

RESEARCH ARTICLE

Assessment of the Prevalence of Proactive Penicillin Allergy Testing in Patients Labeled as Penicillin Allergic in Dhanusadham District of NepalRajesh Chandra Das^{1*}, Bibeka Nand Jha²¹Department of Medicine, Janaki Medical College, Janakpurdham, Nepal, ²Department of Dermatology, Janaki Medical College, Janakpurdham, Nepal**Received: 10 April 2019; Revised: 15 May 2019; Accepted: 11 June 2019****ABSTRACT**

This study aims to promote penicillin allergy testing in an outpatient to penicillin allergy and educate both patients and clinicians about testing. Patients with a history of penicillin allergy were screened for penicillin allergy testing. The results of allergy testing and patient satisfaction after testing were the main outcomes. A total of 82 patients were recruited, although only 37 actually underwent testing. None of these 37 had a positive skin test and none of 36 had a positive oral challenge (one refused it). Following testing, 2 patients (5%) had subjective reactions within 24 h. Three (10%) were subsequently treated with a beta-lactam, and all reported that testing provided important information to their medical history. In conclusion, the penicillin allergy testing safely evaluates patients labeled as penicillin allergic. It is well tolerated and embraced by the patients who undergo testing. In our study, none of the patients tested had an allergic reaction, but we identified multiple barriers to developing a protocol for testing patients from the primary care setting.

Keywords: Beta-lactam, patient safety, penicillin allergy, treatment protocol**INTRODUCTION**

Penicillin is relatively inexpensive and the drug of choice for several bacterial infections including upper and lower respiratory tract infections, meningococcal disease, syphilis, and anaerobic infections. Allergy to penicillin is the most commonly reported drug allergy in the USA and is estimated to affect 7–10% of outpatient populations and up to 20% of hospitalized patients.^[1-3] Relatively few of those individuals have had their “penicillin allergy” verified and avoid the beta-lactam group of antibiotics indefinitely. Recent studies have indicated that >90% of those with a positive history can tolerate penicillins.^[4-9] Possible explanations include the mislabeling of a medication side effect or a disease manifestation.^[2,4]

Furthermore, penicillin allergy is known to wane in most individuals overtime and up to 50% of skin test – positive patients have lost their sensitivity at 5 years and 80% at 10 years.^[10,11] Recently, the associated morbidity of unverified penicillin allergy has become increasingly recognized as a significant public health problem. Hospitalized patients labeled as penicillin allergic are more likely to be treated with broad-spectrum antibiotics such as vancomycin, quinolones, or third-generation cephalosporins, all of which have been shown to contribute to the development of antibiotic resistance and *Clostridium difficile* infections.^[1,12,13] These patients also have increased complications and require longer hospital stays, thereby increasing medical costs.^[14,15] In addition, they may have been told to avoid cephalosporins as well.^[16] This recommendation is based on early reports, in which patients were treated with cephalosporins with similar side chains to penicillin, which are no longer used, or based on testing with reagents contaminated

***Corresponding Author:**Dr. Rajesh Chandra Das,
E-mail: rajesh93chdas@gmail.com

with penicillin.^[17] Current estimates of a penicillin-allergic patient reacting to cephalosporins are proposing that penicillin allergy testing should be performed routinely in patients with self-reported penicillin allergy.^[18] Penicillin skin prick testing (SPT), intradermal testing (IDT), and oral challenge (OC) are safe, well-studied, and validated methods for assessing IgE-mediated penicillin allergy. Skin testing (SPT and IDT) using the major determinant, penicilloyl-polylysine, and the minor determinants, penicilloate, penilloate, and penicillin G reduces the number of OC reactions and has a negative predictive value of 97–99%.^[19,20] In the USA, penicilloate and penilloate are not commercially available, but protocols using penicilloyl-polylysine and penicillin G perform with similar accuracy when combined with OC.^[21] An OC is the gold standard to determine tolerance or confirm an IgE-mediated penicillin allergy. Amoxicillin is typically used for the challenge, as it is more frequently prescribed and has an immunologically similar core structure to penicillin. Penicillin allergy testing can be easily done as an outpatient procedure by a trained allergy specialist but remains underutilized. The aims of this study were to evaluate the penicillin allergy in an outpatient population and to promote referral for testing by primary care physicians (PCPs) by evaluating the incidence of true allergy in those tested and determining patient satisfaction following testing.

