Skin testing in allergy diagnosis

by Dr J. Oppenheimer and Dr H. S. Nelson

Skin testing remains the central test to confirm an allergic response. It is minimally invasive and when performed correctly, has good reproducibility. Results are easily quantifiable and correlate well with end organ challenge. It is imperative however that technicians performing skin tests as well as clinicians ordering/interpreting test results understand the characteristics of the specific tests they are administering, and express test results in a manner that allows easy interpretation by another physician. The failure to consider these issues may be responsible for some of the inaccuracies associated with allergy skin testing.

Credit for the first skin testing goes to Charles H. Blackley, who in 1865 abraded a quarter inch area of his skin with a lancet and then applied grass pollen grains with a piece of wet lint, and covered the scarified area with an occlusive bandage. This resulted in intense itching and a very large cutaneous response [1].

Even today skin testing remains the central test for confirming an allergic response. This is not surprising, as such tests are minimally invasive and when performed correctly have good reproducibility. Skin testing is easily quantifiable and can allow the evaluation of multiple allergens during one testing session. Good correlation has been demonstrated with results of nasal challenge [2], as well as bronchial challenge when allowance is made for non-specific airway responsiveness [3]. It is important however that technicians performing skin tests as well as clinicians ordering/interpreting test results are aware of the factors which can affect the results. These include type of skin test, device used, placement of tests (location and adjacent testing), the particular extracts being used and the potential problem of medication taken that may suppress skin test response. These issues have been reviewed elsewhere in greater detail [4-6]. It is of paramount importance that clinicians consider the positive and negative predictive value of the tests performed and always rely upon tests as an adjunct to patient history and physical examination when making the diagnosis of allergic disease. Finally allergy patients for various reasons may change their physician, and it is important that prior allergy testing records be interpretable by the receiving physician. Several of these issues will be reviewed in greater detail in this article.

Methods of skin testing

Currently skin testing is performed via either the prick/puncture (percutaneous) or intradermal (intracutaneous) technique. Although in the past the scratch method was also used, its use has been abandoned due to greater discomfort for the patient, poorer reproducibility, and the possibility of leaving multiple linear depigmented areas for some time after the test [7].

Intradermal testing is far more sensitive than prick/puncture testing and thus the extract for prick/puncture testing must be at least 1000-fold more concentrated to achieve a similar level of sensitivity. Although direct comparisons indicate that intradermal testing is more reproducible than percutaneous testing, there are many factors which favour the percutaneous test as the routine procedure for allergy testing [7]. These include economy of time, as well as patient comfort and safety. In addition percutaneous testing allows use of the extract in 50% glycerin and thus greater extract stability. Intradermal testing cannot use this diluent, as it results in an irritant response/false positive response [8]. Of greatest importance however, is that studies have demonstrated that percutaneous response correlates much better with clinical allergy.

Clinical utility of intracutaneous versus percutaneous method

Although the intracutaneous test, at the allergen concentration at which it is customarily performed, is more sensitive, it is questionable whether this increased sensitivity is clinically necessary or simply increases the chance of a false positive response. Even the skin-prick test, performed with potent extracts, results in a positive response in many subjects who do not have a personal, or even a family history of allergy [10]. A number of studies have addressed the clinical utility of intracutaneous testing and deserve review [8, 10, 11].

Two recent studies, which examined the intracutaneous test as a predictor of symptoms on natural exposure to the allergen, deserve further comment [10, 11]. In the first study, four groups were compared. Three of the groups had a history of seasonal allergic rhinitis during the grass season: one group had a positive skin-prick test to timothy grass, one group had a negative skin-prick but a positive intracutaneous test to timothy grass, and one group had both skin-prick and intracutaneous tests negative for timothy grass. The fourth group was a non-allergic control. On the basis of nasal challenge with timothy grass pollen, allergic reactions were present in 68 percent of those with positive skin-prick tests to timothy grass and none of the non-allergic controls. In both the groups with negative skin-prick tests to timothy grass, 11 percent were positive whether intracutaneous skin tests to timothy grass were positive or negative. Subjects were then followed though the grass pollen season. Their symptom scores, recorded in a diary, were examined for a correlation with grass pollen counts. A positive correlation was present in 64 percent of those with positive skin-prick tests and none of the non-allergic controls. In the seasonally symptomatic skin-prick test negative groups, positive correlation of symptoms and pollen count was present in 22 percent of those with a positive intracutaneous test and 21 percent of those with a negative intracutaneous test to timothy grass. Both criteria for allergy to timothy grass - a positive nasal challenge and a correlation between symptoms and grass pollen counts - were met in 49% of those with positive skin-prick tests, but in none in the other three groups. Thus under the conditions of this study a positive intracutaneous skin response to timothy grass accompanied by a negative skin-prick test did not indicate clinically significant sensitivity to timothy grass [10].

