Skin prick tests and allergy diagnosis

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Abstract
Skin testing remains an essential diagnostic tool in modern allergy practice. A significant variability has been reported regarding technical procedures, interpretation of results and documentation. This review has the aim of consolidating methodological recommendations through a critical analysis on past and recent data. This will allow a better understanding on skin prick test (SPT) history; technique; (contra-)indications; interpretation of results; diagnostic pitfalls; adverse reactions; and variability factors.

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terases.11 A wheal and enzymes such as mast-cell chymase, tryptase and serine es-

flammatory mediators. Among these are histamine — a This eventually culminates in mast-cell degranulation begin-

ning in seconds, with release of a variety of preformed in-

flammatory mediators. Among these are histamine — a short-lived vasoactive amine that causes an immediate in-

crease in local blood flow and vessel permeability — and enzymes such as mast-cell chymase, tryptase and serine es-

terases.11 A wheal and flare reaction develops within min-

utes after superficial injection of antigen into the epidermis and lasts for up to 30 minutes. On activation, mast cells also synthesize and release chemokines, lipid mediators such as prostaglandins, leukotrienes and platelet-activating factor, and additional cytokines such as interleukins 4 and 13 which perpetuate the Th2 response.13 These changes can some-
times be followed by a late-phase reaction (LPR), which is extremely rare and almost exclusive to patients sensitised to moulds, grass and parietaria pollens.11

In a positive reaction, histamine can be detected only at the centre of the wheal, not in the periphery. It is suggested therefore that after allergen challenge, the mediators re-

leased by the challenged mast cell induce an axon reflex by direct stimulation of c-fibres. This induces the release of neurogenic peptides and mast cell mediators from "the next" mast cell, becoming the major players in the immedi-

ate wheal and flare reaction.12

Skin testing can be used to select eviction measures and/ or specific immunotherapy.11 To optimally define test performance, a method should be reproduceable and validated by comparison with gold stand-

ard methods. Direct challenge tests under supervision of a physician are appropriate ways to confirm or refute the va-

lidity of SPT. It provides objective evidence for sensitivity, specificity, predictive values and likelihood ratios. When compared to gold standard procedures, i.e. organ challenges such as nasal bronchoprovocation challenge or oral provoca-

tion challenge, SPT have demonstrated good results.15-19 The simplicity, rapidity of performance, low cost and high sensi-
tivity make skin testing preferable to in vitro testing for de-
termining the presence of specific IgE antibodies (sIgE). It is important to note the higher sensitivity of SPT when com-
pared to sIgE dosing. Nevertheless, every positive result must be correlated with history and physical findings since a positive skin reaction does not necessarily imply the diagno-
sis of allergy.19

Interpretation of skin tests is highly dependent on the constitutive allergenicity, potency and stability of the aller-
gen extract. For this reason, SPT sensitivity tends to be higher among aeroallergens, in particular pollens, house dust mite, fungi and certain epidermals.10

In clinical practice, skin testing has been extensively used for assessing sensitisation to inhalant allergens. SPT is useful to confirm or exclude a suspected diagnosis of allergic rhinis-
ts, allergic conjunctivitis or asthma triggered by aller-
gens.16,20,21 and to demonstrate sensitisation to inhalant occupational allergens.22,23 Previous observations suggest that skin test positivity at an early age is associated with subsequent development of rhinitis and wheeze.24 The role of allergic sensitisation as a cause of eczema is less clear.25

Skin testing in food allergy is common practice as well, although less reliable for commercial extracts of fruits and vegetables, as explained below.26 The clinical utility of SPT in patients with food allergy suspicion, especially infants and children, has been evaluated in various studies using oral food challenges and sIgE.

Most previous studies on food allergy obtained a concordance rate between SPT with commercial extracts and oral challenges from 60% to 85%28-32, speci-
ficity being generally lower, in the range of 40% to 80%.26 A negative result is use-
ful to exclude type I reactions to food allergens (negative predictive accuracy > 95%)28 but a positive result may or may not be associated with true clinical reactions. The over-
all concordance between a positive SPT and positive oral challenge differs between authors, but consensus exists re-

garding clear superiority of fresh food when compared to commercial extracts, as shown by Ortolani et al.33, Rosen et al.15, and Norgaard et al.34 With fresh food, sensitivity usu-
ally exceeds 90% and can even reach 100%.26 This is particu-
larly important when a strong suspicion of food allergy subsists after negative results with commercial extracts. Fresh food testing makes use of a different procedure, the prick-prick technique.

