
The skin prick test: “more than meets the eye”

Rapid detection of allergen specific IgE is an essential tool in the clinical practice of allergy. Remarkably, the skin test has stood the test of time as the most widely used diagnostic test in allergy. In 1865, Dr. Charles Harrison Blackley performed the first skin test as part of an experiment to demonstrate that pollen particles are responsible for hay fever. Blackley, who had allergic rhinitis, applied pollen grains to a preabraded area on his forearm and, within minutes, noted itching and swelling at the test site.¹ The allergen scratch test evolved and during the first half of the 20th century was used by most allergy practitioners.

Since the 1960s, the modified skin prick test has largely replaced the less sensitive scratch test.² Despite its widespread adoption as the premier method used in clinical practice, many characteristics of the skin prick or puncture test are poorly defined. For example, a variety of needles and devices have been introduced. However, it was not until 1989 that Nelson et al³ and Adinoff et al⁴ performed comparative studies examining relative performance of different commercial skin test devices. In these studies, great variability existed between multitest devices and puncture needles, with a high number of false-positive test results encountered with the multitest device. It is concerning that a standard protocol for skin prick testing has yet to be universally adopted. Arcane systems are still being used to grade skin prick test wheal-and-flare responses (ie, grade 1 to 4+), which greatly impedes communications of results between different clinics. The latter dilemma may be resolved once allergists adopt recently introduced standardized skin test reporting forms, which mandate recording wheal and flare diameters along with detailed descriptions of sources and allergenic potencies of test antigens.

In clinical practice, it is broadly assumed that negative skin prick or intradermal test results can be relied on to exclude clinical allergy to specific allergens among patients who present with positive histories. Skin puncture testing has already been shown to possess excellent negative predictive value (NPV) for excluding allergy to natural rubber latex and chymopapain.^{5,6} Wood et al⁷ defined performance characteristics of skin prick test and intradermal methods with a standardized cat allergen in a well designed study of 120 patients who underwent controlled exposure to a live cat in an enclosed room. A positive skin prick test result was defined as a wheal diameter of at least 3 mm greater than the negative control. When a positive cat challenge was defined by increased upper respiratory tract symptoms after exposure, the positive predictive value (PPV) and NPV were 90% and 87%, respectively.

In this issue of *Annals*, Zarei et al⁸ evaluate prick testing with standardized cat pelt extract antigen that was performed with a Greer Dermapik device (Greer Laboratories, Lenoir, NC) by analyzing receiver operator characteristics (ROCs) in 45 patients referred for allergic evaluations. The authors first examined the predictive value of the traditional 3-mm wheal diameter cutoff used to define a positive test result. When postchallenge nasal symptom scores were used as the gold standard, the 3-mm cutoff value provided both excellent sensitivity (100%) and NPV (100%) and a PPV of 90%, but predictably at the expense of low specificity (74%). The 3-mm wheal diameter cutoff, however, did not perform nearly as well when other diagnostic standards were examined, with the exception of postallergen doubling in prostaglandin D₂ (PGD₂) measured in nasal lavage (sensitivity, 100%; NPV, 100%), which was comparable to the postchallenge symptoms score.

The authors then used ROC analyses to determine wheal size cutoff values that yielded optimal sensitivity, specificity, and predictive values when validated against one or a combination of diagnostic standards (ie, medical history, symptom scores after nasal allergen challenge, and nasal lavage mediators, eg, tryptase and PGD₂ levels) after intranasal allergen challenge. For the most part, wheal diameters between 5.5 and 6.0 mm yielded less than optimal sensitivity or NPV compared with the 3-mm cutoff based on most of the individual diagnostic standards. However, the latter cutoffs were associated with PPVs between 89% and 96%, indicating the prick test with wheal size of approximately 6 mm predicted clinical sensitivity with a higher degree of certainty. Based on ROC analysis, a wheal size of 6 mm yielded the best overall profile in terms of test efficiency, NPV, PPV, and sensitivity when an increase in PGD₂ measured in lavage after challenge was used as the diagnostic gold standard. Although this result is intriguing, it must be interpreted cautiously, in that other investigators have been unable to consistently measure increases in PGD₂ after nasal allergen challenge, indicating that this marker requires further validation.⁹

These results, although interesting, should be interpreted with caution. A potential weakness of this study is the small number of patients studied, and it is unclear if the study is powered adequately. Thus, a larger multicenter study may be required to confirm these data. Other limitations, which the authors correctly identify, are that these results cannot be generalized to different skin test devices or different allergens. Finally, one of the authors' final conclusions that a 3-mm cutoff for the cat allergen skin prick test will overestimate the presence of allergy is correct. However, their final

conclusion that the 6-mm diameter cutoff is more realistic for excluding clinically relevant allergy to cat dander is not entirely accurate. Whereas the 6-mm cutoff clearly provides the highest PPV, which is useful in confirming allergic rhinitis, the data clearly show that the 3-mm cutoff provides the highest NPV (100%) needed to rule out cat-induced nasal sensitivity as defined by the diagnostic symptom score standard (and the PGD₂ standard) used in this study. It is noteworthy that similar results were obtained in a large study of children undergoing evaluation for peanut allergy. In this study, a 3-mm cutoff for the skin prick test yielded 100% NPV for predicting a negative response to double-blind food challenges with peanut, but a 16-mm cutoff was required to absolutely predict a positive challenge test result.¹⁰

Thus, this investigation reported by Zarei et al in this issue of *Annals* should serve as a prototype for future studies examining performance and test characteristics of standardized allergens and skin-testing devices. Use of common procedures, test devices, and antigens combined with clinical validation obtained from challenge studies is likely to increase the overall diagnostic utility of our old friend, the skin prick test.

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