In the second study patients were challenged with exposure to cat allergen for one hour. Both positive skin-prick tests and RASTs to cat were highly predictive of the development of symptoms on exposure to cat. Subjects with a negative skin-prick test were just as likely to have a positive challenge result if they had a negative intracutaneous skin test (31%) as if they had a positive intracutaneous skin test (24%). The authors concluded that, at least with regard to cat allergy, these results strongly suggest that
major therapeutic decisions, such as environmental control or immunotherapy, should never be based on a positive intracutaneous skin test result alone [11].

Both of these studies were performed in adults and both relied upon skin testing with potent allergens (timothy grass and cat). Application of these results to other less potent allergens (ie. dog) and to younger aged patients (especially infants) requires clinical judgment regarding the action which should be taken as a result of the information gleaned.

Skin testing devices

While intracutaneous skin tests are only performed using a hypodermic syringe and needle, percutaneous tests may be performed with a variety of devices [12,13,14]. Comparisons of percutaneous devices have been reviewed elsewhere in greater detail [6,9,12-19]. It is worth mentioning however that some devices have a single stylus with a single or several points, while other devices have multiple heads and allow up to eight tests to be accomplished with one application. The devices for percutaneous testing vary in the degree of trauma that they impart to the skin. They thus differ in the size of positive reactions as well as in the likelihood of producing a reaction at the site of the negative control. They therefore require different criteria to judge what constitutes a positive reaction [Table 1].

Allergy skin testing has recently come under the scrutiny of the USA Department of Labor’s, Occupational Safety and Health Administration (OSHA). In 1995 they alerted their field personnel to the possible health and safety risks that may arise with the practice of using one device per person and wiping the device between tests [20]. OSHA considered this practice to have the potential for a blood borne pathogen exposure incident, should the technician accidently prick himself or herself with the device while wiping it. The implications of this notice have led many allergists to abandon the use of solid bore needles for percutaneous testing, resulting in greater use of the newer devices which are disposed of after each application of a test.

Expressing and scoring of results of skin testing

Skin test results are often only reported by clinicians in semi-quantitative terms [Table 2]. They may record results only as positive or negative, or express them on a 0 to 4+ scale without any indication of what size reactions these numbers represent [24]. It is important however that prior allergy testing records be interpretable should the relevant physician change. At the very least a record of skin testing should give sufficient information to allow another physician to interpret the results and avoid the need to repeat skin testing. Standardised forms for this purpose have been developed and are available through the American Academy of Allergy Asthma and Immunology website (http://www.aaaai.org/).

Although measurement of the area of the wheal and erythema are the most reliable, measurements of longest diameter correlate very well with area with r values greater than 0.9 [25]. The importance of performing such measurements is exemplified by a recent study by

Table 1. Size of wheals that are larger than 99 percent of the wheals with saline using the same device, on subjects’ back, performed by the same operator [12-14]. HS = Hollister-Stier, Greer = Greer laboratories, Lincoln = Lincoln Diagnostics, ALK = ALK America, ALO = Allergy Labs of Ohio.

<table>
<thead>
<tr>
<th>Device</th>
<th>99th quantile of reactions at the negative control sites</th>
<th>Device</th>
<th>99th quantile of reactions at the negative control sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quintess (HS) puncture</td>
<td>0 mm</td>
<td>CutTip (Lincoln) test</td>
<td>9.5 mm</td>
</tr>
<tr>
<td>Smallbox needle (HS) prick</td>
<td>0 mm</td>
<td>BiFurcated needle (ALK) prick</td>
<td>4.0 mm</td>
</tr>
<tr>
<td>DuoTip (Lincoln) prick</td>
<td>1.5 mm</td>
<td>MultiTest (Lincoln) Puncture</td>
<td>4.0 mm</td>
</tr>
<tr>
<td>Lancet (HS) puncture</td>
<td>2.0 mm</td>
<td>BiFurcated needle (ALK) puncture</td>
<td>4.5 mm</td>
</tr>
<tr>
<td>Lancet (ALK) Puncture</td>
<td>3.0 mm</td>
<td>Quick Test (Pantex)</td>
<td>4.0 mm</td>
</tr>
<tr>
<td>Dermarick II (Biomedical)</td>
<td>0 mm</td>
<td>Greer Track (Greer)</td>
<td>3.6 mm</td>
</tr>
</tbody>
</table>

Table 2. Semi-quantitative reporting of skin test results [38].

