

Allergen Prick-Puncture Skin Testing in the Elderly

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Abstract

Many older patients present with rhinitis, conjunctivitis, asthma or itching that the patient attributes to allergies. Yet physicians often dismiss allergy in the elderly as irrelevant. Testing elderly patients for allergies is sometimes challenging as changes in the skin may cause difficulty in applying skin tests, and the response of the skin may be difficult to measure.

The prick puncture skin test is the preferred method of immediate-type allergy testing, but careful examination of the skin prior to skin testing is important. If the area of skin where allergen skin tests are routinely placed is either atrophic or severely sun damaged, a sun-protected area should be sought. If no suitable area of skin can be identified, *in vitro* allergen testing should be considered.

Skin-test results must be interpreted with care in the elderly. Positive skin tests to an allergen must correlate with a history of exacerbation to the allergen. By identifying specific allergens to which the elderly patient is sensitive, avoidance measures or specific allergen vaccination can be recommended, improving the quality of life and decreasing the need for medications.

Allergy is an abnormal immune response to environmental agents resulting in adverse reactions, which may include anaphylaxis, rhinitis, conjunctivitis, asthma and eczema. The term atopy, as proposed by Coca and Cook in 1923, is used to describe a subgroup of clinical 'allergies' involving reaginic or skin-sensitising antibodies (IgE) that are subject to hereditary influences.^[1] Today, the terms allergy and atopy are often used interchangeably to describe immediate-type (IgE) allergy. Clinicians generally require the identification of specific IgE antibodies by either skin, *in vitro* or provocation testing before diagnosing allergies.

Many older patients present to physicians with rhinitis, conjunctivitis, asthma or itching that they attribute to allergies, yet have negative responses to allergy skin testing. The purpose of this review is to

summarise the current literature and ongoing studies to better understand the role of allergy in the elderly, especially as measured by the prick-puncture skin test (PPST) response.

1. History and Background of Allergy Skin Testing

Blackley, who was the first to perform allergy tests, described the application of pollen to the abraded skin to demonstrate allergy in 1873.^[2] Noon^[3] and Freeman^[4] described scratch tests in 1911 and they remained popular in the US until the 1960s. Mantoux^[5] introduced intradermal tests in 1908, which were later adapted for allergy testing by Cooke, offering the advantage of introducing more

allergen into the dermis. PPSTs were first described by Lewis and Grant in 1924.^[6]

All immediate-type allergy skin testing is based on allergens binding to specific IgE antibodies which are attached to mast cells, leading to the release of intracellular mediators, including histamine. The mediators result in the immediate formation of a wheal and flare (swelling and erythema), resembling the natural response to a mosquito bite. The wheal depends upon histamine binding to histamine receptors on the microvasculature, resulting in increased vessel permeability, while the flare is the result of neurogenic vasodilatation. This response is compared with a negative control (diluent only) and a positive control, usually a standard dose of histamine, applied in a similar manner. Levels of significance, relating to the extent of allergen sensitivity, have been ascribed to the diameter of the wheal and/or the flare and the ratio of the response to the histamine control.^[7] Allergy skin test response therefore reflects the presence of allergen antibodies bound to mast cells. Most mast cells in the skin are in close proximity to blood vessels and nerves. The number of mast cells in the skin may vary depending on the thickness, vascularity and location. Furthermore, some individuals have more mast cells than others.^[8]

A positive skin test to an allergen does not by itself demonstrate that the allergen is the cause of a particular clinical illness. A parable might be a positive response to a test for elephant allergy in a person who is not exposed to elephants. This positive test is not clinically relevant. This example is used to illustrate to patients that a positive test to an allergen, such as a pollen that is only present a few months a year or not found where the patient lives, is not the cause of their perennial symptoms. A positive test may also indicate sensitisation to an allergen at a level too low to cause symptoms, an exposure to an allergen in the past, or an allergen that is an irritant or contains impurities that are irritants. Sensitisation describes the existence of specific antibodies to a substance, as exemplified by a positive response to a skin test. This response consequently reflects sensitisation, but not clinical allergy. The

latter depends on individual factors that determine the 'target organ' of a sensitisation. Thus, an IgE-mediated sensitisation can be asymptomatic, or result in an allergic disease, where the possible clinical symptoms range from conjunctivitis, rhinitis, asthma, urticaria or anaphylactic shock upon allergen exposure.

