

Feasibility, Benefits, and Limitations of a Penicillin Allergy Skin Testing Service

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Abstract

Objective: To critically examine the feasibility, benefits, and limitations of an inpatient penicillin skin testing service and how pharmacists can be utilized. **Data Sources:** A PubMed search was performed from July 2016 through September 2016 using the following search terms: penicillin skin testing, penicillin allergy, β -lactam allergy. Additional references were identified from a review of literature citations. **Study Selection and Data Extraction:** All English-language studies assessing the use of penicillin skin testing as well as management and clinical outcomes of patients with a β -lactam allergy were evaluated. **Data Synthesis:** The prevalence of people self-identifying as penicillin allergic ranges from 10% to 20% in the United States. Being improperly labeled as penicillin allergic is associated with higher health care costs, worse clinical outcomes, and an increased prevalence of multidrug-resistant infections. Penicillin skin testing can be a tool used to clarify penicillin allergies and has been demonstrated to be a successful addition to antimicrobial stewardship programs in multiple health care settings. Prior to implementing a penicillin skin testing service, institutions will need to perform a feasibility analysis of who will supply labor and accept the financial burden as well as identify if the positive benefits of a penicillin skin testing service overcome the limitations of this diagnostic test. **Conclusion:** We conclude that institutions with high percentages of patients receiving non- β -lactams because of penicillin allergy labels would likely benefit the most from a penicillin skin testing service.

Keywords

β -lactams, penicillins, allergy, infectious diseases, anaphylaxis

Introduction

Patients commonly report an allergy to penicillin that is subsequently entered into their medical records, effectively labeling them as penicillin allergic. These presumed allergies can range from predictable adverse reactions of a medication, such as gastrointestinal upset, to true immunoglobulin E (IgE)-mediated allergies with anaphylactic symptoms. Because of the generous definition of allergy, the prevalence of people self-identifying as penicillin allergic ranges from 10% to 20% in the United States.^{1,2} A recent study, including nearly 12 000 patients, found that 11.5% of patients were labeled as penicillin allergic.³ The most commonly reported reactions were rash (37%), hives (19%), swelling/angioedema (12%), and anaphylaxis (7%), leaving more than 20% of patients neither being able to recall symptoms nor having documentation of the details of their reaction. Within cohorts of patients labeled as penicillin allergic, the true rate of a type I allergy in which patients are penicillin skin test positive is less than 10%, or approximately 1% of the US population.⁴

Being improperly labeled as penicillin allergic has potential for negative consequences. In a cohort of patients labeled as β -lactam allergic, Jeffres et al⁵ compared rates of clinical

failure between patients treated with β -lactam and non- β -lactam antibiotics. The non- β -lactam group in this study included aztreonam, an antibiotic generally regarded as a safe alternative when Gram-negative coverage is required in patients with a β -lactam allergy. The reason for its inclusion in the non- β -lactam group was based on known reduction in susceptibilities to Gram-negative organisms as compared with other β -lactams. The results found that patients were more likely to experience treatment failure when exclusively treated with a non- β -lactam, and no difference in hypersensitivity reactions was observed between the 2 groups. Macy and Contreras⁶ performed a matched cohort study of more than 100 000 patients. They discovered that patients labeled as penicillin allergic had higher rates of *Clostridium difficile*,

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methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus* species infections as well as longer lengths of stay compared with those without a penicillin allergy label.

Unnecessary avoidance of β -lactam antibiotics has also been shown to increase health care costs for the patient and health care system. A study by Picard et al⁷ found that patients identified as having a penicillin allergy carried an additional cost of more than \$15 000 over a 1-year period because of the use of alternative non- β -lactam antibiotics. As evidenced by Li et al,⁸ non- β -lactam costs can be 1.82- to 2.58-fold higher compared with first-line antibiotics when used as alternative agents in patients with a penicillin allergy.