MATERIALS AND METHODS

Adult patients from an academic internal medicine and pediatrics practice with a history of penicillin/amoxicillin allergy documented in the electronic health record (EHR) were recruited for the study. PCPs screened patients and determined the accuracy of the allergy listing in the EHR, the type of reaction reported by the patients, and their interest in participating. Patients were then referred to the Janaki Medical College for testing. Before testing, patients were called by dermatologist to review their history and current medications.

Exclusion criteria for testing included the following:

1. Poorly controlled asthma or cardiovascular disease.
2. History of severe cutaneous reactions attributed to beta-lactams including Stevens–Johnson syndrome, toxic epidermal necrolysis, drug-induced exfoliative dermatitis, or drug rash with eosinophilia and systemic symptoms.
3. Serious non-IgE-mediated reactions including hepatitis, hemolytic anemia, vasculitis, or interstitial nephritis.
4. Use of medications that interfere with testing and could not be stopped including antihistamines, tricyclic antidepressants, atypical antipsychotics, beta-blockers, or high-dose oral glucocorticoids.
5. Pregnancy: On the day of testing, a thorough clinical history was obtained including the age at onset of reaction, drug implicated, details of the reaction, and any treatment received. Written informed consent was provided by patients who agreed to undergo testing and be included in the study.

Penicillin allergy testing process

The allergy testing consisted of the three-step process. The two skin tests were performed using the major determinant benzylpenicilloyl-polylysine as instructed in the package insert; the minor determinant, penicillin G (10,000 units/mL); a histamine positive control; and a normal saline negative control. SPT was performed on the volar aspect of the patient's forearm and reactions were recorded after 15 min. The Institutional Review Board at Janaki Medical College approved this study before patient recruitment and the study was conducted from January 2018 to December 2018.

RESULTS

Demographics of study

Subjects from January 2018 to December 2018, 82 patients with a listing of penicillin allergy in the EHR were recruited. Of the original 82 patients, 37 ultimately underwent penicillin allergy testing. The most common reaction type was a rash in 20 patients (54.1%), while 10 (27%) reported hives and 2 (5.4%) had reactions consistent with anaphylaxis. Allergy testing of the 37 patients

tested, all had negative results on skin testing (SPT and IDT). Thirty-six patients were challenged with an oral dose of amoxicillin and none reacted. One patient opted not to undergo the OC. During the telephone follow-up, 1 week after testing, two patients reported delayed symptoms, with one describing lightheadedness, pruritus, and sweating 4 h after testing and the other describing lightheadedness the day after testing. Both patient's symptoms were determined to be subjective and unlikely a delayed hypersensitivity or immunologic reaction.

Subject follow-up

Thirty-one patients (83.7% of those tested) completed the 6-month follow-up questionnaire. Eleven (36.6%) required antibiotics during that time. Three (10%) of that group were treated with amoxicillin and none reported a reaction. All 31 subjects thought that undergoing evaluation for penicillin allergy provided valuable information to their medical history and 28 (90%) reported that they would take penicillin/amoxicillin in the future if prescribed.

Provider survey

Seven of 8 (87.5%) referring physicians completed the online survey. According to their estimates, most physicians (83%) asked half of their patients with penicillin/amoxicillin allergy to participate but did not take the time to discuss testing during the patient visit.

DISCUSSION

Penicillin allergy testing is a well-tolerated, reliable procedure used to evaluate patients for IgE-mediated sensitivity to penicillin.^[4,21,22] Ideally, testing should be performed to confirm the allergy soon after the reaction, but this is rarely the case and patients carry the diagnosis of penicillin allergy indefinitely. In this study, no patient had a positive skin test or an immediate reaction during or after the OC with amoxicillin.^[23-25] These results are lower than in the previous studies of penicillin

