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John M. Kelso, MD

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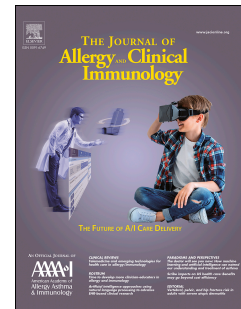
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2
3 John M. Kelso, MD

4
5 Division of Allergy, Asthma and Immunology
6 Scripps Clinic, San Diego CA

7
8 Corresponding Author:

9 John M. Kelso, MD

10 Division of Allergy, Asthma and Immunology

11 Scripps Clinic

12 3811 Valley Centre Drive

13 San Diego CA 92130

14
15 Phone 858-764-9010

16 Fax 858-764-9011

17 E-mail kelso.john@scrippshealth.org

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Penicillin testing: It's all about pre-test probability

John M. Kelso, MD *San Diego, Calif.*

The purpose of testing for specific IgE to penicillin is to help estimate the likelihood that a patient would have an immediate-type hypersensitivity reaction on re-exposure to penicillin. In this issue of the *Journal*, Sousa-Pinto et al conduct a systematic review and meta-analysis of studies in which patients reporting penicillin allergy underwent some test for IgE antibody to penicillin followed by a drug challenge.¹ In these studies, positive or negative test results are compared to the "gold standard" challenge that defines whether or not they have such allergy. These comparisons permit calculation of the sensitivity and specificity of the tests. Only a portion of patients reporting penicillin allergy actually have penicillin allergy (prevalence). The calculated summary sensitivities and specificities were applied to a "plausible range" of possible prevalences (0% to 10%) to calculate a range of possible positive and negative predictive values (Table I).

As the authors acknowledge, the studies combined in the analysis have many important differences. Studies included patients that describe prior reactions to penicillin that were conceivably IgE-mediated (e.g. early-onset hives) and those that were not (e.g. late-onset maculopapular rash). Most also assessed patients reporting mild reactions, and thus the results may not apply to those reporting more severe reactions. The tests included prick and intradermal skin tests and serum specific IgE antibody testing to various penicillin reagents. Studies have suggested that penicillin skin tests, particularly intradermal tests, are more accurate than tests for specific IgE antibody.^{2,3} Further adding to the variability, some studies included testing for minor penicillin determinants or amoxicillin, which may identify more allergic subjects than testing only for penicillin and its major determinant. Studies of children vs. adults, inpatients vs. outpatients and oral vs. parenteral penicillin were all included but may represent different populations with different test characteristics. Most importantly, in many studies, only a minority of patients with positive test results underwent drug challenge, presumably on the assumption that such

patients would have a positive challenge. However, without this part of the evaluation, we cannot know how many challenges would have been positive (true positives) or negative (false positives). Since the number of true positives and false positives go into the calculation of sensitivity and specificity respectively, as well as the calculation of positive predictive value, the omission of these challenges leads to these values being skewed and inaccurate. Most studies, on the other hand, performed drug challenges on all subjects with negative test results, allowing for a more accurate assessment of true negatives and false negatives, making the calculation of negative predictive value more accurate as well. As with the histories of past reactions, the outcomes of the challenges also included both immediate (less than one hour) or delayed (more than one hour) reactions. Inclusion of the latter, which are exceedingly unlikely to be IgE-mediated, clearly muddies the interpretation of the accuracy of a test for immediate hypersensitivity to penicillin.

Pre-test probability is the estimate of the chance that a patient has a condition before a diagnostic test is performed, in this case, the chance that a patient has penicillin allergy before a test is performed. Several studies have suggested that, of all subjects labeled as penicillin-allergic, fewer than 5% are currently allergic.⁴ If nothing else is known about the patient except that they have been labeled penicillin-allergic, then knowing that only 5% of patients so labeled are allergic, one could conclude that the patient's pre-test probability is 5%. However, all patients labeled as penicillin-allergic are not the same. Individual patients also have their own pre-test probabilities.

There are a number of factors about penicillin allergy that inform the likelihood that an individual patient has a current, IgE-mediated penicillin allergy (Table II). Like all IgE-mediated reactions, patients must have had some prior exposure to become sensitized. Parenteral exposure is more likely to sensitize and to cause serious reactions. Once sensitized, a reaction typically occurs within one hour after the first dose of a subsequent exposure. Reactions usually involve hives with or without some combination

of respiratory difficulty, lightheadedness or gastrointestinal upset. Penicillin allergy tends to wane over time.⁴

As suggested by patient histories, in addition to type I / IgE-mediated / immediate-type hypersensitivity reactions, penicillin can also cause other immune, but not IgE-mediated reactions, for example a late-onset, maculopapular “drug rash”, presumed to represent a type IV / cell-mediated / delayed type-hypersensitivity reaction. Although there would be no reason to perform tests for IgE to penicillin in patients with these late-onset, non-urticarial reactions, they are often included in studies of penicillin allergy, including the current meta-analysis. Positive test results indicating the presence of IgE to penicillin in such patients cannot be mechanistically responsible for their rash. It would not be appropriate to count a positive test result in such a patient as a true positive nor to count a negative test result as a false negative. The inclusion of these patients in studies of IgE-mediated penicillin allergy skews the results of the calculated sensitivity and specificity. There are no standardized, available tests to prove whether or not these non-IgE-mediated reactions are due to penicillin nor to predict their recurrence, and advice regarding continued avoidance must be based on the severity of the historical reaction.

