

The Clinical and Financial Impact of a Pharmacist-Driven Penicillin Skin Testing Program on Antimicrobial Stewardship Practices

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Abstract

Purpose: Pharmacist-led penicillin skin testing (PST) was incorporated into antimicrobial stewardship at a community hospital to increase use of optimal antimicrobial therapy, reduce use of broad-spectrum agents, and reduce antimicrobial therapy-related costs. **Methods:** A clinical decision support software alert identified qualifying patients with penicillin allergies. Patients receiving a nonoptimal antimicrobial agent were prioritized for PST. Patients were excluded if they reported a history of extreme hypersensitivity to a penicillin agent, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or mucocutaneous eruption with epidermal detachment. Pediatric patients less than 18 years old and pregnant patients were excluded. Data collected for each patient included the medication that precipitated the reaction; reaction type; age when the reaction occurred; current antibiotic therapy; indication for therapy; preferred antimicrobial agent; days of therapy on each agent used; positive, negative, or ambiguous PST result; recent antihistamine use; and any adverse events that occurred. Outcomes of the PST results, pharmacist interventions made after PST, and resulting cost savings to patients were all reported. **Results:** Among 31 patients tested, 27 were negative for penicillin allergy, 1 was positive for penicillin allergy, and 3 yielded an indeterminate test. Pharmacist recommendation to change therapy based on PST results was accepted in 13 of 15 patients where recommendations were made. Cost savings in antimicrobial therapy alone for patients who received PST was US \$74.75 per day. **Conclusion:** Pharmacist-driven PST provided opportunities to clarify allergies, optimize antimicrobial therapy, and save antimicrobial therapy-related costs to patients.

Keywords

allergy, penicillin, pharmacist, stewardship, skin test

Introduction

Current literature estimates that 10% of patients report an allergy to penicillin.¹ Of these patients, more than 90% are likely tolerant to penicillin and cephalosporin agents.¹⁻³ In addition, IgE antibodies can decline over time, and therefore, even in patients with a history of IgE-related reactions to a penicillin agent, the patient may have a negative penicillin skin test.¹ These IgE-related reactions are typically immediate and often manifest in systemic fashion such as with anaphylaxis or urticarial rashes without blistering. Penicillin skin testing (PST) is a method of clarifying these allergies, allowing for more definitive antibiotic treatment decisions. In a recent study comparing methods of clarifying penicillin allergies, 43 patients were given skin tests, and all 43 tests were negative. Negative penicillin skin tests resulted in a significant increase in the usage of penicillin and cephalosporin agents, as 72% of these patients who received PST moved on

to receive a penicillin or cephalosporin for treatment and experienced no significant adverse effects.³

One multicenter evaluation of beta-lactam skin testing revealed that 99% of patients who received a beta-lactam after a negative skin test tolerated therapy, attesting to the safety of the results of skin testing.⁴ In addition, there is evidence that patients remain nonreactive even after repeated courses of beta-lactams.⁵

Evidence also demonstrates increased rates of infections by *Clostridium difficile*, methicillin-resistant *Staphylococcus*

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aureus (MRSA), and vancomycin-resistant *Enterococcus* (VRE) in patients with recorded penicillin allergies, as shown by a retrospective cohort study comparing patients with or without penicillin allergies on file.⁶ Differences among groups were potentially due to the propensity for penicillin allergic patients to receive fluoroquinolones, vancomycin, and clindamycin.

The use of more expensive, broad-spectrum agents in patients with reported penicillin allergies is a cost burden to patients and institutions. An 861-bed tertiary care hospital estimated an annual savings of US \$82,000 through incorporation of PST to guide antibiotic choices for 146 patients tested.⁷

This study was performed to assess the feasibility and potential benefits to be obtained by incorporating PST into antimicrobial stewardship practices in a 120-bed community hospital. The primary objective was to determine the amount of penicillin allergies clarified using PST. Secondary objectives included the number of patients whose therapy was de-escalated after a negative skin test and quantifying patient charges related to antimicrobial therapy before and after PST. Some current PST protocols exclude patients who have recent exposure to medications with antihistamine properties; however, our study did not exclude these patients to observe the effect antihistamines would have on PST, and our protocol included a positive control to assess histamine response.

Methods

The study was performed in a 120-bed community hospital. In May 2017, a protocol allowing pharmacists and pharmacy residents to provide PST was approved by the Pharmacy and Therapeutics committee. In August 2017, administrative processes were completed. These processes included the approval of a consent form for the procedure, acquisition of the supplies, and the development of an order set and procedure chart note within the electronic medical record. Pharmacists were trained by an allergist, and testing began in September 2017. The study was approved by the hospital ethics committee.