The kind of individual clinical manifestation of a specific sensitisation, i.e. the 'allergy', is evident from history and can be confirmed by conjunctival, nasal, bronchial or oral challenge (provocation tests). Different threshold exposures may be required for sensitisation than for clinical allergy. For example, 2µg of house dust of *Dermatophagoides* group 1 allergen (*Der p1* and *Der f1*) may cause sensitisation, while 10µg of *Dermatophagoides* group 1 may be required to cause asthma symptoms.^[9] Therefore, an individual may have a positive skin test, i.e. be sensitised, but this allergen may not be present at a high enough level to cause symptoms or disease.

Food allergen skin testing results in false positive allergy tests more frequently than aeroallergen skin testing. Before concluding that a positive allergy skin test is clinically relevant, there must be either conclusive historical evidence that exposure to that allergen causes the symptoms present or a provocation test confirming the clinical sensitivity. There are numerous examples of individuals having positive PPST to foods, yet they can ingest the food with impunity. Allergy skin testing may also be negative when there is clear adverse response to a suspected allergen. Irritant responses to air borne particles or volatile organic compounds and food intolerance are examples.

2. Skin Testing Methods

Allergy skin tests may be categorised by the depth of application of the allergen. Epicutaneous allergy tests are placed on the skin surface. An example is the patch test, used for delayed hypersensitivity testing. Intracutaneous tests are performed by injecting the diagnostic allergen into the dermis via a needle to produce a bleb. It allows more allergen delivery, which for weak allergens or mini-

mal sensitivity may be advantageous, but it can lead to more non-specific and false positive tests. Intracutaneous skin tests are commonly called intradermal tests. They are used both for immediate- and delayed-hypersensitivity testing as well as for anergy testing and they are the primary testing method used for *Hymenoptera* or stinging insect hypersensitivity. Percutaneous tests involve placing the allergen beneath the most superficial layers of the skin where they may come in contact directly with mast cells. They are used for immediate-type allergy testing. Examples include scratch testing and PPSTs. This paper concentrates on PPSTs.

The quality and quantification of the strength of allergen included in extracts is paramount when discussing allergy skin testing. Prior to the 1980s there were no established international standards for allergen extracts. The US FDA developed bioequivalent allergy units, which are determined by the amount of allergen extract (diagnostic allergen) that will cause an erythematous response to an intradermal skin test equal to the sum of orthogonal diameters of 50mm in a panel of known allergic control individuals.^[10] However, the adults used are volunteers and do not include elderly individuals or children. Manufacturers standardise their allergen extracts using a variety of *in vitro* methods, which are adjusted to adequately reflect their *in vivo* potency. Without standardised allergen extracts, it is difficult to compare PPSTs to other methods of allergen testing or challenge responses in different age groups, or results between allergy groups.

2.1 Prick-Puncture Skin Tests (PPSTs)

When PPSTs were first used, fine-drawn glass tubing was employed to introduce allergen through the superficial epidermis.^[6] This was not very practical for routine use. When better devices became available in the 1970s, PPST became the preferred method of cutaneous testing in the US.

All prick-puncture methods involve either pricking a drop of a diagnostic allergen through the epidermis or placing the drop of allergen on a device and then puncturing the epidermis. The diagnostic allergen is delivered beneath the superficial layers of

the epidermis but not as deep as the dermis. There are several devices that have been used for PPSTs, including the bifurcated needle used for smallpox scarification, lancets designed for blood collecting, plastic or metal tines and needles imbedded in a plastic holder that limits the depth of the puncture. Squire,^[11] in 1950, estimated the volume of diagnostic allergen delivered by prick puncture to be 3×10^{-6} mL. In comparison, the estimated volume by intradermal injection to raise a minimal visual bleb, is approximately $1-5 \times 10^{-2}$ mL.^[11]

PPSTs must be interpreted carefully, as many factors can cause false negative or positive results. The allergen may not penetrate through thickened keratin, or it may be delivered to an avascular area. The quality of diagnostic allergens may vary with good responses to standardised extracts, but varied reactions to some mould and food allergens. Some diagnostic allergens may include irritants that can cause erythema.

PPSTs have been compared with nasal, bronchial and room allergen challenges and to *in vitro* allergen testing in several studies. Few studies have examined the differences between prick-puncture responses in the elderly and younger adults or children. There are studies that show good correlation between PPST positive results and positive nasal, bronchial and room air challenge in young adults, but no studies were found in a MEDLINE search in the older age group.^[12-14]

In the US it is common practice to define a positive test as a wheal diameter of 3mm or 5mm greater than the negative control. In Europe it is common practice to define a positive test as a diameter ≥ 0.7 mm of the histamine wheal.