Because of the poor clinical outcomes and increased costs associated with being labeled as penicillin allergic, optimizing antibiotic prescribing for these patients has become a priority for antibiotic stewardship programs. Multiple strategies have been implemented in an effort to improve antibiotic use in this population. Strategies range from relatively simple interventions of increasing the rigor of allergy claims made by patients and more accurate documentation of allergic reactions within the medical record, to more extensive interventions, including automatic consultation by an allergist.⁹ An intervention receiving significant attention recently is penicillin skin testing. The resurgence of this diagnostic tool is likely a result of the reintroduction of a commercially available penicillin skin testing kit, benzylpenicilloyl polylysine injection (PRE-PEN), in 2009.

The addition of penicillin skin testing has been a successful addition to antibiotic stewardship programs in multiple settings as described by Unger et al¹⁰ in a recent review. The authors describe how to perform penicillin skin testing, associated costs, results from penicillin skin testing studies, the pharmacist's role, antimicrobial stewardship implications, potential barriers, and misconceptions. The objective of this article is to critically examine the feasibility, benefits, and limitations of an inpatient penicillin skin testing service. The benefits of pharmacy involvement in a penicillin skin testing service are also described.

Data Sources

A comprehensive literature search was performed from July 2016 through September 2016 using PubMed and the following terms: penicillin skin testing, penicillin allergy, β -lactam allergy. Additional references were identified from a review of literature citations. All English-language original research studies and review articles assessing the use of penicillin skin testing as well as management and clinical outcomes of patients with a β -lactam allergy were evaluated. Guidelines in the areas of allergy and antimicrobial stewardship were also identified for inclusion.

Feasibility of Penicillin Skin Testing

A penicillin skin test is simple to administer and the entire process takes less than 1 hour to complete.¹⁰ It begins with obtaining an allergy history followed by 2 sets of skin tests. The first is a skin prick test using the major and minor determinants of penicillin, when available, along with a negative control of saline and a positive control of histamine, all placed on the forearm. If no wheal and flare response is noted, the test is performed using the same concentrations but through an intradermal injection into the forearm. If no reaction occurs again, this is considered to be a negative test. The final assessment is documented in the chart and a recommendation is given to use penicillin or to avoid. The penicillin skin test is highly reliable because it has a negative predictive value (NPV) of greater than 95%.¹¹ An oral or intravenous (for those who cannot take oral medications) challenge of penicillin, typically consisting of 1 or 2 doses, can be given to the patient in the same controlled environment for an added level of safety and assurance after a negative skin test result, which increases the NPV to greater than 99%.¹² The risk of an individual experiencing an allergic reaction to penicillin who has had a negative skin test is no more than that in the general population.¹

The safety of penicillin skin testing has been studied and established in a multitude of patient populations and practice settings. Arroliga et al¹³ described penicillin skin testing in patients with a β -lactam allergy in the intensive care unit in which there was 1 positive skin test out of 96 patients and no reports of an adverse reaction. Penicillin skin testing has also been routinely performed in children of all ages as well as in pregnant women without negative effects.^{14,15} When trained professionals perform the penicillin skin testing with proper technique, the incidence of adverse reactions is rare. Out of 1710 patients administered penicillin skin testing, 2 (0.1%) had systemic reactions.¹⁶ An additional safety concern with penicillin skin testing is the risk of resensitization. A study by Solensky et al¹⁷ demonstrated that the resensitization rate was 0% after 46 patients who were skin test negative received 3 courses of penicillin. Penicillin skin testing was performed prior to each of these courses and at the end of therapy. All tests remained negative, suggesting that repeated skin testing is not necessary.

Currently, the vast majority of antibiotic allergy testing, including penicillin skin testing, is completed by allergy and/or immunology consult services.^{18,19} Collaboration between allergy and pharmacy at one institution has resulted in the development of a penicillin skin testing practice guideline for patients with a β -lactam allergy in need of an intravenous penicillin antibiotic for at least 7 days.²⁰ Guideline implementation resulted in an increase in the appropriateness of ordering skin testing from 17% to 64% and no increase in cost per patient. Of 58 patients with a negative skin test, 54 (93%) had their antibiotics changed.