Patients were prospectively identified between September 2017 and May 2018 to receive PST based on identification via a clinical decision support software alert. This alert would flag any patients admitted as an inpatient who had a reported penicillin allergy regardless of severity who were receiving a nonoptimal antibiotic regimen. Patients who provided written informed consent and who met all qualifications received the skin test, results were documented in the electronic medical record (EMR), and allergy profiles were updated as necessary. Patients were eligible for inclusion if they were admitted to inpatient status and had a recorded penicillin allergy on profile, including rash, hives, anaphylaxis, or unknown. Patients were excluded if they had a history of extreme non-IgE hypersensitivity to penicillins, such as

Stevens-Johnson syndrome, toxic epidermal necrolysis, or mucocutaneous eruption with epidermal detachment. Pregnant patients and pediatric patients less than 18 years of age were excluded. Patient selection is summarized in Figure 1. One notable difference in this study compared with other PST protocols is the lack of exclusion for the use of antihistamines. One aim of this study was to observe the effects of antihistamines on the ability of the patients to produce a histamine response, which is required to proceed with testing.

Baseline patient data collected included recorded allergy, reaction type, and age at which the reaction was experienced. Current antimicrobial therapy and indication for use were noted. Other data included the preferred antibiotic for the indicated infection and whether recommendations to change therapy after PST were accepted. Optimal therapy was determined by adherence to empiric treatment pathways approved by the hospital's antimicrobial stewardship team. The treatment pathways were developed based on the Infectious Diseases Society of America guidelines, local susceptibility data, and taking into account patient-specific factors including, but not limited to, organ function and drug interactions. We prioritized screening for PST on patients who were receiving nonoptimal antibiotics which included meropenem, ertapenem, daptomycin, linezolid, or any other deviation from standard of care. Use of medications with antihistamine properties was recorded to assess how this affected the histamine response in these patients. Medications with antihistamine properties considered in this study included diphenhydramine, trazodone, amitriptyline, famotidine, loratadine, and ranitidine.

Skin testing was performed using a 3-step protocol. Step 1 involved a skin prick test using benzylpenicilloyl polylysine and a compounded penicillin G dilution 10 000 U/mL as the test solutions, saline as the negative control, and histamine as the positive control. A negative result was indicated by an induration of ≥ 5 mm at the histamine (ALK-Abello Pharm Inc., Horsholm, Denmark) site, with an induration of < 3 mm at the saline, benzylpenicilloyl polylysine (AllerQuest, Plainville, Connecticut, USA), and penicillin G (Pfizer, New York, USA) sites. If negative, the patient proceeded to step 2. A positive result on step 1 was indicated by an induration of ≥ 3 mm at the site of testing for benzylpenicilloyl polylysine or penicillin G, and the patient would not move on. An indeterminate test was indicated by an induration of ≥ 3 mm at the saline site or an induration of < 3 mm at the histamine site. Patients with an indeterminate test did not proceed. Step 2 involved intradermal testing using benzylpenicilloyl polylysine and penicillin G dilution, as well as saline for a negative control. A negative result was indicated by a < 3 mm difference between the saline and the antigens. If negative, the patient proceeded to step 3. A positive result was indicated by an induration ≥ 3 mm difference between the saline and either antigen, and the patient would not move on. Step 3 was a challenge dose of oral amoxicillin 250 mg or intravenous ampicillin if the patient could not tolerate oral administration. A set of