The PPST is recommended by the Allergic Rhinitis and its Impact on Asthma (ARIA) workshop report which was conducted in collaboration with the WHO and published in 2001. This report is endorsed by over 50 national and international organisations. The ARIA report recommends the PPST as the preferred skin test for determining immediate-type allergy. They further conclude that there is a high degree of correlation between PPST results and both allergic symptoms and provocative

challenges. Each separate test should be placed at least 2cm apart.^[12]

2.1.1 Allergy Prevalence and Allergen Prick-Puncture Response in the General Population Compared with Older Adults

The National Health and Nutrition Examination Survey II (NHANES II) is the largest prick-puncture skin study reported. It includes 16 204 people from the non-institutionalised US population. The study was conducted at 64 sampling sites in the US between 1976 and 1980. All study participants had PPSTs to eight allergens. This was a general population study, i.e. individuals were not selected because of a history of atopy or asthma. Using the criteria of a mean erythema diameter of 10.5mm, approximately 30% of those aged 12–24 years had at least one positive skin test. This declined to 8% in the group aged 65–74 years.^[15] In a follow-up study to determine if allergen skin test reactivity is a predictor of mortality of the NHANES participants aged between 30 and 75 years (n = 8179), using wheal diameter ≥ 3 mm rather than erythema as in the initial report, 16.3% were positive for at least one of the eight allergens. The study participants were divided into three groups: ages 30–44 (n = 2328, 22.3% allergic), 45–59 (n = 1941, 16.4%), and 60–75 (n = 3910, 12.6%) years.^[16] This suggests a decrease in skin test response with aging but does not differentiate between possible changes in the skin, which could account for these smaller numbers in the elderly versus an actual decline in clinical allergy.

3. PPSTs in the Elderly

Responses to allergen PPSTs in older individuals are frequently very small or negative. Authors report that skin test reactivity to allergens decreases with age.^[5] Most authors also report that, with age, the prevalence of allergies decreases.^[17] This decrease in prevalence is based on negative skin test results. This may be circular reasoning. In order to interpret skin tests in the elderly, the changes in the skin associated with aging must first be understood.

3.1 Changes in the Aging Skin

3.1.1 Aging Process

The epidermis of older people undergoes atrophy resulting in fewer cell layers and a decrease in cellularity and collagen.^[13] In addition, Gilchrist et al. reported that there is a marked reduction in blood vessels and mast cells in the skin of older individuals.^[14] Decreased mast cells offer less potential binding sites for allergen and less histamine to produce a wheal and flare. Dendritic cells are also decreased in the aged skin, resulting in decreased response to delayed hypersensitivity testing.^[18] The epidermis may have as few as three cell layers in older individuals compared with approximately 20 cell layers in younger individuals (Robert Csere, personal communication).

3.1.2 Photo Damage

Most of the changes that occur in the skin of elderly patients are because of photo damage. Sun-damaged skin exhibits both hyper- and hypo-melanotic lesions, along with atrophy of subcutaneous tissue and hypertrophy of the epidermis and increased keratin.^[19] Sun exposure is the major cause of the undesirable skin changes often inaccurately perceived as aging. These changes, known as photoaging, are caused by repeated sun exposure and not by the passage of time. Many of the clinical signs attributed to aging are actually manifestations of solar damage. The two processes are biologically different.^[20] The difference can be demonstrated by comparing the appearance of the skin of the lower sun-protected back with the skin of the upper sun-exposed back. Photo damage can lead to thicker keratin, colour changes (either hyper- or hypo-melanotic changes), increased wrinkling and altered mast cell chemistry. Mast cells altered by solar damage can result in decreased immune surveillance associated with increased prevalence of basal cell carcinoma.^[8] UV light was shown to suppress PPST responses following even a single exposure of a suberythematous dose.^[21]

3.1.3 Other Factors

Other factors that may affect the response to skin testing in the elderly include: medications, especial-

ly antihistamines and tricyclic antidepressants; vasomotor tone; blood pressure; temperature of extremities; location of where skin tests are performed; change in allergen exposure over time; and a hypothesis proposed by Sandmand et al. of a possible shift from a predominately T helper-1 cell response in the healthy adult to a T helper-2 cell response with waning immunity.^[22]

3.2 Interpreting Skin Tests in the Elderly

Prior to the general acceptance of the PPST, many allergists/immunologists preferred to use the intradermal instead of the scratch test for older adults, because skin test responses to scratch testing were minimal and therefore difficult to interpret because of increased keratinisation of the superficial epidermis. There are no studies that compare intradermal to PPSTs in older adults. Intradermal tests are more likely to be positive but many are falsely positive. With the wide spread acceptance of PPSTs, where the allergen is introduced through the most superficial level of the epidermis, intradermal testing may no longer be necessary, especially when standardised diagnostic extracts for all allergens are available.^[12]