allergy testing, in which the percentage of positive skin tests ranged from 9.5 to 28.6%.^[8,26-28] For instance, in a large, prospective study from Australia, of 401 patients referred for evaluation of β -lactam allergy, 42 (12.3%) tested positive. In this study, skin testing was more likely to be positive in those tested within 6 months of an immediate reaction.^[26] In contrast, the reactions reported by most of our patients occurred over 20 years before. It is likely that those with the most recent and most dramatic reactions chose not to participate or were not asked by their physicians. Few studies have taken a proactive approach, i.e. with the explicit goal of enabling those with negative tests to receive penicillins. Macy *et al.* performed allergy testing on 228 hospitalized patients with a penicillin allergy identified.^[21] Two hundred and twenty-three (90.5%) tested negative and had penicillin allergy removed from the EHR. Following negative testing, 77 patients (34%) initiated therapy with a penicillin or cephalosporin while admitted and an additional 8 (3.6%) were prescribed a β -lactam at discharge. To the best of our knowledge, this study is the first to work in cooperation with PCPs to proactively evaluate an outpatient population for penicillin allergy and assess outcomes after testing. Most patients embraced testing and reported that it provided valuable information to their medical history. Unfortunately, providers came across several barriers to patient referral, the most important being lack of time (both on the part of the physician and patient). Despite safe, well-established protocols and the low prevalence of confirmed penicillin allergy in those who undergo testing, very few individuals ever have their allergy evaluated. In the USA, it is estimated that fewer than 15,000 people undergo testing for penicillin allergy annually.^[29] Reasons for the low rate of testing may include lack of provider knowledge, limited access to an allergist, and worry about testing related reactions. In particular, studies have shown that non-allergist physicians have a poor understanding of penicillin allergy.^[30,31] A survey of inpatient providers evaluating baseline knowledge of drug allergies found that 42% of respondents had no prior education in drug allergies. Following the implementation of an educational program with an

accompanying hospital-wide guideline, there was a significant increase in penicillin allergy knowledge, including knowledge of allergy testing and loss of clinical reactivity overtime.^[32] Following negative penicillin allergy testing, it is important to educate both patients and their physicians about the results. In our study, the results and their implications were reviewed in detail with the patients immediately after testing and a results letter was provided to both the patient and their PCP. The information in the letter was reiterated during their subsequent follow-up. Furthermore, after negative testing, it is important to update the drug allergy history in the EHR and to verify this at each patient encounter. Rimawi *et al.* found that 36% of hospitalized patients had penicillin allergy redocumented in their charts in spite of negative skin testing.^[33] Risk factors for redocumentation included history of dementia, acute altered mental status, age >65 years, and residence in a long-term care facility. Patient education, automated alerts in the EHR, and notification of the patients' pharmacies and/or long-term care facilities may help prevent this. A large percentage of patients in this study reported that they would take penicillin/amoxicillin in the future if prescribed, and none of the patients who received a β -lactam following testing had a reaction. Aside from patient satisfaction, the benefits of implementing a penicillin allergy testing protocol in the outpatient setting include cost savings, reduction in complications, and drug-resistant infections. The previous studies evaluating short-term cost savings following penicillin allergy testing in the inpatient setting have found savings of \$225–\$297 per patient while hospitalized.^[15,34] In a natural history study of elective penicillin skin testing in advance of need, 236 patients were followed for a year after allergy testing. In those with negative testing, 93 patients received at least one penicillin. Furthermore, the total cost for antibiotics fell 32% from \$17,211.88 to \$11,648.27, with a roughly 6% reduction in average cost per antibiotic.^[35] Patients and physicians may worry about the theoretical risk of re-sensitization. However, they should be reassured that the rate of re-sensitization in previously allergic patients with negative skin testing is approximately

3%. This is similar to the rate of reaction in the general population. Repeat testing in the future is, therefore, generally not necessary.^[22,30]

This study identified multiple barriers that need to be overcome to achieve large-scale penicillin allergy testing. First, the identification and recruitment of patients with presumed penicillin allergy can become a routine part of office procedures. However, adopting these procedures takes time and was occurring as our study was coming to an end. Second, the reticence of the patients – including fear of suffering a reaction during the testing or later, lack of appreciation of the benefits of negative testing, and unwillingness or inability to take the time needed for testing. These issues can be addressed by more effective education by their PCPs, by making testing less threatening, more convenient, and accessible. Studies have shown that low-risk patients such as those with non-immediate reactions occurring over 1 h after dosing or those with reactions localized to the skin may be able to undergo direct OC without skin testing.^[36,37] This involves administration of a partial dose (usually 1/10th) followed by a full dose with an hour of observation after each dose. While direct OCs might, in theory, make it easier to test patients in primary care offices, they still need to be done under the guidance of an allergy specialist and someone trained in treating immediate drug reactions.