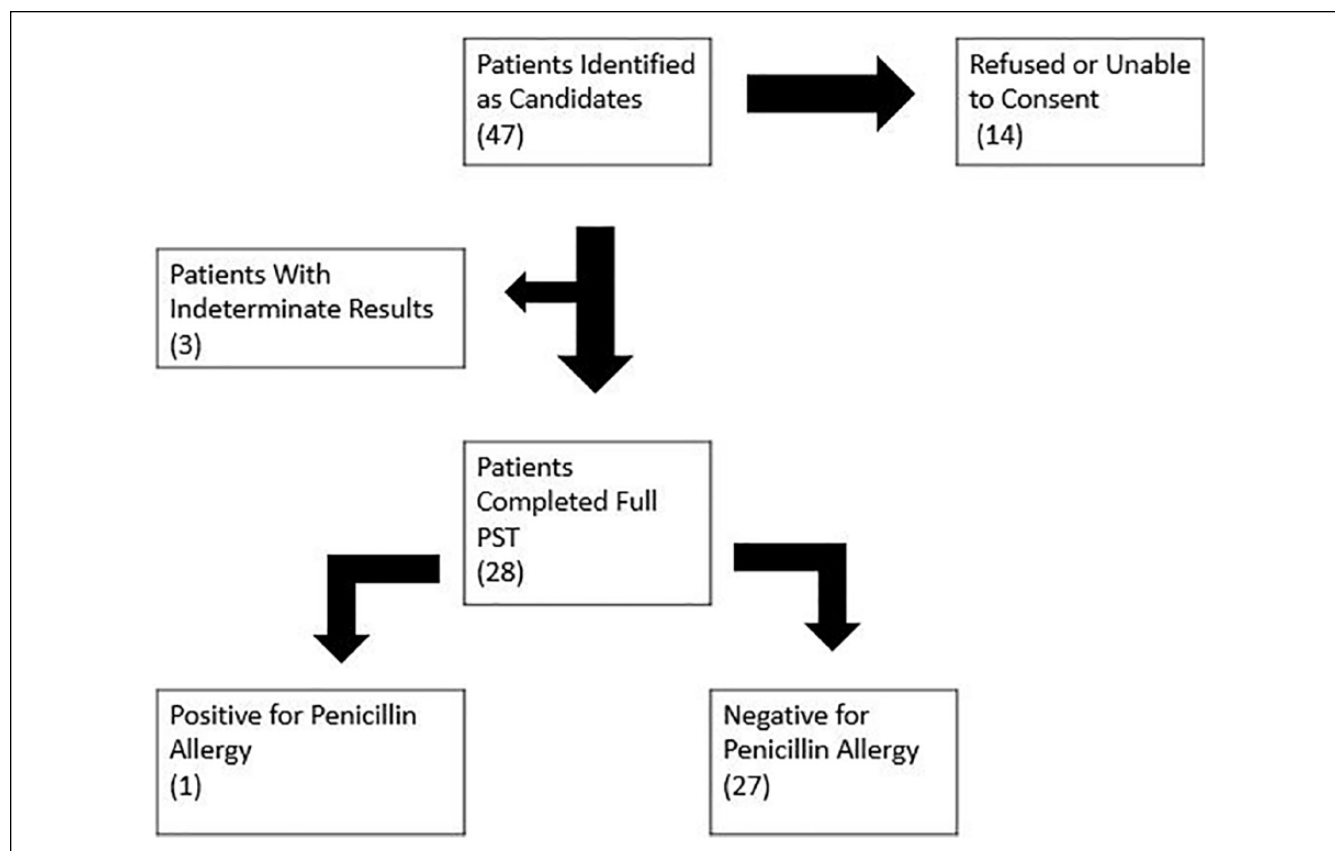


Figure 1. Study population selection.

Note. PST = penicillin skin testing.

allergic reaction medications were added to the patient profile as needed to use any time a skin test was being performed and were available in the automated dispensing cabinets located on each nursing unit. These included epinephrine, diphenhydramine, and hydrocortisone cream for local irritation.

Outcomes

The primary outcome was the number of allergies clarified after placing penicillin skin tests. This was determined by collecting the number of positive and negative tests. Adverse events were also recorded. Indeterminate skin tests were recorded to decide whether there was a clear correlation between antihistamine use and lack of histamine response.

A secondary outcome was the number of patients whose antimicrobial therapy was de-escalated upon the results of a negative penicillin skin test. This included those patients in whom de-escalation was appropriate based on the indication for therapy.

As seen in Table 2, a total of 31 patients were tested, and of these patients, 28 allergies were clarified using PST. Twenty-seven (96%) of these tests were negative, indicating no immediate penicillin allergy. In these 27 patients, allergy was removed from the patient profile. One test resulted in a

positive reaction, which was seen during the skin prick step of the test. The patient did not proceed with the test and the allergy was confirmed positive on the allergy profile. Three indeterminate tests were seen, and all 3 of these patients had taken antihistamines prior to their test. Among the patients with an indeterminate test, the average time since their last dose of antihistamines was 7 hours (1-17 hours). Average time since last antihistamine dose in the 8 patients whose test results were definitive despite antihistamine use was 18 hours (2-32 hours). Diphenhydramine was the only histamine-1 receptor antagonist on formulary.

