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Penicillin skin testing in hospitalized patients with β -lactam allergies Effect on antibiotic selection and cost

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ABSTRACT

Background: A history of a penicillin allergy generally leads to the use of broad-spectrum antibiotics that may increase complications and cost.

Objective: To determine the cost-effectiveness of performing penicillin skin testing (PST).

Methods: A retrospective analysis was conducted on adult inpatients with a β -lactam allergy who underwent PST and oral challenge performed by an allergist. The primary outcome was overall antibiotic cost savings for patients switched to a β -lactam antibiotic (BLA). Secondary outcomes included subsequent admissions that required antibiotics and total number of days a BLA was prescribed.

Results: Fifty patients had PST performed (mean age, 62 years). The most common β -lactam allergy reported was penicillin (92%). Cutaneous reactions were reported in 54% of patients, and 56% had a reaction more than 20 years ago. Fifty percent of patients had aztreonam prescribed before PST. The results of PST were negative in all patients, and 1 patient had anaphylactic symptoms during the oral amoxicillin challenge (98% skin test or oral challenge negative). Thirty-seven patients (75.5%) were changed to a BLA. Overall cost savings were \$11,005 (\$297 per patient switched to a BLA). There were 31 subsequent admissions that required antibiotics for patients who tested negative on skin test and oral challenge. A BLA was prescribed in 22 of 31 readmissions, totaling 147 days of BLA therapy.

Conclusion: After the implementation of a PST protocol, we observed a decrease in non-BLA use in patients with previously documented β -lactam allergy. PST is a safe and cost-effective procedure to serve as a negative predictor test for penicillin hypersensitivity mediated by IgE.

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Introduction

Penicillin allergies are the most common drug allergies reported in the United States. Recent publications evaluating both inpatient and outpatient populations have revealed an incidence of penicillin allergies between 9% and 12%.^{1–3} Most patients with penicillin allergies cannot describe the nature of their reaction and receive more broad-spectrum and/or costly antibiotics.^{1,2,4,5} A recent large retrospective cohort study comparing patients with and without a penicillin allergy found a significantly higher use of fluoroquinolones, clindamycin, and vancomycin in patients with penicillin allergies.¹ Consequently, patients with penicillin allergy also

had higher rates of developing *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus* infections compared with patients with no history of penicillin allergy.^{1,6} In addition to the development of infections with multidrug resistant organisms, the use of alternative antibiotics is also associated with a higher acquisition cost compared with standard of care regimens that contain a β -lactam antibiotic (BLA).²

At our institution, the pharmacy department performed a cost analysis in 2012 for 2 hospitals within our health system, focusing specifically on higher-cost agents (aztreonam and tigecycline) in patients who had a documented β -lactam allergy. During a 6-month period, 122 patients were identified, and a potential cost difference of more than \$60,000 was identified when an aztreonam- or tigecycline-based regimen was used rather than when a β -lactam-based regimen was used, which was considered standard of care at our institution (Nikunj Vyas, PharmD, unpublished data, 2013).

With these financial implications, the pharmacy department, a hospital-affiliated allergist, and the internal medicine department

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developed a penicillin skin testing (PST) protocol that was piloted within 1 of the hospitals in our health system. The purpose of this study was to describe the effect of allergy consultation and PST on inpatient cost of antibiotic therapy in patients with a documented β -lactam allergy who underwent PST.

Methods

Hospitalized patients with a β -lactam allergy who were receiving high-cost, broad-spectrum agents (HCBSAs) were screened daily by a clinical pharmacist at 500-bed community-teaching medical center. HCBSAs included aztreonam, tigecycline, daptomycin, and linezolid. All HCBSAs except aztreonam are restricted to infectious diseases physicians. These patients were identified for eligibility for allergy consultation based on whether a BLA would be appropriate for the treatment of their current infection. Although aztreonam is a monobactam antibiotic, it was not grouped into the category of BLAs for the purpose of this study. The attending and infectious diseases physician (if consulted) were then contacted to discuss allergy consultation and possibly PST. Additional requests from physicians for PST were made for β -lactam allergic patients receiving other non-BLAs (ie, fluoroquinolones, vancomycin).

PST Process

A thorough allergy history was performed by a hospital-affiliated allergist before PST. PST was performed on medical/surgical floors and consisted of a 3-step process (Fig 1). Skin prick and

intradermal testing consisted of benzylpenicilloyl polylysine (Pre-Pen [ALK, Round Rock, Texas], major determinant), penicillin G (10,000 U/mL, minor determinant), histamine base (Histatrol [ALK, Round Rock, Texas], positive control), and normal saline (negative control). If the patient had negative results on skin prick and intradermal tests, an oral amoxicillin graded challenge up to 250 mg was administered.^{7,8} Written informed consent for PST was obtained for patients who underwent testing.