Park et al²¹ also described how community pharmacists and allergists could collaborate to ensure that patients with a β -lactam allergy received education regarding their allergy and a referral to the allergy clinic to have penicillin skin testing performed, if indicated. More than 500 patients with β -lactam allergies were identified by pharmacists at an outpatient pharmacy located within the hospital. Although only 71 of 503 patients referred by pharmacy were evaluated by an allergist, these patients had a significantly higher percentage of subsequent β -lactam use than the patients who were not evaluated. The intervention was successful in reducing the overall number of non- β -lactam prescriptions.

When allergy or immunology consult services are not available, skin testing can be administered by other health professionals, including pharmacists, with sufficient training by allergists. Wall et al²² published their experience with a pharmacy-led skin-testing initiative at Iowa Methodist Medical Center. Pharmacists were trained by a board-certified allergist at the hospital, with the end goal of being able to independently administer a penicillin skin test and interpret the results. Didactic training included content about hypersensitivity reactions and a review of allergy guidelines. Skills training included administering both the scratch test and the intradermal test to volunteers. A total of 26 patients had been tested by the service 1.5 years after it had been implemented, and it was successful in avoiding 48 doses of vancomycin per patient and 12 doses of levofloxacin per patient. There were no documented adverse reactions from the penicillin skin test or antibiotics administered. The service was also noted to be well received by physicians.

Wall et al²² provide a template for pharmacy departments to develop a skin testing service supported by allergy and/or infectious diseases departments. However, this level of support by physician specialties may not be present at all hospitals. Without physician specialty support, pharmacists would need to receive training from outside sources but could then staff a penicillin skin testing service at their own institution. Under the guidance of a pharmacist, pharmacy residents and students could also play an integral role in a penicillin skin testing service as they have proven to be effective members of an antimicrobial stewardship team.²³ Opportunities include identification of patients labeled as penicillin allergic, completion of an allergy history, and updating allergy history after completion of the penicillin skin test.

Infectious diseases (ID) medical fellows have also successfully implemented penicillin skin testing at a large academic medical center.¹⁸ The fellows were trained to perform penicillin skin testing and update the allergy section of the chart as part of a hospital-wide allergy consult service for adult patients under the supervision of an ID physician. The service was successful in performing penicillin skin testing in 76 patients, of whom 84% experienced changes in antibiotics. The majority of these patients received narrower

spectrum and more cost-effective therapy. A secondary objective of the study was to survey all ID fellowship program directors ($n = 156$) in the United States to identify barriers to an ID fellow-run penicillin skin testing service. Of the 50 respondents, 92% replied that the fellowship program lacked the personnel and time required to implement a penicillin skin testing service at their own institution.

Pharmacists are well positioned to administer penicillin skin testing because they are typically already involved with obtaining medication and allergy histories and verifying allergies prior to approving medications ordered by physicians for inpatient use. With their knowledge of antibiotics and adverse effects as well as their advocacy for antimicrobial stewardship, they are best suited to identify predictable reactions and delabel these patients by updating allergy information in the medical record. Additionally, pharmacists are an obvious choice for disseminating the results of a penicillin skin test to the patients' community pharmacy and primary care provider in the outpatient setting in order to reduce future unnecessary use of non- β -lactam antibiotics.

Benefits of a Penicillin Skin Testing Service

Increased β -Lactam Use

Penicillin skin testing is the most reliable method for evaluating patients with a history of a presumed IgE-mediated penicillin allergy and can serve as a useful antimicrobial stewardship tool.¹⁷ The Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) Antimicrobial Stewardship guidelines in fact promote the use of penicillin skin testing when resources are available in addition to collaboration with allergists to develop allergy assessment and treatment strategies in patients with a β -lactam allergy.²⁴