Most patients labeled as penicillin-allergic give a history of a reaction that occurred in the distant past, involved a rash that may or may not have been urticarial and do not recall other symptoms. They are often unable to say how long they had been taking the penicillin before the rash began. Such a patient is very unlikely to be allergic to penicillin. Using the “all-comers” pre-test probability of 5% for such a patient seems reasonable. However, a patient who received intravenous penicillin in the hospital 3 months ago and developed hives and hypotension 5 minutes after the first infusion began, is highly likely to be allergic to penicillin. Using a pre-test probability of 5% for this patient would be a gross underestimate.

Sousa-Pinto et al share this view that an overall prevalence is not an appropriate pre-test probability for all patients, stating, “our systematic review points to the need for further studies minimizing the risk of selection bias and providing, if not individual-level participant data, at least results by type of index reaction clinical presentation. Such evidence would help in patient stratification, so that penicillin allergy delabeling could be safely performed in the most accurate way for each patient.” Nonetheless, for purposes of the meta-analysis, the authors combine these studies despite their heterogeneity and calculate a summary sensitivity for penicillin skin tests of 30.7%. This implies that nearly 70% of patients with penicillin allergy were not identified with the test. Why were these 70% “missed”? Commercially-available penicillin skin test reagents in the United States include penicillin and its major metabolite penicilloyl in the form of benzylpenicilloyl polylysine (PRE-PEN®). Although some false negative skin test results with these reagents may be due to patients making IgE antibody to minor metabolites such as penilloate and penicilloate or to a side chain such as that found on amoxicillin, this is uncommon.^{3, 5} Some may be because less sensitive prick skin tests were used and not more sensitive intradermal tests.

¹ Many may have had non-immediate and/or non-urticarial reactions to their challenges that are not IgE-mediated and thus could not have been “picked up” by the tests. The remainder are patients whose IgE-mediated penicillin allergy was missed because even the most sensitive test available (intradermal skin testing) is not sufficiently sensitive to pick them up. On the other hand, the summary specificity for skin tests found by Sousa-Pinto et al is 96.8%. This implies that only about 3% of patients without penicillin allergy have positive test results. The low sensitivity and high specificity lead to poor positive predictive values but excellent negative predictive values.

If only about 5% of patients labeled penicillin-allergic are at risk for immediately hypersensitivity reactions to penicillins,⁴ how is it that 95% are not? Some may have been allergic in the past and lost the allergy over time and thus may have been correctly labeled initially. However, it seems likely that the majority were never allergic in the first place. Many are patients where the nature and timing of

their reactions did not suggest an IgE-mediated mechanism. Rashes that develop days into, or shortly after a course of penicillin are common, but rarely represent immediate hypersensitivity to penicillin, being more likely related to underlying infection or T-cell mediated allergy.⁶ It had previously been thought that labeling such patients as penicillin-allergic was appropriate to avoid the risk of a more severe reaction with a subsequent exposure and because other antibiotics could be used instead. Many patients carry these labels for decades or life-long. We now know that being mislabeled is not benign, but instead carries real risks, since use of alternative antibiotics is often more expensive and less effective and has consequences related to side-effects such as *C. difficile* infection and worsening drug resistance.⁷ Thus, patients with non-serious, late-onset or non-urticarial reactions should not be labeled as penicillin-allergic or should receive prompt referral to an allergist for evaluation to prevent a long-term misdiagnosis.

We have a gold standard for telling us if a given patient does or does not have current IgE-mediated penicillin allergy, namely a clinical reaction to an administered dose, the nature and timing of which are consistent with mast cell degranulation. Given that our tests for penicillin allergy are imperfect, patients undergoing evaluation for this allergy who have negative test results are challenged with amoxicillin and observed for a reaction.⁵ Almost all anaphylactic reactions to penicillin are to parenteral administration, i.e. such reactions to orally administered penicillin are rare.⁸ This allows us to use an oral challenge with relative safety. The observation period is typically one hour because reactions that occur beyond that would be much less likely to have an IgE-mediated mechanism.