PST Pilot Evaluation

This was a retrospective analysis of all adult inpatients with a β -lactam allergy who had PST performed between October 2013 and September 2014. The primary outcome was overall cost savings, which was defined as total cost of therapy for patients switched to a BLA minus total cost of therapy if initial non-BLA before PST were continued plus cost of skin testing materials for all patients tested. Daily cost of antibiotic therapy was calculated using the defined daily dose for each antibiotic prescribed based on actual acquisition cost during the period of the analysis. Defined daily dose was obtained from the World Health Organization.⁹ Secondary outcomes included number of subsequent admissions that required antibiotics and total number of antibiotic days during subsequent admissions with receipt of a BLA. Subsequent admissions were evaluated in February 2015, between 5 and 16 months after the initial admission when PST was performed. Additional data collected included baseline demographics, β -lactam allergy history, infection sources, and antibiotic data before and after PST.

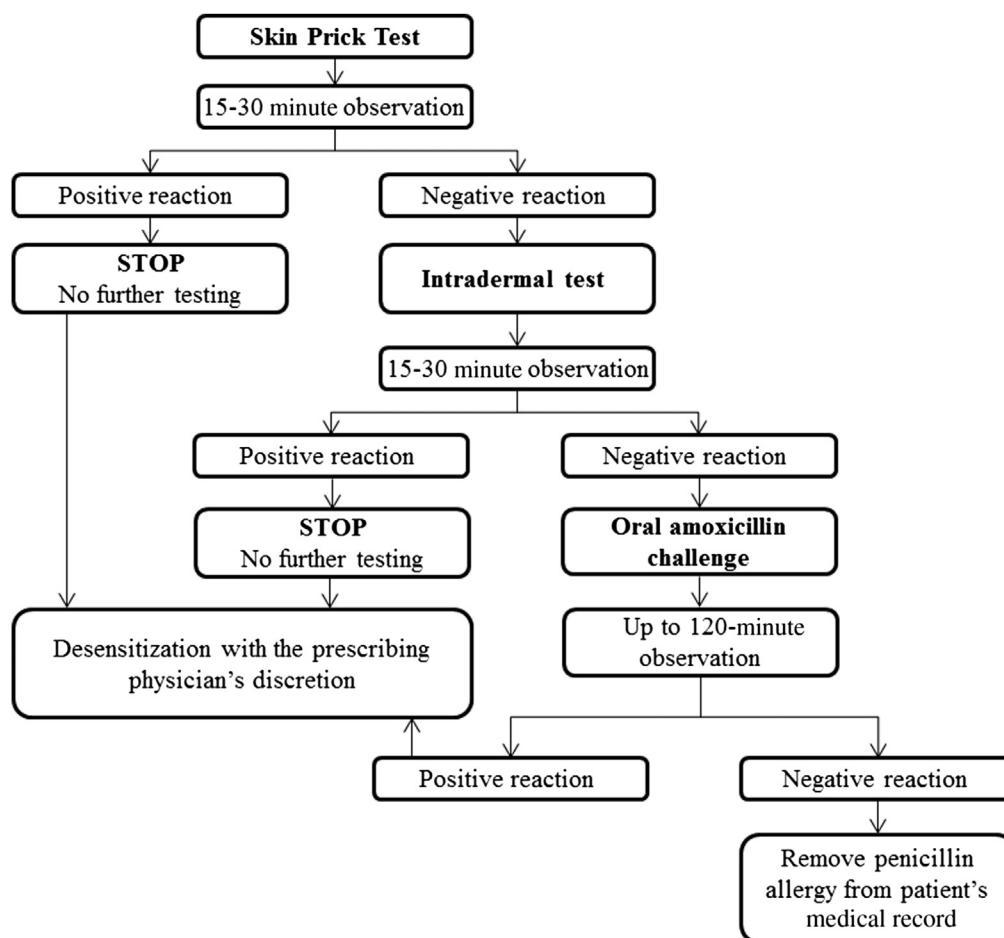


Figure 1. Penicillin skin testing protocol.

Descriptive statistics were used to portray the data collected. Approval to perform this study was obtained through the Atlantic Health System Institutional Review Board.