Limitations

This study had several limitations, some that were anticipated and others that were noted along the way. First, the study is limited by its small sample size and by the large percentage of patients, who despite being recruited by their PCPs, either never scheduled testing or did not show up after being scheduled. Improved procedures for referral and the implementation of penicillin allergy clinic days, in which an allergist has dedicated hours at a primary care facility, may improve this. Second, our patients were, as a consequence of who was asked and who agreed to participate, at low risk of having a positive test. Yet freeing even low-risk patients of the label of allergy to penicillin is of

great value. Third, the study included only adults, but children may have longer term benefits and more cost savings by having their penicillin allergy evaluated earlier in life. Fourth, the study took place at a single academic center with an affiliated allergy practice that could easily perform allergy testing, which may limit its generalizability. Last, we followed patients for only a short period of time after testing. Consequently, we were not able to evaluate the impact of negative allergy testing on future antibiotic selection and on subsequent health-care costs.

CONCLUSION

The label of penicillin allergy is common and associated with increased morbidity and cost but is rarely evaluated. Penicillin allergy testing is a safe and effective way of identifying an IgE-mediated sensitivity to penicillin and its derivatives. Our study showed that a proactive penicillin allergy testing protocol safely confirmed tolerance to penicillin in all who were tested. It was embraced by the patients and led to changes in antibiotic prescription by prescribers, but several barriers were noted during the study that limited patient recruitment. In the future, a large-scale proactive approach to evaluating patients with a history of penicillin allergy should become a regular part of primary care with the expectation that it will reduce morbidity and medical costs overtime and be well accepted by both providers and patients.

REFERENCES

- Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. *J Allergy Clin Immunol* 2014;133:790-6.
- Khan DA, Solensky R. Drug allergy. *J Allergy Clin Immunol* 2010;125:S126-37.
- Albin S, Agarwal S. Prevalence and characteristics of reported penicillin allergy in an urban outpatient adult population. *Allergy Asthma Proc* 2014;35:489-94.
- Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. Drug allergy: An updated practice parameter. *Ann Allergy Asthma Immunol* 2010;105:259-73.
- Borch JE, Andersen KE, Bindslev-Jensen C. The prevalence of suspected and challenge-verified penicillin allergy in a university hospital population. *Basic Clin Pharmacol Toxicol* 2006;98:357-62.
- Silva R, Cruz L, Botelho C, Castro E, Cadinha S, Castel-Branco MG, *et al.* Immediate hypersensitivity to penicillins with negative skin tests the value of specific IgE. *Eur Ann Allergy Clin Immunol* 2009;41:117-9.
- Bousquet PJ, Pipet A, Bousquet-Rouanet L, Demoly P. Oral challenges are needed in the diagnosis of beta-lactam hypersensitivity. *Clin Exp Allergy* 2008;38:185-90.
- Sagar PS, Katelaris CH. Utility of penicillin allergy testing in patients presenting with a history of penicillin allergy. *Asia Pac Allergy* 2013;3:115-9.
- Macy E, Schatz M, Lin C, Poon KY. The falling rate of positive penicillin skin tests from 1995 to 2007. *Perm J* 2009;13:12-8.
- Blanca M, Torres MJ, García JJ, Romano A, Mayorga C, de Ramon E, *et al.* Natural evolution of skin test sensitivity in patients allergic to beta-lactam antibiotics. *J Allergy Clin Immunol* 1999;103:918-24.
- Picard M, Paradis L, Bégin P, Paradis J, Des Roches A. Skin testing only with penicillin G in children with a history of penicillin allergy. *Ann Allergy Asthma Immunol* 2014;113:75-81.
- Picard M, Bégin P, Bouchard H, Cloutier J, Lacombe-Barrios J, Paradis J, *et al.* Treatment of patients with a history of penicillin allergy in a large tertiary-care academic hospital. *J Allergy Clin Immunol Pract* 2013;1:252-7.
- Lee CE, Zembower TR, Fotis MA, Postelnick MJ, Greenberger PA, Peterson LR, *et al.* The incidence of antimicrobial allergies in hospitalized patients: Implications regarding prescribing patterns and emerging bacterial resistance. *Arch Intern Med* 2000;160:2819-22.
- Sade K, Holtzer I, Levo Y, Kivity S. The economic burden of antibiotic treatment of penicillin-allergic patients in internal medicine wards of a general tertiary care hospital. *Clin Exp Allergy* 2003;33:501-6.
- King EA, Challa S, Curtin P, Bielory L. Penicillin skin testing in hospitalized patients with β -lactam allergies: Effect on antibiotic selection and cost. *Ann Allergy Asthma Immunol* 2016;117:67-71.
- Batchelor FR, Dewdney JM, Weston RD, Wheeler AW. The immunogenicity of cephalosporin derivatives and their cross-reaction with penicillin. *Immunology* 1966;10:21-33.
- Gralnick HR, Wright LD Jr., McGinniss MH. Coombs' positive reactions associated with sodium cephalothin therapy. *JAMA* 1967;199:725-6.
- Penicillin Allergy in Antibiotic Resistance Workgroup. Penicillin allergy testing should be performed routinely in patients with self-reported penicillin allergy. *J Allergy Clin Immunol Pract* 2017;5:333-4.
- Macy E, Mangat R, Burchette RJ. Penicillin skin testing in advance of need: Multiyear follow-up in 568 test result-negative subjects exposed to oral penicillins.