<table>
<thead>
<tr>
<th>Criteria to read Prick/Puncture skin tests</th>
<th>Device</th>
<th>99th quantile of reactions at the negative control sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>0</td>
<td>No reaction or no different from control</td>
</tr>
<tr>
<td>One plus</td>
<td>+</td>
<td>Erythema &lt; a nickel in diameter</td>
</tr>
<tr>
<td>Two plus</td>
<td>++</td>
<td>Erythema &gt; a nickel in diameter</td>
</tr>
<tr>
<td>Three plus</td>
<td>+++</td>
<td>Wheal with surrounding erythema</td>
</tr>
<tr>
<td>Four plus</td>
<td>++++</td>
<td>Wheal with pseudopods and surrounding erythema</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Criteria to read intracutaneous tests when control ≥ 2 mm</th>
<th>Device</th>
<th>99th quantile of reactions at the negative control sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>0</td>
<td>No different from control</td>
</tr>
<tr>
<td>One plus</td>
<td>+</td>
<td>Wheal 1/2 to 3 times control or definite erythema &gt; a nickel in size</td>
</tr>
<tr>
<td>Two plus</td>
<td>++</td>
<td>Wheal 3-5 times control</td>
</tr>
<tr>
<td>Three plus</td>
<td>+++</td>
<td>Wheal &gt; 5 times control</td>
</tr>
<tr>
<td>Four plus</td>
<td>++++</td>
<td>Wheal with pseudopods</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Criteria to read intracutaneous tests when control &lt; 2 mm</th>
<th>Device</th>
<th>99th quantile of reactions at the negative control sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>0</td>
<td>No difference from control</td>
</tr>
<tr>
<td>One plus</td>
<td>+</td>
<td>3-4 mm wheal with erythema or erythema &gt; a nickel in size</td>
</tr>
<tr>
<td>Two plus</td>
<td>++</td>
<td>4-8 mm wheal without pseudopods</td>
</tr>
<tr>
<td>Three plus</td>
<td>+++</td>
<td>&gt; 8 mm wheal without pseudopods</td>
</tr>
<tr>
<td>Four plus</td>
<td>++++</td>
<td>Wheal with pseudopods and erythema</td>
</tr>
</tbody>
</table>

Table 3. Comparison of criteria for a positive prick skin test to dog.

Suggested proficiency testing/quality assurance technique for skin prick testing

- Using desired skin test device, perform skin testing with positive (Histamine 1 to Histamine 10) and negative controls (Saline 1 to Saline 10) in an alternate pattern on a subjects back
- Record histamine results at 8 minutes by outlining wheals with a felt tip pen and transferring results with transparent tape to a blank sheet of paper
- Record saline results at 15 minutes by outlining wheal and flares with a felt tip pen and transferring results with transparent tape to a blank sheet of paper
- Calculate the mean diameter X=(D+d)/2; D=largest diameter and d=perpendicular diameter at midpoint of D
- Histamine: Calculate the mean and standard deviations of each mean wheal diameter
  - Determine coefficient of variation = standard deviation/mean
  - Quality standard should be less than 30%

Saline: All negative controls should be <3mm wheals and <10mm flares

Table 4. Comparison of criteria for a positive intracutaneous skin test to dog.
Various investigators have suggested different means of determining a positive skin test response. To assess the reliability of different means of interpreting results of skin-prick testing, Vanto and colleagues studied a group of patients sensitive to dogs [30]. A determination of sensitivity to dog was made in 202 children based on a composite score from patient history, RAST, and bronchial or conjunctival allergen challenges. The results of three common means of expressing results are shown in Table 3. Although the overall efficacy of the histamine reference method (in which allergy skin test response is compared to a histamine control, with a positive response considered > histamine control) was greatest in this study, maximal sensitivity was achieved when using a cutoff of > 3 mm wheal. Thus if a clinician wishes to maximise sensitivity the latter criterion would be most useful [27].

**Proficiency testing**

Like all other laboratory tests, it is imperative that quality assurance standards be met to ensure that testing technique is accurate. To confirm such standards, it is recommended that all technicians performing skin testing undergo evaluation of their technique [28]. The USA National Committee for Clinical Laboratory Standards recommends such quality control procedures for daily performance of in vitro allergy testing, with a recommended coefficient of variation of less than 20% following repeated skin test control applications [30] and the recent Childhood Asthma Management Programme study required that a coefficient of variation of less than 30% be attained to confirm proficiency in skin testing. A suggested protocol for quality assurance testing/proficiency testing for skin testing technicians is included in the insert above.

**Conclusion**

Allergy skin testing remains an essential tool in the evaluation of allergic patients. To improve upon the predictive values of allergy skin testing, there are several controllable variables that when addressed can result in more reliable skin test results. It is also imperative that allergists document results appropriately, as well as ensure quality standards with proficiency testing so that others can easily interpret results. In so doing, healthcare workers can improve upon the most effective diagnostic tool available for the diagnosis of allergic disease.

**References**

27. Skin tests used in type 1 allergy testing Position paper. Sub-Committee on skin tests of the European Academy of Allergology and Clinical Immunology Allergy 1989; 44: 1-59.

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