Results

There were 50 patients who had PST performed. Baseline characteristics are given in Table 1. The mean age of patients undergoing PST was 62 years. Penicillin was the most commonly reported β -lactam allergy (92%), and more than 50% of patients had a reaction to a β -lactam more than 20 years ago. The reaction type was reported as a rash in 34% of patients, and 28% could not recall their allergic reaction.

Most patients (96%) were being followed up by an infectious diseases physician, and all patients were receiving antibiotics at the time of PST (Table 2). Fifty percent of patients received aztreonam as either monotherapy or in combination. Seventeen patients (34%) received 2 or more antibiotics. The most common indication for antibiotic treatment was urinary tract infection, followed by intra-abdominal and skin or soft tissue infections (Fig 2). The median time from initiation of antibiotics to PST was 3 (range, 1–12) days.

Of the 50 patients tested, all had a negative results on skin prick and intradermal tests. Forty-nine patients had a negative graded oral amoxicillin challenge, and 1 patient experienced anaphylactic symptoms. The patient's penicillin allergy history was more than 20 years ago, and the reaction noted was hives. This patient did not experience any reaction to the 0.01- or 0.1-mg amoxicillin dose, but at 1 mg the patient expressed metallic taste in mouth and throat tightening but no shortness of breath or wheezing. The patient was administered 0.3 mg of epinephrine intramuscularly and 50 mg of diphenhydramine orally, and symptoms resolved.

Thirty-seven patients (75.5%) who had negative skin test and oral challenge results were changed to a BLA. For patients switched to a BLA, total cost of antibiotic therapy after PST was \$4,840. Total cost of antibiotic therapy if initial therapy before PST were continued was \$20,623. Approximate cost for PST materials for 50 patients was \$4,778. Overall cost savings was \$11,005. The most common β -lactam prescribed after PST was cefepime (Table 3).

Subsequent admissions within a year of PST occurred in 23 of the 49 patients with negative skin test and oral challenge results. Fourteen patients had 1 admission and 9 patients had 2 or more admissions (range, 2–4 admissions), accounting for a total of 38 admissions. Of those admissions, 31 patients required antibiotic

Table 2

Antibiotics at the Time of Penicillin Skin Testing

Antibiotic	No. of antibiotics
Aztreonam	25
Vancomycin	17
Fluoroquinolones	11
Metronidazole	4
Carbapenems	3
Daptomycin	2
Linezolid	2
Azithromycin	2
Tigecycline	1
Clindamycin	1
Aminoglycosides	1

therapy. A β -lactam was prescribed in 22 of those 31 admissions requiring antibiotic therapy, accounting for 147 days of therapy.

Discussion

PST is a generally safe and reliable procedure to help rule out IgE-mediated penicillin allergy.^{7,10–14} This is the first inpatient PST pilot program to demonstrate actual cost savings with the use of allergy consultation with PST in hospitalized patients. Previous analyses have reported the effect of a PST program increasing the appropriateness of antibiotic therapy but were unable to find significant reduction in costs.¹⁴ Forrest et al¹⁴ primarily skin tested patients receiving vancomycin in efforts to narrow therapy to penicillin-based therapy, which at the time was considerably less expensive. The investigators calculated mean daily costs of antibiotics alone to be \$37 before and \$30 after PST implementation. When accounting for the cost of skin testing, the mean daily cost was similar at \$40 before PST and \$38 after PST. A potential reason for the similar cost before and after PST implementation is that patients were included in the cost analysis if they did not have PST performed and continued to take vancomycin, which may have inflated the cost for the post-PST analysis.

Given the introduction of several high-cost antibiotics used for penicillin allergic patients since previous analyses, we observed a

Table 1
Baseline Characteristics^a

Characteristic	Finding (N = 50)
Age, mean (SD), y	62 (17)
Male sex	23 (46)
Antibiotic allergy	
Penicillin	46 (92)
Amoxicillin with or without clavulanate	2 (4)
Piperacillin-tazobactam	1 (2)
Cephalexin	1 (2)
Timing of allergy	
<1 year	0
1–5 years	6 (12)
5–10 years	6 (12)
10–20 years	3 (6)
>20 years	27 (54)
Unknown	8 (16)
Reaction type	
Rash	17 (34)
Hives	9 (18)
Anaphylaxis	7 (14)
Other	3 (6)
Unknown	14 (28)

^aData are presented as number (percentage) of patients unless otherwise indicated.