This recommendation is based on data in which penicillin skin testing has significantly reduced the use of non- β -lactam antibiotics in the inpatient setting. Using a validated approach, Harris et al²⁵ conducted skin tests in patients who were in need of either prophylactic or therapeutic antibiotics in the inpatient setting. The addition of skin testing for penicillin allergies resulted in a significant decrease in the number of vancomycin, fluoroquinolone, and clindamycin orders as compared with what would have initially been prescribed if skin testing had not been performed. Similarly, a retrospective review by Nadarajah et al²⁶ described 101 patients identified as having undergone penicillin skin testing and who were originally given non- β -lactam antibiotics on admission. The use of non- β -lactam antibiotics was significantly reduced, with 97% of the patients with negative skin tests receiving a β -lactam during hospital admission. The implementation of penicillin skin testing has also served as an

effective means for reducing the use of vancomycin in the perioperative setting. In a study at a large hospital, patients with a β -lactam allergy undergoing an elective orthopedic procedure were referred to an allergy clinic for penicillin skin testing. This practice resulted in a reduction in vancomycin use from 30% to 11% compared to historical controls.²⁷

Future Antibiotic Selection

Perencevich et al²⁸ evaluated the use of antibiotics in subsequent hospital admissions in patients who were no longer considered to be penicillin allergic based on negative skin test results. A total of 38 patients were retrospectively studied over a period of 2 years after their negative skin test, and it was found that β -lactams were prescribed in 86% of admissions. All patients requiring antibiotics after the skin test received a β -lactam on at least 1 admission. A similar study was published by King et al²⁹ who followed 50 patients at a community hospital who had completed penicillin skin testing and an oral challenge during an admission. All patients had negative results except for one who experienced a reaction to the oral challenge. Patients were followed for up to 16 months after the initial admission. The 22 out of 31 admissions that followed included administration of β -lactams. These 2 studies support the utility of penicillin skin testing, in that the use of β -lactams and delabeling of these patients persist beyond the time of initial testing.

Accuracy of Documented Allergies

Obtaining a patient's allergy history is a key component in the process of providing excellent patient care. Goals of the allergy history are to identify the specific medication that resulted in an allergic reaction, the timing of the reaction (immediate vs delayed), and the symptoms of the reaction. Unfortunately, a patient's history is often unreliable, especially in cases where the allergic reaction occurred years ago or when the patient was a child. Patients with a type 1 allergic reaction to penicillin typically experience waning sensitivity. Over time, they will gradually lose IgE antibodies, with up to 80% of patients losing sensitivity to penicillin within 10 years.¹

When the exact details of the reaction are unclear, it can be difficult to confidently rule out a type I allergic reaction. The accuracy of patient-reported allergies was investigated by Hjortlund et al.³⁰ They studied 342 patients who were referred to an allergy clinic for suspected β -lactam allergy. The authors hypothesized that patients with histories of immediate, or IgE-mediated, reactions would be more likely to have a positive skin test than patients with a delayed reaction. Five of 36 (14%) patients claiming to have an immediate reaction had positive skin tests compared with 6 of 235 (2.5%) patients with a history of a delayed reaction. These results show that a patient's recall

of previous allergic reaction symptoms does not accurately predict future allergic reaction symptoms. The vast majority of patients could safely have their β -lactam allergy history either removed based on a negative penicillin skin testing or updated to reflect the timing of the reaction (immediate vs delayed).

Cost Savings

The implementation of penicillin skin testing could lead to cost savings for institutions with regard to decreased broad-spectrum or alternative antibiotic use, which tends to be more expensive and may lead to longer hospitalizations and increased resistant infections. King et al²⁹ assessed the effect of penicillin skin testing and allergy consultation on antibiotic cost in hospitalized patients with a β -lactam allergy. A total of 50 patients were skin tested, and all but one were skin-test and oral challenge negative. More than 75% of these patients had their antibiotics changed to a β -lactam-based regimen. The total cost savings for all patients was a little more than \$11 000—approximately \$300 per patient—after taking into account the cost of skin testing materials. The mean daily cost of antibiotics for patients switched to a β -lactam was \$116 before penicillin skin testing and \$27 after testing.

