
Clinical outcomes of penicillin skin testing

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Background: Penicillin or cephalosporin allergy is a common problem with antibiotic drug prescribing in hospitalized patients.

Objectives: To study the various clinical outcomes of penicillin skin testing (PST) in a community teaching hospital and to determine the percentage of patients who have an antibiotic drug modification after PST.

Methods: This study was a retrospective medical record review of all inpatients who underwent PST in 6.6 years. Information was collected on 101 patients using a detailed data collection form. Data were summarized using descriptive statistics, including frequencies and percentages.

Results: Of the 101 patients who underwent PST, 92 had a negative result and 5 had a positive result; in 4 patients the test result was indeterminate. There was a 96% (67/70) reduction in the use of vancomycin and a 96% (23/24) reduction in the use of fluoroquinolones after PST in patients with negative results. Forty-nine percent of patients with negative PST results were administered a penicillin-based drug, and 48% were given a cephalosporin. Cultures were positive most commonly for *Staphylococcus aureus* and enterococcus. There were no serious adverse reactions to PST or to the use of penicillins or cephalosporins after a negative PST result.

Conclusions: Penicillin skin testing lowered the use of vancomycin and fluoroquinolones and increased the use of penicillin-based drugs and cephalosporins in patients with a history of β -lactam drug allergies.

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INTRODUCTION

Ten percent to 20% of hospitalized patients have a history of penicillin allergy.¹ However, of these patients, 80% have a negative skin test result, and among these patients, 2.9% can have an acute allergic reaction if challenged,² whereas most patients with positive skin test results will react if challenged. Allergic reactions are common in patients receiving penicillin, but it is also one of the most useful antibiotic drugs, with the lowest cost and toxic effects.³ As an alternative, this group of patients commonly receives vancomycin and fluoroquinolones. Cephalosporin use may also be restricted in this patient population owing to a 2% cross-reactivity with penicillins.³ In one study,⁴ 1.7% of hospitalized patients reported a cephalosporin allergy. We studied hospitalized patients who underwent penicillin skin testing (PST) during a 6.6-year period (between January 1, 1997, and July 31, 2003) to determine whether PST resulted in an antibiotic drug change.

MATERIALS AND METHODS

This study was a retrospective medical record review of all the patients who underwent PST at a community teaching hospital (Abington Memorial Hospital) during 6.6 years. Patients were identified by looking at those whose physician had consulted an allergist. From these medical records, 101 patients who underwent PST were identified. Patients who did not undergo PST because of a high risk of reactions were

excluded from the study. The following data were collected for each patient using a detailed data collection form: age, sex, antibiotic drug allergies, type of penicillin allergy, antibiotic agent used before and after PST, diagnoses requiring PST, organism culture was positive for, PST result, any adverse reaction to PST, any adverse reaction to penicillins or cephalosporins when used after a negative PST result, and antibiotic drug allergies documented in the medical record in a subsequent hospital admission.

Penicilloyl polylysine, penicillin G sodium, and sodium benzyl penicilloate were used for PST. Penicilloyl polylysine was purchased (PrePen; Hollister-Stier, Spokane, WA), and the other 2 substances were made at Abington Memorial Hospital. The preparation of testing solutions of penicillin G sodium and sodium benzyl penicilloate are described as follows. Step 1: A 5,000,000-U vial of penicillin G sodium (Geneva Pharmaceuticals, Broomfield, CO) was added to 3 mL of sterile isotonic sodium chloride solution to make 1 million U/mL of penicillin G sodium. Three milliliters of reconstituted penicillin G sodium (1 million U/mL) was added to 0.21 mL of sterile isotonic sodium chloride solution and 1.59 mL of sodium hydroxide to make 1 million U/mL of sodium benzyl penicilloate. Step 2: A total of 4.5 mL of sterile isotonic sodium chloride solution was added to 0.5 mL of penicillin G sodium, 1 million U/mL, to produce penicillin G sodium at 100,000 U/mL concentration, and 4.5 mL of sterile isotonic sodium chloride solution was added to 0.5 mL of sodium benzyl penicilloate, 1 million U/mL, to obtain 100,000 U/mL of sodium benzyl penicilloate. The expiration date for these solutions is 1 month. Step 3: To obtain the testing concentration, 1.8 mL of sterile isotonic sodium chloride solution was added to 0.2 mL of penicillin G sodium,

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100,000 U/mL, and 1.8 mL of sterile isotonic sodium chloride solution was added to 0.2 mL of sodium benzyl penicilloate, 100,000 U/mL, to obtain penicillin G sodium, 10,000 U/mL, and sodium benzyl penicilloate, 10,000 U/mL, respectively. These solutions are discarded after use.