Recommendations to alter antimicrobial therapy were made for 15 patients based on judgment by the antimicrobial stewardship team, and the providers accepted the recommendation(s) in 13 patients. The 2 patients for whom recommendations were not accepted were due to complexity of the patient case. In some cases, combination therapy was streamlined to a single agent, resulting in less antibiotics accounted for in the group of antibiotics accounted for after PST. The average time to therapy change was 1.7 days (0.75-4.33 days). This measure started at the time of empiric antibiotic initiation to the time of new therapy initiation after PST and included time involved in performing the test.

Table 1. Study Population and Antibiotic Trends.

Characteristic	No. of patients (%) (N = 31)
Allergy history	
Anaphylaxis	7 (22.6)
Rash	14 (45.1)
Hives	2 (6.5)
Unknown	8 (25.8)
Antibiotics prior to PST	No. of antibiotics (%) (N = 29 recorded antibiotics)
Cephalosporin	9 (31)
Daptomycin	1 (3.4)
Doxycycline	4 (13.8)
Ertapenem	3 (10.4)
Flouroquinolone	7 (24.1)
Meropenem	2 (6.9)
Vancomycin	3 (10.4)
Antibiotics after PST	No. of antibiotics (%) (N = 22 recorded antibiotics)
Amoxicillin with or without clavulanate	3 (13.6)
Ampicillin/Sulbactam	7 (31.9)
Cephalosporin	8 (36.4)
Doxycycline	1 (4.5)
Flouroquinolone	2 (9.1)
Piperacillin/Tazobactam	1 (4.5)
Type of antihistamine use	No. of antihistamines (%) (N = 14 recorded antihistamines)
Amitriptyline	2 (14.3)
Diphenhydramine	4 (28.6)
Famotidine	4 (28.6)
Loratadine	1 (7.1)
Ranitidine	2 (14.3)
Trazodone	1 (7.1)
Hours since last antihistamine dose	No. of patients (%) (N = 11 patients taking one or more antihistamines)
0-10	3 (27.2)
10-20	4 (36.4)
20-30	2 (18.2)
30+	1 (9.1)
Unknown	1 (9.1)

Note. PST = penicillin skin testing.

An analysis of charges was performed for those patients who completed a full skin test and were also receiving antimicrobial therapy, as seen in Table 3. The charges to a patient receiving a penicillin skin test amounted to US \$175.02, which our institution only charges for the costs of PST supplies. The charges accrued from antimicrobial therapy prior to receiving PST amounted to US \$9552.16 for 51 days of therapy. In these same patients, the charges

accrued from antimicrobial therapy after PST amounted to US \$5514.75 for 49 days of therapy. This was an average charge reduction of US \$74.75 per day of antimicrobial therapy.

Two patients developed adverse reactions after PST. This included one local reaction in the area of skin testing and one patient who reported a full body rash. These reactions are further discussed below.

Table 2. Penicillin Skin Test Results.

Outcome	No. of patients (%) (N = 31)
Skin test + Oral/IV challenge negative	27 (87.1)
Scratch test positive	1 (3.2)
Indeterminate test	3 (9.7)
De-escalation opportunity	15 (48.4)
Recommendation to de-escalate accepted	13 (41.9)

Table 3. Charges to Patients.

Antimicrobial therapy	Days of therapy	Total charges to patients	Average antimicrobial cost/day
Prior to PST	51	US \$9552.16	US \$187.30
After PST	49	US \$5514.75	US \$112.55

Note. PST = penicillin skin testing.

Discussion

In our institution, we incorporated PST into Antimicrobial Stewardship workflow to take advantage of the benefits PST may offer in the acute care setting. Many patients in acute care may benefit from clarification of penicillin allergies given literature to support better clinical outcomes when beta-lactams are used to treat various infections such as those associated with methicillin-sensitive *Staphylococcus aureus* and surgical site infections.⁸⁻¹⁰ PST is typically done by allergists; however, these services are not always available and may be limited to outpatient care. Pharmacists have the unique ability to both perform the test and make clinical recommendations based upon the results, expediting the process of clarifying allergies and optimizing therapy from a stewardship standpoint. Our study showed that PST allowed many allergies to be clarified, resulting in the ability to adjust therapy for acute conditions quickly. The results of PST were well received by physicians and provided peace of mind for both providers and patients when a penicillin agent was desired. Despite literature estimating less than 3% cross-reactivity between penicillin and cephalosporin agents,¹¹ PST was often a way of encouraging patients and providers that the use of a cephalosporin agent would also be safe in these patients with reported penicillin allergies. The PST often gave our stewardship team leverage to optimize therapy using a cephalosporin as well as a penicillin agent.