Limitations of a Penicillin Skin Testing Service

Limited Clinical Utility

Outside of neurosyphilis, penicillins can often be substituted with cephalosporins or carbapenems in patients labeled as penicillin allergic when creating either empirical or targeted antibiotic regimens. Within the past decade, there has been a growing consensus that historical definitions of cross-reactivity between β -lactam classes are largely incorrect. Contemporary knowledge supports the hypothesis that multiple β -lactam allergic reactions are caused by similar side chains between specific β -lactams and not a general cross-reactivity between β -lactam classes. DePestel et al³¹ explain the mechanism and implications of penicillin and cephalosporin side chain cross-reactivity in a comprehensive review. In short, penicillins have only 1 side chain at the 6 position, whereas cephalosporins have 2 side chains at the 7 and 3 positions. Thus, patients with penicillin or cephalosporin allergies should avoid β -lactams with similar side chains. Fortunately, cefazolin, ceftriaxone, and cefepime, the most commonly utilized intravenous cephalosporins in the in-patient setting, do not share a side chain with penicillin, amoxicillin, or ampicillin.³¹ The implication of this is that these 3 cephalosporins can be used even in the presence of a type I (IgE-mediated) penicillin allergy. Conversely, cephalixin has a similar side chain with

amoxicillin and ampicillin and should be avoided in patients with a known or suspected amoxicillin or ampicillin allergy. It is important to remember that patients can have independent allergic reactions to multiple antibiotics, including unrelated cephalosporins.³²

Because of the low incidence of patients having a confirmed type I allergic reaction to penicillin, some facilities have created protocols that skip skin testing and proceed directly to an oral challenge for patients with a history of a delayed reaction. The use of graded challenge without skin testing has also been proposed for patients with low-risk reactions, including those with unknown reaction history or history of a rash.³³ The protocol was developed after the completion of a large study, with the goal of delabeling patients with β -lactam allergies. The authors performed skin prick testing, intradermal testing, and an oral challenge for all patients labeled with one or more β -lactam allergies.³⁴ More than 400 patients underwent penicillin skin prick testing and intradermal testing, and 42 (12%) patients tested positive to a penicillin determinant, amoxicillin, cefazolin, or cefuroxime. A subgroup of 355 patients received a penicillin oral challenge, 3 of whom experienced mild cutaneous or subjective reactions, resulting in a 99.2% NPV.

Blumenthal et al³⁵ describe the development of a clinical guideline by allergy, infectious diseases, and pharmacy to assist providers in managing patients with a reported penicillin or cephalosporin allergy. The guideline recommended obtaining a detailed allergy history, including characterization of rashes. If the provider believed the allergy to be valid, the guideline recommended (1) using a third- or fourth-generation cephalosporin or carbapenem at full dose, (2) using a test dose of desired β -lactam, or (3) consulting an allergist who could administer a penicillin skin test if appropriate. The number of test doses significantly increased from 49 prior to the guideline to 183 after implementation. There was no difference in the rate of allergic reactions between those receiving antibiotics after test doses and skin testing. This indicates that increased use of penicillin skin testing was not any safer than providing test doses of the antibiotics. However, there was a significant increase in the number of patients receiving both penicillins and cephalosporins and significantly fewer patients receiving alternative antibiotics after the guideline. The authors concluded that skin testing is largely unnecessary and that later-generation cephalosporins and carbapenems should be utilized without the intermediate step of penicillin skin testing. If providers had opted to follow the recommendation, 164 skin tests would have been avoided.

Identification of Only IgE-Mediated Reactions

A penicillin skin test largely detects the presence of allergen-specific IgE on a patient's mast cells. Patients with a type I or an immediate allergy to penicillin will experience

activation of mast cells and basophils after receipt of penicillin. This activation results in release of an array of vasoactive mediators, which causes the signs and symptoms of anaphylaxis. Although anaphylaxis is one of the more severe allergic reactions, it represents less than 10% of reactions and is rarely fatal.³⁶ Penicillin skin testing does not rule out type II, III, or IV reactions. This means that, even in the face of a negative penicillin skin test, a patient could still develop other serious reactions, including hemolytic anemia, serum sickness, Stevens-Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN). Currently, there are no diagnostic tools available to predict the development of SJS and/or TEN.