- J Allergy Clin Immunol 2003;111:1111-5.
20. Sogn DD, Evans R 3rd, Shepherd GM, Casale TB, Condemi J, Greenberger PA, *et al.* Results of the national institute of allergy and infectious diseases collaborative clinical trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. *Arch Intern Med* 1992;152:1025-32.
 21. Macy E, Ngor EW. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-polylysine, penicillin, and oral amoxicillin. *J Allergy Clin Immunol Pract* 2013;1:258-63.
 22. Unger NR, Gauthier TP, Cheung LW. Penicillin skin testing: Potential implications for antimicrobial stewardship. *Pharmacotherapy* 2013;33:856-67.
 23. Romano A, Guéant-Rodriguez RM, Viola M, Pettinato R, Guéant JL. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. *Ann Intern Med* 2004;141:16-22.
 24. Medicine ABoI; 2014. Available from: <http://www.choosingwisely.org/doctor-patient-lists/american-academy-ofallergy-asthma-immunology>. [Last accessed on 2019 Jan 19].
 25. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, *et al.* Executive summary: Implementing an antibiotic stewardship program: Guidelines by the infectious diseases society of America and the society for healthcare epidemiology of America. *Clin Infect Dis* 2016;62:1197-202.
 26. Bourke J, Pavlos R, James I, Phillips E. Improving the effectiveness of penicillin allergy de-labeling. *J Allergy Clin Immunol Pract* 2015;3:365-34.
 27. Meng J, Thursfield D, Lukawska JJ. Allergy test outcomes in patients self-reported as having penicillin allergy: Two-year experience. *Ann Allergy Asthma Immunol* 2016;117:273-9.
 28. Chen JR, Tarver SA, Alvarez KS, Tran T, Khan DA. A proactive approach to penicillin allergy testing in hospitalized patients. *J Allergy Clin Immunol Pract* 2017;5:686-93.
 29. Macy E. Penicillin allergy: Optimizing diagnostic protocols, public health implications, and future research needs. *Curr Opin Allergy Clin Immunol* 2015;15:308-13.
 30. Bittner A, Greenberger PA. Incidence of re-sensitization after tolerating penicillin treatment in penicillin-allergic patients. *Allergy Asthma Proc* 2004;25:161-4.
 31. Puchner TC Jr., Zacharisen MC. A survey of antibiotic prescribing and knowledge of penicillin allergy. *Ann Allergy Asthma Immunol* 2002;88:24-9.
 32. Blumenthal KG, Shenoy ES, Hurwitz S, Varughese CA, Hooper DC, Banerji A, *et al.* Effect of a drug allergy educational program and antibiotic prescribing guideline on inpatient clinical providers' antibiotic prescribing knowledge. *J Allergy Clin Immunol Pract* 2014;2:407-13.
 33. Rimawi RH, Shah KB, Cook PP. Risk of redocumenting penicillin allergy in a cohort of patients with negative penicillin skin tests. *J Hosp Med* 2013;8:615-8.
 34. Rimawi RH, Cook PP, Gooch M, Kabchi B, Ashraf MS, Rimawi BH, *et al.* The impact of penicillin skin testing on clinical practice and antimicrobial stewardship. *J Hosp Med* 2013;8:341-5.
 35. Macy E. Elective penicillin skin testing and amoxicillin challenge: Effect on outpatient antibiotic use, cost, and clinical outcomes. *J Allergy Clin Immunol* 1998;102:281-5.
 36. Confino-Cohen R, Rosman Y, Meir-Shafir K, Stauber T, Lachover-Roth I, Hershko A, *et al.* Oral challenge without skin testing safely excludes clinically significant delayed-onset penicillin hypersensitivity. *J Allergy Clin Immunol Pract* 2017;5:669-75.
 37. Mill C, Primeau MN, Medoff E, Lejtenyi C, O'Keefe A, Netchiporouk E, *et al.* Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and nonimmediate reactions to amoxicillin in children. *JAMA Pediatr* 2016;170:e160033.