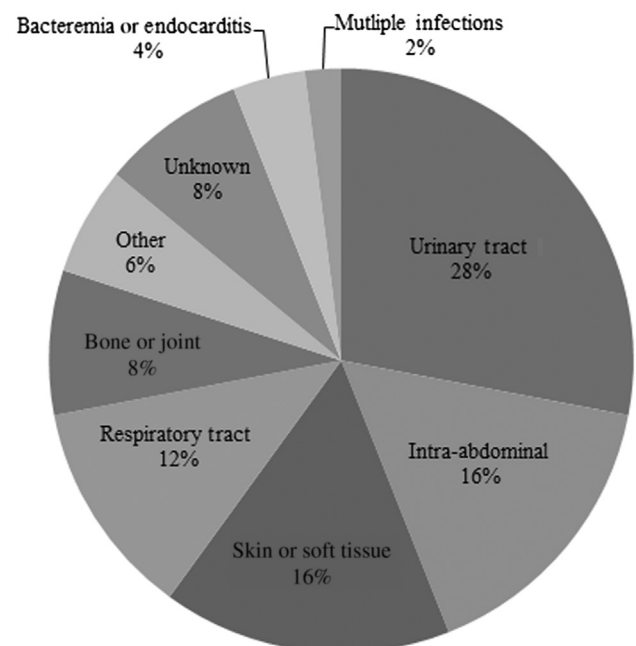


Figure 2. Infection sources.

Table 3
 β -Lactams Prescribed After Penicillin Skin Testing

Antibiotic	No. of antibiotics
Cefepime	13
Cefazolin	8
Ceftriaxone	5
Aminopenicillin with or without β -lactamase inhibitor	4
Piperacillin-tazobactam	3
Carbapenem	3
Cefuroxime	2
Oxacillin	1

substantial decrease in overall cost in patients with PST performed and switched to a BLA. Although 24.5% of patients were not switched to a BLA, we were still able to observe an overall cost savings, including the cost of skin testing material used to test these patients. For patients who were switched to a BLA, our calculated mean daily cost of antibiotics alone before PST was \$116 per day compared with \$27 after PST. Our overall cost savings were \$297 per patient for treatment after PST, which included the cost of PST supplies (approximately \$96 per test). A recent analysis in Canada evaluating antibiotic selection in patients with a history of penicillin allergy admitted to a tertiary medical center found similar cost differences as our study. No skin testing was performed in this study, but the authors calculated an additional cost of \$326 per patient for patients prescribed a non-BLA compared to if they had received a standard-of-care regimen with a β -lactam.²

Additional potential cost savings were observed and will continue to be observed if patients are hospitalized again. We evaluated antibiotic use during subsequent admissions between 5 and 16 months after the hospitalization when PST was performed in the 49 patients who tested negative on skin tests and oral challenges. Using the mean cost of antibiotics before and after PST, this would provide an additional cost savings of \$13,096. Although antibiotic therapy prescribed on discharge was not evaluated, there may have been additional cost savings for patients sent home with intravenous or oral antibiotics.

Of the 50 patients tested, only 1 patient had a positive reaction to skin testing or oral amoxicillin challenge. Our 2% rate of positive PST results is consistent with a recent evaluation of 500 patients who underwent similar skin testing with oral amoxicillin challenge that found a 1.6% positive rate.⁷ A history of β -lactam allergies are present in more than 15% of all patients admitted to our institution (Nikunj Vyas, PharmD, unpublished data, 2013), and thus decisions regarding empiric- and pathogen-directed antimicrobial therapy are often confounded by these purported reactions. PST is a safe method to ensure that the patient has no greater likelihood of having an IgE-mediated reaction and allows for more treatment options during acute illnesses.

During our pilot study, we found that only 75.5% of patients were switched to a BLA. Some explanations for continuing or switching to a non-BLA included organisms not susceptible to β -lactams, antibiotic treatment discontinued because infection was ruled out, need for oral agents with high bioavailability (ie, fluoroquinolones vs β -lactams), and prescriber preference. Similar reasons were found for not prescribing a β -lactam in subsequent admissions.

Cost savings demonstrated in this pilot program were purely based on the savings in the ability to use BLAs compared with more costly alternative agents. However, there are several unintended consequences of the use of non- β -lactam antibiotics in patients with β -lactam allergies that may be even more important in the care of acutely ill patients. First, patients with penicillin allergies have higher rates of infections because of multidrug-resistant organisms most likely attributable to the higher use of

