

Skin testing in allergy

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ABSTRACT

Skin tests are used in addition to a directed history and physical examination to exclude or confirm immunoglobulin E (IgE) mediated diseases, such as allergic rhinitis, asthma, and anaphylaxis, to aeroallergens, foods, insect venoms, and certain drugs. There are two types of skin testing used in clinical practice: percutaneous testing (prick or puncture) and intracutaneous testing (intradermal). Prick testing involves introducing a needle into the upper layers of the skin through a drop of allergen extract that has been placed on the skin and gently lifting the epidermis up. Various devices are available for prick testing. Intracutaneous (intradermal) testing involves injecting a small amount of allergen into the dermis. The release of preformed histamine from mast cells causes increased vascular permeability via smooth-muscle contraction and development of a wheal; inflammatory mediators initiate a neural reflex, which causes vasodilatation, which leads to erythema (the flare). Prick testing methods are the initial technique for detecting the presence of IgE. These may correlate better with clinical sensitivity and are more specific but less sensitive than intradermal testing. Sites of skin testing include the back and the volar aspect of the arm. By skin testing on the arm, the patient can witness the emergence and often sense the pruritus of the skin test reaction. Because more patients are sensitized (have IgE antibodies and positive skin test reactions) than have corresponding symptoms, the diagnosis of allergy can be made only by correlating skin testing results with the presence of clinical symptoms.

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Skin tests are used in addition to a directed history and physical examination to exclude or confirm immunoglobulin E (IgE) mediated sensitivity to aeroallergens, foods, insect venoms, and certain drugs.¹ Skin testing attempts to detect the presence of allergen-specific IgE bound to mast cells by eliciting mast cell degranulation to the specific allergen tested. This may help confirm the suspicion that a patient's symptoms are related to immediate hypersensitivity to the allergen of concern and evaluates if the allergen(s) is contributing to diseases, such as allergic rhinitis; allergic conjunctivitis; asthma; and allergic reactions, including anaphylaxis. Two types of skin testing are widely used in clinical practice, which include percutaneous testing (prick or puncture) and intracutaneous testing (intradermal). Prick testing involves introducing a needle at a 45° or 60° angle into the upper layers of the skin through a drop of allergen extract that has been placed on the skin and gently lifting the epidermis up, which allows the extract to penetrate through the break in the skin. Puncture testing differs by using the skin device at a 90° angle. Several percutaneous skin testing implements are available commercially. Intracutaneous (in-

tradermal) testing involves injecting a small amount of allergen, 0.01–0.05 mL, into the dermis.¹

Prick testing methods are the initial technique for detecting the presence of cutaneous IgE. These may correlate better with clinical sensitivity and are more specific but less sensitive than intradermal testing.¹ Previous studies demonstrated that intradermal testing carries a slightly higher risk of a systemic reaction, 0.05% versus 0.03% for a prick test.² More recent studies indicate that these rates may be slightly higher, but the definition of systemic reaction and methodology may differ among studies, so this should be considered.^{3,4} A large single-center study evaluated 31,000 patients who had prick testing and found an incidence of 0.077% for systemic reactions with food being the most common culprit.³ Another study that evaluated the rate of reactions to the prick test and the intradermal test found 0.04% versus 3.2%, respectively.⁴ Seven fatalities were attributed to skin testing.^{5–7} Five of these were attributed to intradermal testing in patients with preexisting asthma and a lack of preceding prick testing.⁶ One fatality was attributed to prick testing, which, to our knowledge, is the only one ever reported as a death due to prick testing; this patient received > 90 prick tests to food allergens at one time and had preexisting asthma.⁷ Based on these studies, which showed an increased risk for systemic reaction, including fatality, testing should begin with prick testing and then proceed to intradermal testing if the prick testing result is negative and there remains a high degree of clinical suspicion. Intradermal testing has not proven to be of benefit in the diagnosis of food allergy, therefore, the risk to patients is not justified. A physician

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Table 1 Pharmacokinetics of first- and second-generation H₁ antihistamines

H ₁ Antihistamine	Elimination Half-Life, hr	Recommended Discontinuation (before the day of the skin test)*
First generation		
Diphenhydramine	2–8	24 hr
Hydroxyzine	20	24–48 hr
Chlorpheniramine	20–24	24 hr
Doxepin (of active metabolite)	28–52	7 days
Second generation		
Cetirizine	8.3	3–5 days
Levocetirizine	8–9	3–5 days
Fexofenadine	14	3–5 days
Loratadine (of active metabolite)	28	3–5 days

*For some patients, skin testing remains accurate, even if the patient has not discontinued H₁ antihistamines and thus can be performed and interpreted confidently; however, for research studies, the investigator must adhere to the protocol that specifies times for discontinuation before testing.

should always be available while patients are being tested to give emergency treatment if necessary, and patients should be observed for at least 20 minutes after testing is completed.

H₁ antihistamines should be held for a minimum of 24–72 hours before skin testing based on the specific pharmacokinetics of each drug. Refer to Table 1 for the elimination half-lives of commonly prescribed H₁ antihistamine medications. Other drugs with antihistaminic properties, such as tricyclic antidepressants; benzodiazepines; certain atypical antidepressants, including quetiapine and mirtazapine, may affect test results and should be held 5–7 days before testing, if possible.⁸ Other antidepressants, such as bupropion, eszopiclone, trazodone, and zolpidem, have shown less effect on histamine response but may have clinical significance, such that stopping up to 3 days earlier should be considered.