Under carefully defined circumstances, SPT can also be used as a primary approach to drug and hymenoptera ven-
on. In such cases however, intradermal tests are usually required for a correct diagnosis. For most chemicals asso-
ciated with occupational allergy it is not indicated, with the exception of agents known to be implicated in IgE reactions, such as platinum salts, acid anhydrides, poly-
isocyanates, sulfonechloramide and succinylcholine ana-
logues.29,30

Technique

The goal for the allergist is to perform skin testing with de-

vices which minimise both false positive and false negative results while reducing patient discomfort. SPT should be a non-traumatic procedure (blood-free) and several sharp in-

struments such as a hypodermic needle, solid bore needle,
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The technique appears to be more precise than the original SPT reactivity as well. Therefore, a minimum of 2 cm distance for skin prick testing has varied between 2 and 5 cm. Recommendations have been made regarding the appropriate placement of allergen extracts. The recommended distance for skin prick testing has varied between 2 and 5 cm and test sites should be marked with an appropriate code.

The SPT are usually performed on the volar surface of the forearm, at least 5 cm above the wrist and 3 cm below an antecubital fossae, the least and most reactive areas of the upper arm, respectively. The tests can also be done on the upper arm or the back, with special attention to avoid reactivity differences between locations.

For positive control, histamine dihydrochloride 10 mg/ml (54.3 mmol/1), equivalent to 6.14 mg/ml of histamine base, or codeine phosphate at 9% can be recommended. Some authors advocate the use of histamine at 1 mg/ml; however, in a study by Morais de Almeida et al., the concentration of 1 mg/ml consistently presented negative results in more than 10% of the patients. Therefore, histamine at 1 mg/ml should be definitely abandoned.

The prick-prick test requires a different procedure, prick ing the food first, and then the skin, using the same needle; or prick ing the skin through food in a single manoeuvre. Foods with a hard consistency, such as peanut, can be ground, diluted in buffered saline at 1/3 weight/volume (w/v), or 500 mg of food to 1.5 ml of saline.

Dreborg recommends at least two parallel tests performed with the same material in every patient with the exception of infants, in order to assure precision, as single negative tests (5%) will be obtained in sensitised patients even with skilled technicians. In duplicate tests, the diameter should not vary more than 1 mm. Several publications have provided innovative methods to assure skin test validity. A suggested protocol for quality assurance testing and proficiency testing for SPT can be found in literature. In Europe, a coefficient variation of less than 20% after histamine control test has been suggested, whereas a recent Childhood Asthma Management Study considered a variation inferior to 30.

Reading and interpretation

The size of the papule is of paramount importance in SPT. However, both erythema and wheal should be measured for proper interpretation.

Østerballe and Weeke demonstrated that the wheal size with histamine peaks earlier (9-12 min) than with allergens (13-16 min). In a recent study, using laser Doppler flow imaging and scanning of drawn wheal sizes, the maximum histamine wheal size was reached at 20 minutes. We therefore propose a consensus reading time for both positive control and allergen reactions at 20 minutes post-prick.

A valuable option concerning appropriate documentation of skin test results consists in outlining the wheal and flare reaction with a felt-tip pen and transferring results with transparent tape to a blank sheet of paper.

Various indices have been used for interpretation of skin reactions. The papule's area is the most accurate and less painful than other synthetic devices with 1.4 or 1.6 mm penetration limits. Metal lancets with 1 mm penetration limit are considered equally efficient and less painful than other synthetic devices with 1.4 or 1.6 mm penetration limits. The penetration limit is therefore a determinant factor when considering test efficacy and patient comfort, rendering metal lancets preferable when compared to other synthetic devices.

Nevertheless, an objective comparison has not shown a clear-cut advantage for any single or multitest device and optimal results can be obtained by choosing a single prick/ puncture device, and properly training its use.

Antiseptic solutions are recommended before SPT and skin should be totally dry before procedure.

Recommendations have been made regarding the appropriate placement of allergen extracts. The recommended distance for skin prick testing has varied between 2 and 5 cm and test sites should be marked with an appropriate code.

It is possible, however, for a positive reaction to enhance false-positive skin reactions at an adjacent site, even over the range of 5 cm.

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Lancets should be sterilised, a fresh lancet for each prick, with normalised measures and each lancet should be used only once for each extract, in order to avoid unintentional pricks, blood borne infections and allergen contamination. Metal lancets with 1 mm penetration limit are considered equally efficient and less painful than other synthetic devices with 1.4 or 1.6 mm penetration limits. The penetration limit is therefore a determinant factor when considering test efficacy and patient comfort, rendering metal lancets preferable when compared to other synthetic devices.