A skin prick test with negative findings was followed by an intradermal skin test. The wheal in a positive skin test reaction was twice that of the negative control (saline was used as the negative control and histamine as the positive control). A wheal greater than that of the control but less than twice that of the negative control or a negative histamine control was considered an indeterminate test result. The data were entered into a spreadsheet program (MS Excel; Microsoft Corp, Redmond, WA). Descriptive statistics, including frequencies and percentages, were used to summarize the data. Analysis was performed using a statistical software program (SPSS for Windows version 11.5; SPSS Inc, Chicago, IL). This study was approved by the institutional review board of Abington Memorial Hospital.

RESULTS

Overall Results

Of the 101 patients who underwent PST, 92 had a negative result and 5 had a positive result; in 4 patients, the test result was indeterminate. Approximately equal numbers of men (45.5%) and women (54.5%) were tested. There were no adverse reactions to PST. Most patients (86% [87/101]) had a history of penicillin allergy, 8% (8/101) had a history of cephalosporin allergy, and 6% (6/101) had a history of both penicillin and cephalosporin allergy. Nearly all the patients (99% [100/101]) were already taking a nonpenicillin antibiotic drug before PST. The duration of antibiotic drug treatment before PST ranged from 0 to 18 days. Rash and urticaria were the most frequently documented allergies (Table 1). Table 2 lists the antibiotics used before and after PST. Some patients received more than 1 antibiotic, either before or after PST. Endocarditis was the most common diagnosis requiring PST (Table 3). *Staphylococcus aureus* and enterococcus were the most frequently cultured pathogens (Table 4). Most patients (96% [24/25]) whose culture was positive for *S aureus* received vancomycin before PST; the other 4% (1/25) received vancomycin after PST.

Table 1. Allergic Reactions to Penicillins or Cephalosporins Documented in the History for 101 Patients

Allergic reaction	Frequency, No. (%)
Unknown	30 (28)
Rash	27 (25)
Urticaria	25 (23)
Other	15 (14)
Itching	6 (6)
Angioedema	4 (4)
Anaphylaxis	1 (1)

Table 2. Antibiotics Used Before and After Penicillin Skin Testing (PST) in 101 Patients Studied*

Antibiotic used	Patients, No. (%)	
	Before PST	After PST
Vancomycin	78 (77)	8 (8)
Fluoroquinolones	26 (26)	3 (3)
Penicillin	0	7 (7)
Semisynthetic penicillin	0	27 (27)
First-generation cephalosporins	0	32 (32)
Second-generation cephalosporins	0	0
Third-generation cephalosporins	4 (4)	13 (13)
Imipenem	0	12 (12)
Aztreonam	20 (20)	0
Aminoglycoside	20 (20)	11 (11)
Clindamycin	9 (9)	2 (2)
Others	3 (3)	1 (1)

* Some patients received more than 1 antibiotic drug. Some antibiotic drugs used (eg, metronidazole) were not reviewed.

Patients With Negative PST Results

Ninety-one percent (92/101) of the patients had negative PST results. There was a 96% (67/70) reduction in the use of vancomycin and a 96% (23/24) reduction in the use of fluoroquinolones after PST. Before PST, 4% (4/92) of patients were taking a third-generation cephalosporin. Approximately 48% of patients with negative PST results were given a cephalosporin, and 49% were given a penicillin-based drug. Table 5 gives the distribution of the types of penicillin and cephalosporin used. The outcome of patients receiving some other antibiotic drugs (eg, metronidazole) was not reviewed. There were no serious adverse reactions to the use of penicillins or cephalosporins when used after a negative PST result (1 patient reported nausea, and in another patient drug fever was considered).

Patients With Positive PST Results

All 5 patients with positive PST results received vancomycin initially, and 60% (3/5) received vancomycin after PST. A patient with *S aureus* septic arthritis was changed to clindamycin therapy after PST. The organism was sensitive to the

Table 3. Diagnoses in Patients Requiring Antibiotic Drugs and Subsequent Penicillin Skin Testing

Diagnosis	Patients, %
Endocarditis	22
Pneumonia	16
Skin infections	16
Urinary tract infection	13
Bone and joint infections	10
Other infections	8
Bacteremia	6
Localized infections	4
Intra-abdominal infections	3
Central nervous system infections	3

Table 4. Growth of Organism on Culture in 101 Patients Who Underwent Penicillin Skin Testing