Among the patients who received PST in our study, 96% tested negative for a penicillin allergy, which is consistent with other available literature stating that 90% or greater of patients who report a penicillin allergy may actually tolerate a penicillin agent.¹ In the single patient who tested positive, the reaction was detected on the first step of the test, which involves only a skin prick. The patient was noted to have an induration where the test was placed, and did experience minimal urticaria at the site, which dissipated with a single dose of diphenhydramine. This supports PST as a safe way of clarifying

allergies without using graded challenges or desensitization, which have the propensity to cause systemic reactions. This element of safety was ideal for our institution, as about one-third of the patients tested were unable to give a reliable allergy history. Without this history, providers were unable to determine the safety of giving a graded challenge or proceeding to desensitization without PST. Of the allergy histories able to be confirmed, it was notable that all 7 patients who reported a history of anaphylaxis tested negative for a penicillin allergy.

Upon allergy clarification, the penicillin allergy was completely removed from the patient profile, and a progress note was added to the patient encounter describing the test results. For one patient, this resulted in the readdition of the allergy upon readmission when older skilled nursing facility records were reviewed to update the medication and allergy list. Future programs that adopt PST may consider alternative ways to note the change in allergy status, such as inserting a placeholder allergy describing the test results.

Our protocol was unique for the lack of exclusion for recent history of antihistamine use. As shown in Table 1, all patients who had been administered medications with antihistamine properties had received it within the 48 hours preceding PST. Given the use of histamine as a positive control in the scratch test, we were able to identify patients in whom the antihistamine was taking effect and forgo testing if no histamine response was observed. In 8 (73%) of the 11 patients who had received such a medication, the histamine response was demonstrated, and we were able to proceed with testing. On average, the indeterminate results were seen in patients who had received an antihistamine more recently than those who did produce a histamine response. Two of the patients had received the antihistamine within 2 hours preceding the skin test. The third had received the last dose 17 hours prior to the test, but was noted to be on 2 antihistamines chronically. However, a very large range in time from last administration was seen in both groups, ranging from 1 to 32 hours, showing an element of

patient-specific response. More studies examining this phenomenon would be needed to make a determination regarding the time frame in which an antihistamine would affect a patient's histamine response specifically relating to PST. For the purposes of our antimicrobial stewardship efforts, our institution will continue to rely on the accuracy of the histamine as positive control in the skin prick test, rather than exclude all patients who have recent antihistamine administration.

Two delayed reactions were noted even after PST. One patient who tested negative and proceeded to receive ampicillin/sulbactam developed a large induration in the area where intradermal testing was performed 3 days after PST. The patient noted urticaria in the area for approximately 24 hours; however, the urticaria and induration dissipated within another 24 hours after initial development. The patient experienced no systemic signs of allergic reaction; therefore, ampicillin/sulbactam was continued, and the patient had no other reactions.

Another patient who tested negative and proceeded to receive ampicillin/sulbactam without reaction as an inpatient received amoxicillin/clavulanate upon discharge. The patient reported a full body rash and presented to urgent care after discharge. It was noted that the patient had been receiving diphenhydramine after the test was complete for a nonrelated indication, but the patient did display histamine response during PST. Delayed maculopapular rash during ampicillin treatment is described elsewhere, with no initial reaction upon administration.¹² The cause of the rash could not be fully determined, as the patient had started multiple new medications upon discharge.

One limitation of this study is the small sample size of patients. This was in part due to the small size of the study facility. In addition, although 47 patients were initially identified as candidates, 14 patients declined to give consent for testing. Many patients declined due to fears of experiencing an allergic reaction during the procedure. Due to this small sample size, it is difficult to make a general conclusion regarding the effect of antihistamines on testing.

Another limitation of this study was the lack of guideline to determine necessity of skin testing based upon patient allergy history. All patients were included as eligible for skin testing with the exception being a history of Stevens-Johnson syndrome, toxic epidermal necrolysis, or mucocutaneous eruption with epidermal detachment. To create a more efficient workflow, it may be reasonable for PST services to incorporate an algorithm to determine whether patients require testing or whether it is safe to give a test dose based on reaction history.

Conclusion

Pharmacist-driven PST in an inpatient setting resulted in clarified allergies in 90% of patients tested, opportunities to de-escalate or optimize antimicrobial therapy at the point of care, and cost savings of US \$74.75/antimicrobial day of

therapy. PST will continue to be performed when appropriate at our institution as a valuable antimicrobial stewardship intervention.

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