Medication Interactions and Contraindications

Antihistamines are known to interfere with the histamine skin test that is administered along with saline and penicillin. Patients should discontinue the use of antihistamines for several days prior to outpatient penicillin skin testing.³⁷ This practice is not as feasible in the inpatient setting. Beyond antihistamines, the list of medications that have potential to interact with the histamine skin test include systemic corticosteroids, topical steroids, and psychotropic medications, including tricyclic antidepressants and antipsychotics with potent histamine-blocking mechanisms. Geng et al³⁸ investigated factors associated with negative histamine skin tests. Their multivariable logistic regression model identified systemic corticosteroids and histamine 2 receptor blockers as risk factors for lack of histamine response compared with controls. Vasopressors, furosemide, serotonin and norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors were not found to be related to lack of histamine response. Notably missing from the analysis were antipsychotic medications.

In addition to patients who would be ineligible for penicillin skin testing as a result of medication interactions with histamine, there is a significant group of patients in whom it would be contraindicated. Macy et al³⁹ recommend that patients with a history of TEN, SJS, hemolytic anemia, hepatitis, nephritis, or oral and/or skin blisters associated with or attributed to the previous use of a penicillin class antibiotic should not be skin tested because it may trigger a repeat reaction. More general recommendations can be found in the PRE-PEN package insert, where PRE-PEN is contraindicated in those patients who have exhibited either a systemic or marked local reaction to its previous administration and in patients known to be extremely hypersensitive to penicillin.

Potential Institutional Costs

There are several costs associated with a pharmacist-run penicillin allergy skin testing service. First, the cost of the

PRE-PEN skin testing kit is approximately \$150 per patient. Skin testing is also time-consuming. In a 2014 interview, Dr Geoffrey Wall, who has been part of a pharmacist-run allergy service since 2003,²² stated that skin testing consumes 45 minutes to an hour of a pharmacist's time.⁴⁰ Unfortunately, this time commitment may end up having to be repeated for patients who do not understand the implications of a negative skin test and continue to inform providers that they are penicillin allergic. Redocumentation of a previously removed penicillin allergy is an unfortunate reality of a penicillin skin testing service. In one health care system, a retrospective study revealed that 36% of patients had their penicillin allergy redocumented within a year of the negative penicillin skin test.¹² None of the cases of redocumentation were associated with an allergic reaction.

Conclusion

In conclusion, penicillin skin testing can provide reassurance in administering the safest and most effective antibiotic therapy in patients of all ages and backgrounds with a reported penicillin allergy in nearly all practice settings. The feasibility of implementing a penicillin skin testing service is limited by personnel availability though it has been shown to be both safe and effective. The feasibility of a pharmacist-run penicillin skin testing service increases when pharmacy residents and/or interns supply the labor needed. The benefits of penicillin skin testing include clarifying and confirming true penicillin allergies, increased β -lactam use, and reduced vancomycin, fluoroquinolone, and clindamycin use. The decrease in use of non- β -lactam antibiotics has likely resulted in fewer treatment failures and adverse reactions commonly associated with these medications. Limitations of a penicillin skin testing service include the inability to identify type II, III, or IV allergic reactions; medication interactions resulting in histamine suppression; and contraindications in patients with a known history of severe cutaneous reactions.

Institutions with high percentages of patients receiving non- β -lactams because of penicillin allergy labels would likely benefit the most from a penicillin skin testing service. Health care systems that already have a high rate of cephalosporin or carbapenem use for patients labeled as penicillin allergic are unlikely to benefit as much from this service. Future research should focus on the identification of the tipping point of non- β -lactam use in which an institution would benefit from a penicillin skin testing service.

Declaration of Conflicting Interests

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