Organism	Frequency, No. (%)
<i>Staphylococcus aureus</i>	25 (24)
Enterococcus	17 (16)
No growth	15 (14)
<i>Pseudomonas</i>	9 (9)
Other	8 (8)
<i>Streptococcus viridans</i>	7 (7)
Group B streptococcus	7 (7)
<i>Acinetobacter baumannii</i>	6 (6)
<i>Escherichia coli</i>	4 (4)
<i>Klebsiella</i>	3 (3)
Group G streptococcus	3 (3)
<i>Streptococcus pyogenes</i>	1 (1)

penicillins and clindamycin. In another patient, use of vancomycin was discontinued and the patient received a fluoroquinolone and an aminoglycoside for *Klebsiella pneumoniae*. In a third patient, the use of vancomycin and aminoglycosides was initially continued after PST, and a few days later treatment was changed to a fluoroquinolone after culture results revealed *Pseudomonas aeruginosa*. Of the 2 patients who continued vancomycin use after PST, 1 had streptococcal viridans endocarditis and 1 had an enterococcal urinary tract infection. The initial allergy to penicillin was not known in 1 patient; 2 patients had a rash, and 2 patients had urticaria.

Patients With Indeterminate PST Results

Of the patients with indeterminate results, 75% (3/4) were taking vancomycin before PST. After PST, 1 patient was administered vancomycin. He had group B streptococcal endocarditis that was sensitive to vancomycin and the penicillins. The second patient was successfully desensitized to imipenem. The third patient tolerated a test dose of ceftazidime, and this antibiotic therapy was continued without any serious adverse effects, and the fourth patient continued vancomycin use.

Subsequent Hospitalization and Allergist Consult Trends

Of 51 patients subsequently hospitalized, 47 had negative PST results and 4 had indeterminate results. In 68% (32/47) of the patients with negative PST results, penicillin allergy was documented in the subsequent medical record. The number of consults to an allergist for inpatient PST per year between January 1, 1997, and July 31, 2003, is illustrated in Figure 1. For 2003, data were collected for the first 7 months and extrapolated for the rest of the year.

DISCUSSION

The PST is a useful procedure for identifying patients with an IgE-mediated allergy to penicillins. In the present study, 101 patients underwent PST, and there were no adverse reactions to the test. A similar systemic reaction rate (0%) was observed by Arroliga et al.⁵ In their study, 96 patients underwent PST. In an inner-city sexually transmitted disease clinic,

Table 5. Penicillin and Cephalosporin Treatment in 92 Patients With Negative Penicillin Skin Testing Results

Penicillin Used	Patients, No. (%)
Penicillin	7 (8)
Semisynthetic penicillin	27 (29)
Imipenem	11 (12)
First-generation cephalosporins	32 (35)
Second-generation cephalosporins	0
Third-generation cephalosporins	12 (13)
Total	89 (97)

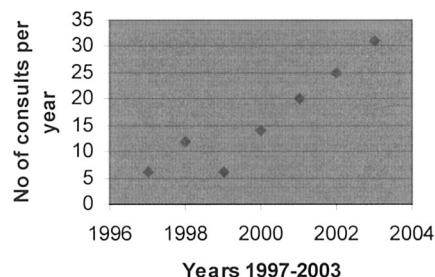


Figure 1. Trend in allergy consults for penicillin skin testing.

the systemic reaction rate was 0.26% of all patients who underwent PST (N = 5,063),⁶ and another study⁷ reported a lower systemic reaction rate to PST of 0.12% for all patients tested but a higher rate if the PST result was positive (2.3%).

The PST has been shown to modify antibiotic drug use. As part of an antibiotic control policy, Harris et al⁸ noted that 36 patients (95% of those with negative PST results) received a penicillin-based drug. We found that 97% (89/92) of our patients received a penicillin-based drug or cephalosporin after a negative PST result. Most of the allergy consults at Abington Memorial Hospital were generated by the infectious disease physicians, and they were guided by the microbiologic culture and susceptibilities. Thus, one can assume that the antibiotic drug change was due to the PST result.