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Of the criteria explained above, mean wheal diameter is the most commonly used. The skin reaction is considered positive if the wheal’s area is 7 mm² or higher, which corresponds approximately to a mean diameter of 3 mm.¹⁰-¹²,¹⁴,¹⁵

The degree of erythema (flare) is considered to be a non-specific reaction of the skin to the trauma of the puncture.¹⁶ Nevertheless, some authors consider a positive reaction if the mean flare diameter is over 10 mm.¹⁶

The results obtained can only be correctly assessed and taken into account with valid positive and negative control reactions. Thus, histamine’s papule mean diameter should be greater than 3 mm and negative control should not exceed 3 mm with erythema diameter inferior to 10 mm. Devices that systematically produce negative control wheals over 3 mm should be avoided.⁎⁶ Stuckey et al. found that patients with more positive sensitisations and higher total IgE have larger histamine papules.⁴⁸

Qualitative scoring (0 to 4; 0 or +) is no longer recommended because of marked variability between observers.⁶⁹,⁷⁰ Wheal size has assumed greater diagnostic significance due to the positive correlation with clinical symptoms severity.⁷¹-⁷³ Investigating graduated test responses and establishing probability decision points might improve diagnostic accuracy and predict positive reactions during organ challenge.⁷¹ In a previous study, especially regarding food allergy, Spörki⁶⁹ defined specific wheal diameters as ‘100 % diagnostic’. In his work, cut-off values were proposed for cow’s milk (≥ 8 mm), hen’s egg (≥ 7 mm) and peanut (≥ 8 mm), suggesting that children exceeding these limits are allergic to this specific food. These recent advances might obviate the need for oral challenge in the future.⁷¹-⁷³

These cut-off points vary for different allergens, being more accurate for cow’s milk and hen’s egg than for soy or wheat. Additionally, different populations may exhibit significant variability. Even though there is a correlation between SPT result or sIgE and likelihood of a clinical reaction, sensitisation level does not always correlate with allergic manifestations.⁷⁴-⁷⁷

One study points to between 7.5% and 19% asymptomatic sensitisations among Finnish schoolchildren.⁷⁸ Skin test reactivity to inhalant allergens is reduced in asymptomatic sensitisations when compared with symptomatic patients.⁷⁹ Asymptomatic sensitisation is generally considered a pre-morbid state of allergic disease, and has been proven to be a risk factor for the development of allergic rhinitis in children and young adults.⁸⁰,⁸¹ Bodegård et al., in a 3-years follow-up study, showed that adults with asymptomatic skin sensitisation to birch pollen have an increased risk (about 60%) of developing hay fever.⁸²

Several studies have demonstrated that positive SPT in infancy, especially for milk and hen’s egg, predicts subsequent presence of eczema in childhood.⁸³,⁸⁴ Thus, sensitisation in asymptomatic children can precede and predict the development of eczema.⁸⁵

Limitations

In the past, the manufacture of skin test solutions imposed important technical limitations. The recent availability of standardised commercial extract solutions constitutes a major achievement in allergy testing. Allergen extracts are complex mixtures derived from natural source materials and as such are prone to natural variation, requiring proper standardisation to ensure consistency and reproducibility. Some physicians report non-negligible variability between extracts from different manufacturers, easily attested in our daily practice.⁸⁶-⁸⁸ Quality of allergen extracts is dependent on several parameters such as raw material quality, proper test extractions, adequate processing and removal of low molecular weight components by dialysis or filtration.⁹° Stability, potency and allergen concentration are also determinants.

The most internationally recognised way to express allergen extract strength is micrograms of major allergen because this appears to correlate well with overall biological potency of the extract.⁹¹ In-house references should be characterized with respect to dry weight, allergen complexity, major allergen content and IgE binding capacity. Biological activity should ideally be assessed in vivo, with skin testing.⁹²,⁹³ However, the methods used differ from manufacturer to manufacturer, making products from different companies impossible to compare.⁹⁴ Non-related allergen mixtures may account for loss of biological potency as a consequence of excessive dilution or enzymatic deterioration of the epitopes. Time and higher temperatures can also accelerate the decay process. To assure stability, allergens are usually preserved with 50% glycerine and stored under cold (4 ºC).⁹⁴-⁹⁵

Recombinant allergens offer future interesting perspectives as in vivo diagnostic tools. These genetically engineered molecules appear to be highly specific, safe and biologically active. Their sensitivity, however, appears to be lower when compared to natural allergen extracts.⁹⁶-⁹⁸ Which allergens to test is a common doubt in daily practice. A recent survey performed in the United States showed that most allergists do not rely on history when choosing which allergens to use to perform skin testing.⁹⁹

When considering inhalant allergy, several criteria should be thought-out before choosing skin testing reagents, such as botanical and aerobiological surveys. Flowering season, types and levels of pollens and spores along the year and peak days of pollination should be considered. Annual pollen sampling data in various countries are now available on-line.⁰° Air composition and concurrent allergy symptoms during recurrent seasons constitute the best indicators in the selection of appropriate outdoor aeroallergens for skin testing.⁰¹

The influence of pollen load is more evident in sIgE changes than on SPT reactions or clinical symptoms.⁰² Regarding food allergy, SPT can be performed both with commercial allergen extracts and fresh foods. Fresh food is often used as it more accurately reflects the patient’s life. In a French study it was demonstrated that fresh foods were more reliable in food allergy diagnosis than commercial extracts.⁰³ Commercial extracts of fruits and vegetables (e.g., apples, oranges, bananas, potatoes, carrots, and celer), are likely to lose biological properties with time, reinforcing the role of prick-prick method with fresh food.⁰⁴ This technique is also valuable when there are differences in the allergenicity of different cultivar strains (e.g., apples) or when no commercial extracts are available.⁰⁵ Although prick-to-prick tests are widely used, it is important to notice that they are not standardised, often give
false-positive results, and still bear the risk of systemic re-
actions, as discussed in later sections.

