

Penicillin Skin Testing: A Major Role for the Minor Determinant and Amoxicillin?



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In patients with a history of type 1 hypersensitivity reactions to penicillin, it has been recognized since the 1960s that allergic reactivity can be detected by skin testing with major and minor determinants.¹ In this issue of the *Journal of Allergy and Clinical Immunology: In Practice*, Voelker et al² add to this body of literature, demonstrating that penicillin skin test (PST) positivity is decreasing over time, whereas PST positivity to penicilloate and amoxicillin is increasing. There are several key publications and issues to address in light of these new data and the current status of (1) difficulty obtaining the major determinant, (2) continued absence of commercially available aminopenicillin and minor determinants for testing, (3) existence of literature suggesting that a direct challenge is an option in low-risk individuals, and (4) increased awareness that allergist-immunologists can clarify the risk of beta-lactams allergy and safely delabel patients. We have a vital role in penicillin allergy delabeling.

In 1977, Green et al³ demonstrated the importance of benzyl penicilloyl-polylysine (BPL) with the findings of the Penicillin Study Group of the American Academy of Allergy (as it was known, then) from PST with penicillin G and BPL. Skin tests were positive in 19% of history-positive and 7% of history-negative patients.³ In those with an anaphylaxis history, PST was positive in 46% of patients, compared with urticaria at 17% and maculopapular rash at 7%, demonstrating the effect of pretest probability on results.³ In the 1992 NIAID study of 1539 hospitalized patients exploring the utility of BPL and 3 minor determinants, including penicillin G, at least 1 skin test was positive in 18% of 825 history-positive patients compared with 4% of 610 history-negative patients and 4% of history-indeterminate patients.⁴ PST were positive in 31% of patients whose histories were life-threatening.⁴ In this study, the BPL and/or penicillin G potassium identified 91% of PST positive patients.⁴ Just 16% of patients with

positive PST reacted to 1 or more minor determinants, which is a harsh reality, considering the current state of difficulty obtaining commercially available BPL. Voelker et al's² retrospective study design does not allow for such comparison between the historically reported reaction and PST result.

The question also remains whether to skin test with amoxicillin at 20 mg/mL and if all PST are negative, challenge with amoxicillin 250 mg orally.⁵ Voelker et al's² data demonstrate that the amoxicillin sensitivity is increasing based on skin testing, with 12% to 32% of PST positives (3 mm cutoff) being solely amoxicillin positive in their cohort. These data agree with those of a prospective study of 455 reported penicillin-allergic, nonhospitalized adults who were tested with BPL, 3 minor determinants, and amoxicillin.⁵ Sixty-three (13%) of patients were PST positive.⁵ Four of 63 (6.3%) patients were skin test positive exclusively to amoxicillin.⁵ Overall, the negative predictive value of the 5 skin tests and amoxicillin challenge was 97.9%.⁵ We believe that it remains to be determined whether to skin test with amoxicillin or to identify such amoxicillin-only reactors during the post-PST challenge with amoxicillin.

Adkinson Jr. et al⁶ have published an encyclopedic review of the literature since 1961 to assess the relevance of testing with minor determinants. In studies published from 1969 to 2017, skin testing with the major determinant and at least 2 minor determinants identified positive test(s) in 17.4% of patients, negative in 81.6% of patients, and equivocal in 1%.⁶ Stated differently, across all studies and decades, approximately 1 of 6 patients reporting penicillin allergy have evidence of anti-penicillin major and/or minor determinant IgE antibodies. They identified 3 studies that included skin testing with BPL, 3 minor determinants, and amoxicillin. In skin test positive patients, from 12% to 40% patients reacted solely to BPL, and 23% to 28% patients were positive exclusively to 1, 2, or 3 minor determinants.⁶ Between 2% and 8% of patients reacted only to amoxicillin.⁶ The most recent data provided by Voelker et al² demonstrate that among the different cohorts using the 3 mm cutoff, 18% to 34% were positive only to BPL, 11% to 31% were positive only to penicillin G potassium, and 8% to 27% were positive only to penicilloate. Given the available data showing that some patients are solely skin test positive to penicilloate and penicillin G potassium, it remains a serious issue that there is no commercially available source of minor determinants.

There is certainly a range of positive PST rates cited in the literature.^{2,5-7} The Solensky study above reports a rate of PST positivity at 13%, when others,⁷ including Voelker et al,² have reported considerably lower rates. In the Macy study,⁷ the authors included penicillin-allergic patients from the medical record diagnoses, which included patients with a broader range of symptoms,⁷ whereas Voelker et al's data do not report historical reaction data.² These data show how pretest probability based on the characteristics of the reaction affects the results from PST.

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There remains the question of whether patients with a low-risk penicillin reaction history are better served by a direct challenge without contemporaneous PST. A 2019 randomized study by Mustafa et al⁸ comparing PST (using penicillin G potassium and BPL followed by a dose of amoxicillin) with a 2-step direct challenge to amoxicillin demonstrated that PST may “overcall” penicillin allergy as compared with a direct challenge. In patients with a cutaneous-only reaction 10 or more years ago, 10 of 80 (12.5%) patients had positive PST, whereas only 3 of 79 (3.8%) patients had a positive direct challenge, with minor reactions.⁸ If the goal is to delabel as many patients as possible, using a direct challenge in low-risk individuals may limit false-positive testing while expanding capabilities to delabel by eliminating logistics associated with PST.

Voelker et al² demonstrate that although PST positivity rates are falling, the rates of minor determinant and amoxicillin positivity are rising, and BPL remains an important component of PST.² The data presented in this article, and others before it, continue to support that all components of PST should be available to allergist-immunologists. If all tools are available, it is our job as allergist-immunologists to decide when to use them based on our knowledge and experience to optimize patient care and antibiotic stewardship.

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