics such as vancomycin, fluoroquinolones, and third-generation cephalosporins and the increased use of penicillin are helpful strategies in the management of antibiotic resistance.[12] After PST, 57.4% of inpatients were changed to β-lactam antibiotics, and this percentage was even higher (70.3%) in those admitted to the ICU. More than half of the patients receiving vancomycin (55%) and fluoroquinolones (65%) were changed to β-lactam antibiotics, which were well tolerated; PST had a high negative predictive value (99.3%) for identifying patients at low risk for developing an IgE-mediated reaction to β-lactams. Despite the fact that we did not use a minor determinant preparation and instead used penicillin G, only 2 patients given a β-lactam antibiotic had a reaction within 12 hours of administration of the medication. One of those patients developed immediate flushing and urticaria during an infusion of piperacillin-tazobactam. Repeated skin testing was performed to PrePen, penicillin G, ampicillin, piperacillin, and piperacillin-tazobactam. The test reaction was positive to piperacillin and piperacillin-tazobactam and negative to PrePen, ampicillin, and penicillin G. These results suggest the presence of side-chain specific IgE to β-lactams.[13] Side-chain specific IgE has been reported with other β-lactams, such as cephalosporins and amoxicillin.[14,15]

Most patients seen in the outpatient settings were not receiving antibiotic therapy at the time of PST (Table 4), were of pediatric age, and were more likely to have a positive PST reaction compared with the adult population (16.1% vs 6.0%; $P < .001$). The lack of antibiotic therapy in outpatients was probably because β-lactam antibiotic use was anticipated and PST was requested by the treating physician. In adults, the long period since the initial reaction may be an important determinant of a low positive rate because up to 80% of patients become PST negative after 10 years of having a penicillin reaction, and the skin test response is being said to decrease by 10% annually.[9,16]

Of the 49 patients with a positive PST result, 44 reacted to PrePren and 21 to penicillin G. Most patients (n = 35) reacted to only 1 reagent, the most common being PrePen intradermal (24 patients) and PrePen prick (5 patients). One of the 596 patients who underwent PST had a reaction immediately after the test (0.17%). Low rate of systemic reactions during PST has also been reported in other studies. Valyasevi and Van Dellen[17] reported a systemic reaction rate

of 0.12%, and Nadarajah et al[18] did not have any reaction in 101 patients who underwent PST.

This large study has limitations that we need to acknowledge. The first is that this is a retrospective study with all the biases that go along with this method. The second is that we did not use a preparation of minor determinants mixture because none were on the market at the time of the study. Even with that limitation, the PST performed using PrePen and penicillin G as the source for minor determinants was very safe in this population. Again, we believe that the older the patient, the less likely that he or she will react to the antibiotic associated with the initial reaction. A major limitation for implementation of this strategy is that PrePen is not currently available. Despite these limitations, the present study expands our experience[7,8] and the experience of others[18–22] that demonstrated the usefulness of PST to modify antibiotic therapy in patients allergic to penicillin. We hope that PrePen, a major tool for the evaluation of adverse drug reactions, may be available again soon.

CONCLUSIONS

Patients with a history of penicillin allergy can safely use β-lactam drugs again if indicated when negative PST results guide the physician in such therapeutic decisions. A strategy that includes PST and close communication among the physician, allergist, and infectious diseases specialist can significantly reduce the use of vancomycin and fluoroquinolones and thus has the potential to reduce the emergence of drug-resistant organisms and other complications.

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