Although the 2008 Updated Practice Parameters for Allergy Diagnostic Testing¹ report that H₂ blockers may cause mild suppression and recommend withholding for 24 hours, a study by Shah *et al.*⁸ showed that H₂ blockers alone did not affect histamine response in their cohort, unless taken with other antihistaminic medications. Selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, proton-pump inhibitors, and leukotriene antagonists do not significantly affect testing results and do not need to be held. The β_2 -adrenergic agonists, decongestants, theophylline, and cromolyn will not affect skin testing.⁹ Short courses of oral corticosteroids will not affect testing results; however, topical corticosteroids may decrease or inhibit skin reactivity. Such topical agents should not be applied to the test site for at least 1 week before testing. Patients who are receiving sub-

cutaneous immunotherapy may have decreased skin reactivity to the allergens being injected.

Sites of skin testing include the back and the volar aspect of the arm. Although the back is more reactive, the significance of this difference is minimal.⁹ Use of the arm as the test site has the advantage of being able to place a tourniquet above the site should a systemic reaction occur and for educational purposes for the patient, who witnesses the results. The site chosen for testing should be clear of dermatitis or severe dermatographism. The site chosen is cleaned with alcohol. Allergen extract(s), a positive control (histamine), and a negative control (saline solution or allergen diluent) are placed a minimum of 2.5 cm apart and should avoid areas 5 cm from the wrist and 3 cm from the antecubital fossa.¹ One source of skin testing error is in placing the sites too close together, which results in spread of one allergen extract to another site, and an inability to accurately record the extent of erythema from two positive sites close together. False-negative or false positive reactions may occur with insufficient or excessive skin penetration. If prick testing reveals minimal or equivocal reaction to an allergen, one might choose to proceed with intradermal testing with a 100- to 1000- fold dilution of allergen extract (with exception being food for which intradermals are contraindicated).

Standardized extracts should be used to facilitate comparisons between clinicians. At this time, available standardized extracts include cat hair, cat pelt, mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), short ragweed, grass (Bermuda, Kentucky bluegrass, perennial rye, orchard, timothy, meadow fescue, red top, sweet vernal), and Hymenoptera venoms (honeybee, yellow hornet, white-faced hornet, yellow jacket, paper wasp).¹⁰ Note that use of standard-

Table 2 Grading system for skin testing

Grade	Skin Appearance
0	No reaction
1	Erythema < 20-mm diameter
2	Erythema > 20 mm; wheal < 3 mm
3	Wheal > 3 mm, with surrounding erythema
4	Wheal with pseudopods and erythema

ized doses does not always confer equal potency. Nonstandardized extracts are available for foods, tree and weed pollens, animal danders (except cat), pests (including cockroach and mice), and fungal extracts. Extracts should be refrigerated at 4°C. They should contain glycerin to decrease the loss of potency that occurs with time.¹

Testing should be graded within 15–20 minutes.¹ Several different grading systems exist, but none are standardized. One example is shown in Table 2. The mean diameter of the wheal and the erythema are recorded with the presence or absence of pseudopodia. Physicians should quantitate the actual size on the data sheet and not solely a grade, so that results might be better shared among practitioners and limit interphysician variability in interpretation. Clinicians also are urged to use a comprehensive data sheet and record the brand of extract, dilutions used, device chosen, mean diameters of the wheal and erythema, and specific grading system key.

Interpretation of skin tests may be more difficult in patients with dermatographism. False-positive reactions with dermatographism can be distinguished from true-positive reactions that are secondary to IgE because the former fade more quickly. Special attention should be paid to the difference between the sizes of the reactions from the allergen extracts compared with the negative control, with a positive reaction considered to be a ≥ 3 -mm wheal compared with the negative control, and associated with flare. No significant differences in skin test reactivity have been noted for gender; however, the phase of the menstrual cycle in females may be associated with an increased histamine response.⁹ Infants and the elderly, however, may have decreased skin reactivity and thus a smaller wheal size.⁹ One study showed a positive correlation with body mass index and histamine response.⁹ In addition, darkly pigmented skin can have larger histamine-induced wheals compared with light skin; however, erythematous flare may be more difficult to appreciate.¹

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Skin Test Wheal and Flare Mechanism

- Introduction of the antigen into the skin causes local mast cell activation and degranulation *via* cross-link-

ing of preformed, antigen-specific, membrane-bound IgE.

- The release of preformed inflammatory mediators, especially histamine, from mast cells causes increased vascular permeability and extravasation of fluid *via* smooth-muscle contraction and development of a wheal; inflammatory mediators initiate neural reflex vasodilation, which leads to development of flare.

CLINICAL PEARLS

- Skin testing is a practical, reliable, and a well-tolerated method of establishing IgE-mediated disease.
- Interpretation of skin testing should be done by an experienced practitioner in the presence of positive and negative controls, and may be confounded by dermatographism or antihistamine use.
- The presence of a positive skin test result documents the presence of allergen-specific IgE antibody (*i.e.*, sensitization) but not allergy. The diagnosis of allergy can be made only by correlating skin testing results with the presence of clinical symptoms.

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