

Letter to the Editor

Patients with positive skin test results to penicillin should not undergo penicillin or amoxicillin challenge

To the Editor:

The American Academy of Allergy, Asthma & Immunology leadership asked the authors to comment on the following question: Should patients with a positive skin test result to penicillin undergo a penicillin or amoxicillin challenge?

Penicillin allergy is the most common drug allergy, currently reported in approximately 8% of the population using health care in the United States and often in over 10% of hospitalized cohorts.¹ Many individuals are incorrectly identified as being penicillin allergic and declining rates of positive penicillin skin test results have been documented over the past 20 years.² Only about 1 in 20 individuals currently in the United States with a penicillin allergy history will have a positive penicillin allergy evaluation using skin testing and oral challenge, with the remainder having never been allergic or having lost the allergy over time. Penicillin is the only drug allergy for which a Food and Drug Administration (FDA)-approved skin test reagent, the “major” penicillin determinant benzylpenicilloyl-poly-lysine (PRE-PEN; AllerQuest, Plainville, Conn), is available. Testing with this reagent identifies patients with penicillin-specific IgE antibodies who are thus at risk for an immediate (IgE-mediated) allergic reaction to penicillin but not delayed reactions to penicillins. Allergists/immunologists in the United States have performed immediate hypersensitivity skin testing to confirm or rule out penicillin allergy for the past 40 years with FDA-approved benzylpenicilloyl-poly-lysine and off-label use of minor determinants penicillin G, penicilloate, penilloate, and amoxicillin.³⁻⁶ Skin testing with these reagents has been shown to be safe and effective, with a high negative predictive value, as determined by oral challenge with penicillin or amoxicillin; that is, virtually all patients with negative skin test results tolerate the administration of penicillin.^{3,5,6}

A major reason that penicillin skin testing is underutilized is that it requires the use of off-label, non-FDA-approved products. An easy-to-use penicillin skin testing kit that includes unit doses of not only benzylpenicilloyl-poly-lysine but also a minor determinant mixture containing penicillin G, penicilloate, penilloate, and amoxicillin would be a great advance in the evaluation of penicillin allergy in the United States.

The authors feel that on the basis of the current literature and standard of care, performing oral challenges to penicillins in subjects with positive skin test results to minor determinant mixture and/or amoxicillin to demonstrate the positive predictive value for these skin test reagents is unnecessary, potentially dangerous, and unethical. Previous evaluations to validate penicillin skin testing with PRE-PEN and/or minor determinants were conducted to estimate the negative predictive value of these tests and not their positive predictive value because of ethical considerations and a concern for patient safety.^{3,6}

The oral challenge is considered the criterion standard test to determine acute penicillin tolerance and the lack of clinically significant IgE-mediated penicillin allergy.⁷ There have been no prospective studies done in the United States to date with mandatory oral penicillin challenges in individuals with positive skin

test results. Limited retrospective data from the United States imply that about one-third to one half of penicillin skin test-positive individuals will have a clinically significant adverse reaction after inadvertent oral therapeutic penicillin use.⁸ For this reason, and the fact that these reactions could be severe and life-threatening, we believe that the prospective challenge of penicillin skin test-positive individuals with oral penicillins is an unnecessary and potentially harmful procedure. Instead, it is standard of care for penicillin skin test-positive individuals who require administration of a penicillin or penicillin-like drug to undergo a desensitization procedure.^{9,10} Penicillin desensitization is a relatively safe procedure in which incremental doses of penicillin are given orally or intravenously to induce clinical tolerance. Furthermore, performing an oral challenge in skin test-positive individuals would not benefit the patient, and the scientific knowledge gained (whether, eg, 20% or 70% of the skin test-positive patients react to a challenge) would not affect the clinical practice because the current standard of care for all skin test-positive patients who require penicillin is to undergo desensitization. Thus, the benefit of oral penicillin and/or amoxicillin challenge—whether administered as a single dose or in a graded-dose fashion—does not outweigh the potential for harm (ie, severe or even life-threatening allergic reaction).¹¹

Although relatively few skin test-positive patients have been challenged and reported in the literature, these data support the contention that patients with a positive penicillin skin test result are at statistically significantly increased risk for IgE-mediated reaction from penicillin or a penicillin-like drug than is the general population.⁷ The most recent practice parameters for drug allergy, developed by the Joint Task Force of the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma and Immunology, recommended that “penicillin skin test-positive patients should avoid penicillin, but if they develop an absolute need for penicillin, rapid induction of drug tolerance may be performed” (see Summary Statement 83 in *Annals of Allergy, Asthma and Immunology* 2010;105:273e20).⁹

Hence, the authors believe that the determination of the positive predictive value for skin testing reagents is not sufficient justification from an ethical standpoint for oral challenges in subjects who are skin test-positive to penicillin. It is standard of care to treat such patients with alternative antibiotics, or to offer penicillin desensitization.

An important, unmeasured, and underappreciated aspect of penicillin allergy is the morbidity/mortality and economic costs associated with the unnecessary withholding of appropriate therapy in the large number of patients mistakenly labeled as allergic to penicillin.¹² Vancomycin is often prescribed in the hospital setting solely because patients are labeled “penicillin allergic.”^{13,14} Similarly, patients who report penicillin allergy are significantly more likely to be treated with carbapenems, clindamycin, macrolides, and quinolones than are patients not labeled as penicillin-allergic.¹² Use of these alternate antibiotics is associated with poor outcomes such as a higher incidence of *Clostridium difficile* colitis, vancomycin-resistant enterococci, and cardiac arrhythmias. More widespread utilization of penicillin allergy testing would have a substantial and favorable public health impact: use of broad-spectrum antibiotics would be reduced,

leading to fewer emergences of resistant bacteria and lower medical expenditures.^{12,15}

Delaying the approval of these reagents can compromise the evaluation of thousands of patients with a history of penicillin allergy, who are in fact not allergic, and would otherwise receive alternative antibiotics that may be more expensive and/or entail greater risk for untoward effects.¹² Performing an adequately powered clinical trial to assess the positive predictive value of immediate hypersensitivity skin testing for penicillin or amoxicillin allergy would require enrolling a substantial number of skin test-positive patients. Successfully enrolling subjects in such trials would be challenging—not only because of the infrequency with which skin test-positive patients can be identified but also based on an understandable reluctance on the part of skin test-positive individuals to proceed with an exposure to penicillin or amoxicillin that could be serious or even life-threatening.

For the above reasons, the authors encourage the expedited approval by the FDA of a penicillin skin test kit that includes benzylpenicilloyl-poly-lysine, penicillin G, penicilloate, penicilloate, and amoxicillin (Pre-Pen Plus), without the requirement to perform penicillin challenges in skin test-positive patients. We also encourage the development and approval of diagnostic testing reagents for allergies to other antibiotics and drugs via appropriately scientific and clinical testing that do not put patients at risk.

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California Permanente Medical Group, which has received funding from ALK, as well as consultancy fees from BioMarin and Ultragenyx. D. M. Lang serves on the AAAAI Board of Directors; has received consultancy fees from Merck, Quest, and Hycor; and has received or has grants pending from Merck, Genentech, and Novartis, from which he has also received payment for delivering lectures. M. A. Park declares no relevant conflicts of interest.

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