Older patients frequently present with complaints suggesting respiratory allergies but the criteria for interpreting skin test results do differ between younger and older patients. Although fewer older patients appear to have positive skin tests, some older patients whose skin is 'well-preserved', i.e. sun protected, have very positive skin tests. Several older men who have absent or small histamine controls on their upper back, have larger histamine control responses when the same test is placed just below the belt line.^[23]

Reports of differences in skin reactivity to stroking and histamine were reported by Lewis and Grant in 1924,^[6] who noted that the thickness of the skin was proportional to the size of the response to stroking and to histamine. The skin of the back reacted more than the arms, and the thicker skin of the proximal arm was associated with larger reactions than the thinner skin of the wrist. Alexander and McConnel also suggested that the size of the wheal

was directly proportional to the thickness of the skin and that this probably resulted from a greater number of capillaries in thicker skin and more opportunity for release of H substance (histamine).^[24] They also tested the back, thigh, forearm and abdomen and found the abdomen and back more reactive than either the forearm or thigh. A study by Nelson et al. noted that the back was more reactive than the forearm and that this difference was greater for allergen than for histamine skin tests (though statistically significant, he did not feel this difference was clinically relevant).^[25] The lower back is a suitable area for allergy testing especially in those patients with photo-damaged skin (table I).

Skassa-Brociek et al.^[26] reported a decrease in skin test reactivity to histamine after the age of 50 years reaching a plateau after age 60 years.^[26] They also report a wheal to histamine in all subjects aged over 70 years of age but the flare, in some, was difficult to detect. They recommended that "the interpretation of skin tests should not only take into account the wheal size but rather a ratio between histamine- and allergen-induced wheals as it is standardised in Europe" (see table I). This accounts for the generally reduced skin reactivity of the elderly to allergens. This recommendation is similar to that by

Table I. Considerations for using prick puncture skin testing (PPST) in the elderly

Prior to performing PPST in the elderly, the area of skin where the tests are to be placed must be examined for atrophic or photo changes

When the skin is atrophic or photo-damaged, a sun-protected area of the skin should be used for testing, such as the lower back

If no suitable area of skin can be identified, *in vitro* allergen testing should be considered

A standard allergen PPST should always include a histamine PPST. The intensity of the skin response is expressed as the ratio between allergen- and histamine-induced wheals. This accounts for a generally reduced skin reactivity of the elderly to allergens

Positive PPSTs to an allergen must correlate with a history of exacerbation to the allergen. Ideally, a provocation challenge test should be done to confirm true allergy

By identifying specific allergens to which the elderly patient is sensitised, avoidance measures or specific allergen vaccination can be recommended. This improves the quality of life and decreases the need for medications, the latter of which are expensive and may cause adverse effects

Meinert et al. in their paper 'Influence of Skin Prick-Puncture Test Criteria on Estimation of Prevalence and Incidence of Allergic Sensitisation in Children'.^[27] They noted, as children age, the sizes of the wheals increase. They did not look at the effects of sun damage and age, especially in older people.

Simola et al.^[28] followed a group of allergic patients for 20 years and compared skin test and nasal challenge results at baseline and 20 years later. They found less reactivity and fewer positive nasal challenges in those individuals in the 20-year post-test group who were older than 54 years compared with those aged less than 54 years. In a further study, PPST responses, *in vitro* (ImmunocapTM) test results and skin colouration in younger (20–50 years) and older (60–78 years) individuals with rhinitis were compared. In sun-protected skin, histamine wheals were larger than in sun-exposed skin, and females had larger histamine wheals than did males. PPST results correlated with *in vitro* specific IgE in both age groups and gender.^[23] Nasal challenge to *D. pteronyssinus* was less often positive in older than younger subjects with positive PPSTs.^[29] When PPSTs are inconclusive, when the skin is badly photo-damaged or there is strong clinical evidence for an allergy with a negative prick test, we recommend performing *in vitro* tests for specific IgE to the suspected allergen(s) [table I].

4. Conclusions

In conclusion, PPST is the preferred method for allergy testing in the elderly; however, they must be interpreted carefully, as many factors can cause false negative or positive results. The quality of the diagnostic allergen may vary with good responses to standardised extracts but with varied responses to mould and food allergens. Some diagnostic allergens may include irritants that cause erythema. In older patients, the condition of the skin, the general health and medications may alter the results. Long-acting antihistamines and some psychotropic medications, especially tricyclic antidepressants, commonly cause a decreased response. While antihista-

mines are often discontinued prior to skin testing, other medications such as imiprazines, phenothiazines and topical corticosteroids are often not.

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