While the sensitivity of tests for IgE to penicillin would certainly be higher than that calculated by Sousa-Pinto et al if applied only to more appropriate patients, their results still suggest that some allergic patients will be missed by existing testing (false negative). Similarly, although their calculated specificity is likely accurate and high, some percentage of patients with positive tests are not allergic (false positive). In either case, the gold standard drug challenge is necessary to determine whether or not they

are allergic. Instead of testing every patient with a history of “penicillin allergy”, it would seem appropriate for us to use our imperfect tests more judiciously. Performing tests for IgE antibodies in patients who developed non-immediate or non-urticarial rashes while taking penicillin seems inappropriate. Even in patients who may possibly have had IgE-mediated reactions to penicillin, the test may still not be indicated if the reaction was mild and in the distant past. Like all laboratory tests, we should ask ourselves what we are going to do with the result, either positive or negative. We should consider only performing the test in situations where the result will change our management. The vast majority of patients have histories that suggest a very low likelihood of current penicillin allergy, e.g., those with distant, mild or unknown reactions. Since our pre-test probability in such patients is very low, even combined with a positive test result, we would still think the patient is likely not penicillin-allergic, and it would be appropriate to proceed with the challenge anyway, i.e., the test result would not change our management and may be unnecessary. A much smaller number of patients have histories that suggest a high likelihood of current penicillin allergy, e.g., a history of a recent, immediate, anaphylactic reaction. Since our pre-test probability in such patients is very high, even combined with a negative test result, we would still think the patient is likely penicillin-allergic, and it would be appropriate to recommend continued avoidance or desensitization; again, the test result would not change our management and may be unnecessary. Testing may be most appropriate in patients with intermediate pre-test probabilities in whom testing may change management. Although additional studies in more carefully defined groups of patients may improve the predictive capabilities of testing, such studies will never be able to provide us with tests that have 100% positive or negative predictive values. Thus, clinicians will continue to need to consider factors such as those in Table II to determine whether or not an individual patient’s pre-test probability of penicillin allergy warrants testing that would change management. Our goal is to “delabel” the vast majority of patients labeled as penicillin-allergic who are not. Given that for most patients the pre-test probability of penicillin allergy is low,

many protocols now support the idea of “direct challenge” in such “low-risk” patients, i.e. skip the skin tests and go right to the oral challenge.^{4,9} Similarly, as above, a few patients will have such high pre-test probabilities that testing would not change our approach. Our tests for IgE to penicillin may best be used in those patients with intermediate pre-test probabilities in whom the results would be most likely change our management.

1. Sousa-Pinto B, Tarrio I, Blumenthal KG, Araújo L, Azevedo LF, Delgado L, et al. Accuracy of penicillin allergy diagnostic tests: A systematic review and meta-analysis. *Journal of Allergy and Clinical Immunology*.
2. Macy E, Goldberg B, Poon KY. Use of commercial anti-penicillin IgE fluorometric enzyme immunoassays to diagnose penicillin allergy. *Ann Allergy Asthma Immunol* 2010; 105:136-41.
3. 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.e1.
4. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. *JAMA* 2019; 321:188-99.
5. Macy E, Ngor EW. Safely Diagnosing Clinically Significant Penicillin Allergy Using Only Penicilloyl-Poly-Lysine, Penicillin, and Oral Amoxicillin. *Journal of Allergy and Clinical Immunology: In Practice* 2013; 1:258-63.
6. Caubet JC, Kaiser L, Lemaitre B, Fellay B, Gervais A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *Journal of Allergy and Clinical Immunology* 2011; 127:218-22.
7. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin “allergy” in hospitalized patients: A cohort study. *The Journal of allergy and clinical immunology* 2014; 133:790-6.
8. Aberer W, Macy E. Moving Toward Optimizing Testing for Penicillin Allergy. *J Allergy Clin Immunol Pract* 2017; 5:684-5.
9. Tucker MH, Lomas CM, Ramchandrar N, Waldram JD. Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy in a cohort of Marine recruits. *J Allergy Clin Immunol Pract* 2017; 5:813-5.

Table I. Calculation of sensitivity, specificity, positive predictive value and negative predictive value.

Disease	
Present	Absent

Test	Positive	A	C
Result	Negative	B	D

A = true positives

B = false negatives

C = false positives

D = true negatives

Sensitivity = percentage with disease who have a positive test result ($A/A+B$)

Specificity = percentage without disease who have a negative test ($D/C+D$)

Positive predictive value = percentage with positive test who have disease ($A/A+C$)

Negative predictive value = percentage with negative test who do not have disease ($D/B+D$)

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198 Table II. Factors that increase the pre-test probability that a patient labeled as penicillin-allergic is
199 currently at risk for an immediate hypersensitivity reaction to penicillin

- 200 • Known administration prior to the course related to the suspect reaction
- 201 • Reaction within one hour after first dose of subsequent course
- 202 • No known tolerance of administration subsequent to the suspect reaction
- 203 • Parenteral administration
- 204 • Recent reaction
- 205 • Reaction consisting of hives with or without some combination of respiratory, cardiovascular or
- 206 gastrointestinal symptoms

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