fluoroquinolones, clindamycin, and vancomycin.^{1,6} Although we evaluated a smaller number of patients receiving fluoroquinolones compared with previous studies because our pilot study was designed to primarily target patients receiving HCBSAs, fluoroquinolones were still the third most common antibiotic prescribed. Second, hospitalized patients with an antibiotic allergy have been found to have higher lengths of stay, intensive care unit admissions, receipt of more than 1 antibiotic, and mortality compared with patients without any antibiotic allergies.^{1,15} Third, β -lactams have been able to retain their spectrum of activity and are first-line empiric agents of choice for most bacterial infections, whereas β -lactam alternatives, such as fluoroquinolones and aztreonam, have rapidly developed resistance in the last several years. For example, our institution's inpatient *Pseudomonas aeruginosa* antibiogram derived susceptibilities for aztreonam and ciprofloxacin are 74%, whereas the combination of piperacillin and tazobactam remains 96% susceptible. In addition, alternative agents (ie, vancomycin) have been found to be inferior to β -lactams and are not recommended as first-line therapy for treatment of several gram-positive infections,^{16–19} further driving the importance of ruling out penicillin allergies through PST.

Three patients who had PST performed were receiving a carbapenem because of a penicillin allergy history. Although carbapenems are still considered β -lactams, the cross-reactivity between penicillins and carbapenems has been found to be less than 1% in several recent evaluations.^{20–22} Depending on the severity of a patient's penicillin allergy history, these agents are occasionally used as an alternative to penicillins or cephalosporins. Once PST was performed, 2 of the 3 patients receiving carbapenems were narrowed to a penicillin or cephalosporin. This finding further underscores the importance of ruling out β -lactam hypersensitivity to help prevent further carbapenem resistance.

The choice to use minor skin determinants, including penicilloate, penilloate, and amoxicillin, has been recently debated.²³ The use of minor skin determinants has been previously found to identify 10% to 15% more persons with positive results compared with benzylpenicilloyl polylysine and penicillin G alone, but the clinical significance of these additional patients is still unknown.^{10,23,24} In addition, the lack of commercially available products for these minor skin determinants has precluded physicians from using PST to rule out IgE-mediated penicillin allergies. For our study, we did not use additional minor skin determinants because of the lack of commercially available products and based on the most recent recommendations stating that the use of benzylpenicilloyl polylysine and penicillin G alone provides an adequate negative predictive value for PST.¹⁰ In regard to the value of performing an oral challenge to further rule out penicillin allergy, recent literature suggests a positivity rate between 0.8% and 2.5% in patients with a negative skin test result to benzylpenicilloyl polylysine and penicillin G.^{7,25} In our study, we identified 1 patient (2%) who had a negative skin test result who experience an anaphylactic reaction to the oral amoxicillin graded challenge.

Implementation and evaluation of our PST program presented some limitations and challenges. Our initial internal cost saving estimates before implementing PST revealed a mean potential savings of almost \$492 per patient, but we were only able to find an actual savings of \$297 per patient. There are 2 possible explanations for the lower actual cost savings. First, many patients were unable to undergo skin testing the day alternative antibiotics were initiated, as we observed that the median time to PST was 3 days. Second, our initial cost analysis included only patients who were receiving HCBSAs, and during the study pilot, several patients received less costly antibiotics before PST. Future strategies to fully optimize antibiotic management in hospitalized patients should include prophylactic PST in the outpatient setting for patients with suspected β -lactam allergies.

Our institution has a hospital-affiliated allergist who was able to perform PST in an inpatient setting, which may limit the generalizability of our study. Although some institutions may not have allergists on staff with privileges, there are reports of institutions that have safely and effectively implemented PST programs using other trained health care professionals, which may be an option in more resource-limited settings.²⁶ In addition, long-term follow-up for signs of non-IgE-mediated reactions, such as delayed T-cell-mediated reactions, were not monitored. We also evaluated a small cohort of patients with a focus on higher-cost agents, and the antibiotic cost savings observed in our study may not be generalizable to all institutions if these agents are not commonly used. Alternatively, cost savings with PST performed in institutions that use less expensive agents (ie, fluoroquinolones vs aztreonam) may be seen with the prevention of collateral damage associated with these agents. Lastly, because we did not have a comparator group of patients with β -lactam allergies who did not have PST performed, our study was unable to confirm a reduced length of stay and complications previously described with the use of β -lactam regimens after PST. Because most patients in the PST program received non-BLAs before PST, effects during the index hospitalization are likely to be confounded; however, it is possible that morbidity during future hospital admissions may be prevented. Future studies assessing the full effect of PST and patient outcomes for longer periods is required.

In conclusion, an inpatient PST program resulted in significant short-term cost savings. Furthermore, several observational analyses have found improved outcomes in those patients without documented allergies to β -lactams. Further analysis of the effect of PST programs is warranted to determine the full potential effect of testing larger populations for penicillin allergies.

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