Nearly 14% (14/101) of our patients had a history of cephalosporin allergy, and all except 1 had a negative PST result (1 had an indeterminate PST result). Three patients with negative PST results received a cephalosporin. There were no serious adverse reactions to the use of penicillin or cephalosporin when used after a negative PST result. In a study⁹ of 151 patients with a history of penicillin allergy and negative PST results, there were 2 reactions when cephalosporins were administered. Penicillin-allergic patients are 8 times more likely to have an allergic reaction to a cephalosporin than patients with no history of penicillin allergy.¹⁰ Penicillin skin testing can be useful in patients with a history of allergy to a cephalosporin who need a penicillin-based drug.¹⁰ However, patients with an allergy to a specific cephalosporin should not receive that same cephalosporin again because PST does not identify side chain-specific hypersensitivity. Our study population excluded patients with a serious IgE-mediated reaction to penicillin unless there was an ab-

solute clinical indication for its use. Especially, patients with a recent history of anaphylaxis did not undergo PST. Thus, our study showed a 5% positive skin test result compared with 7.1% to 18% in the literature.² Also, patients with a history of non-IgE-mediated reactions, such as Stevens-Johnson syndrome, did not undergo PST because these reactions cannot be identified by PST.

Inappropriate use of vancomycin is widespread. Its use is more frequent among penicillin- or cephalosporin-allergic patients compared with patients with no allergy (39.7% vs 17.4%).³ We found that there was a 96% (67/70) reduction in the use of vancomycin in patients with negative PST results. Li et al¹¹ showed that in orthopedic patients with penicillin or cephalosporin allergy, PST reduced prophylactic vancomycin use. In a study by Cieslak et al,¹² 31% of vancomycin prescriptions were for penicillin allergy. *Staphylococcus aureus* and enterococcus were the most frequent pathogens in our study. Ninety-two percent of all patients whose cultures were positive for *S aureus* were changed from vancomycin to another antibiotic drug after PST. Previous vancomycin use is a commonly noted risk factor for vancomycin-resistant enterococcus (VRE) emergence.^{13–15} On the contrary, in some studies,^{16,17} vancomycin had no effect on VRE emergence. In 126 intensive care unit patients, vancomycin and third-generation cephalosporins were used more frequently in patients with VRE.¹⁸ Intravenous clindamycin, fluoroquinolones, and metronidazole have also been associated with VRE prevalence.^{16,17} The presence of VRE is associated with increased cost, increased mortality, and higher recurrence after adjusting for illness severity.¹⁹

Fluoroquinolones are another class of antibiotics frequently used empirically to treat infections. We found that there was a 96% (23/24) reduction in the use of fluoroquinolones in patients with negative PST results. Fluoroquinolone (levofloxacin) use was more frequent in penicillin-allergic compared with nonallergic patients (21% vs 8%).³ Previous exposure of patients to first- and second-generation fluoroquinolones is a risk factor for quinolone resistance.²⁰

A little more than half (51/101) of our study patients had a subsequent admission to the hospital. Of these patients, 92% (47/51) had a negative PST result, and among these patients, 68% (32/47) had penicillin or cephalosporin allergy documented as present. In 2 prospective studies^{21,22} in adults, resensitization after oral penicillin use was 0% and 3%. A study²³ in children showed a higher resensitization rate of 14% (26/189). In a series of 38 patients with negative PST results there were 35 re-admissions that required an antibiotic agent.²⁴ A β -lactam antibiotic was used in 86% of re-admissions without any adverse reactions.²⁴ Resensitization after parenteral penicillin administration was higher. Parker et al²⁵ showed that resensitization after parenteral penicillin use could be up to 20% (3/15). This response is uncommon and occurs with high doses of parenteral penicillin. Documentation of the result of PST in the medical record as a diagnosis would help the clinician in choosing the right antibiotic. A repeated PST may be required before administration of fur-

ther penicillin. We, as investigators, will still retest patients with a history of anaphylaxis. At present, the information on whom and when to retest with PST is unclear.

The widespread use of fluoroquinolones, vancomycin, and third-generation cephalosporins has been associated with the generation of VRE and other multidrug-resistant bacteria. Our study showed that PST could decrease the use of vancomycin and fluoroquinolones in patients with a history of penicillin allergy. Most of the antibiotic drug change was to a penicillin-based drug or a cephalosporin. Although the use of third-generation cephalosporins and imipenem was higher in our study, these were guided by culture and sensitivity results, and the change was mostly from vancomycin or a fluoroquinolone. There has been an increase in the number of consults to an allergist per year for PST at Abington Memorial Hospital. Skin testing of appropriate patients and reconsidering penicillin therapy could result in favorable antibiotic drug modifications.

The withdrawal of PrePen from the market makes this clinical tool temporarily unavailable, but the allergy community is actively working to return this valuable reagent to clinical use. Although all studies have limitations and biases, this retrospective study shows that when allergists become involved in the clinical question of penicillin allergy there seems to be a meaningful improvement in patient care regarding the inappropriate overuse of vancomycin and fluoroquinolones.

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