Instead of fresh food, freezing aliquots may facilitate skin
prick testing in particular cases. Freezing cow’s milk and
hen’s egg at –20 °C has been tested and it does not alter the
allergenic properties of each component.106 However, these
results cannot be transferred automatically to other foods
without further testing.

Furthermore, commercial extracts may produce false-neg-
ative results since storage, cooking or digestive process may
induce immunological alterations in relevant allergens, ren-
dering a particular food more allergenic than achieved by
commercial extracts.107

The presence of active cutaneous lesions, as commonly
observed in patients with active atopic dermatitis, impair
the proper SPT reading, and constitute a contra-indication
to skin test procedures.4,48 Nevertheless, SPT can be per-
formed in eczematous infants since no lesions exist on test-
ing area. This can be useful as infants with eczema in the
first 2 years of life with concomitant allergic sensitisation
have a greater risk of childhood asthma and allergic rhinitis
than infants with non-atopic eczema.49

Patients with dermatographism should be excluded as it is
difficult to distinguish between a true or false positive re-
result, invalidating any conclusions.4

In such circumstances involving extensive skin disease; or
in patients under skin test suppressive therapy (for exam-
ple, antihistamines) that cannot be discontinued; uncoop-
erative patients; or when the history suggests an unusually
high risk of anaphylaxis from skin testing, sIgE immunosassays
may be preferable to skin testing.

False-positive reactions can be due to skin trauma, mostly
in patients with dermographism4, as explained above, but
also to contaminated allergen extracts (occurring during ex-
tract preparation or simply for not changing lancets during
SPT)108 or cross-reactivity phenomena.106 Cross-reactivity de-
pends on the type of allergens involved, in particular their
structural and sequential similarity.106 Pan-allergens respon-
sible for cross-reactivity in vegetables are pathogen-related
proteins (PRP) and profilins.109 For invertebrates, tropomy-
osin is the most implicated protein. For vertebrates, several
allergens are implicated: parvalbumin (fish), iVsetin and
ovotranferin (egg and birds) and casein (milk).108

Extensive cross-reactivity has been described among aer-
ogenous allergens-sensitised patients.106 House dust mites, epider-
mals, but most of all, pollens have been widely studied.

Therefore, testing with multiple locally prevalent pollens
may be required to avoid significant omissions. Cross-aller-
genicity among major classes of airborne fungi has not been
well delineated so far.10

With regard to food allergy, we shall briefly mention the
most interesting and relevant syndromes as it can be useful
to better understand skin test results. Patients with: 1) birch
apple; 2) artemisia-celery-carrot-ses; 3) grass-peach;
4) plantago-melion; 5) latex-fruits; 6) dust mites-seafood;
7) bird-egg; 8) pig-cat; 9) shellfish; 10) peanut, soybean and
other legumes; 11) tree nuts; 12) rosaceous fruits; and
13) cereal grains can be expected to show cross-reactivity
with SPT.

Concerning false-negative results, special attention should
be given to patient’s age, concomitant drugs and diseases
such as HIV infection or chronic renal insufficiency, which
may inhibit skin reactivity.10 Even when all quality parame-
ters are considered, patients with evident allergic symptoms
still have negative SPT. It is important to consider that
non-IgE mechanisms, impossible to be assessed by SPT,
can be implicated in patient’s complaints. Powe et al.110 de-
monstrated that inflammation in non-allergic rhinitis may be
a consequence of localized IgE-mediated reactions, not involv-
ing systemic Th2 responses or atopy. Therefore, local IgE pro-
duction in non-allergic patients could explain the presence
of symptoms in SPT negative patients (localised mucosal al-
lergic disease in the absence of atopy – “entopy”).110

Adverse reactions
In the last thirty years, the occurrence of systemic reactions
with SPT for inhalant extracts has decreased dramatically.111
Recent surveys indicate an overall risk inferior to 0.02% for
anaphylactic reactions to SPT, whereas IDT are more likely
to induce systemic reactions.111 Most of the systemic reac-
tions incited by SPT were related to fresh food (prick-prick
tests with kiwi, fish, fresh pine nut and milk)112-114, latex (SPT
with natural rubber latex and commercial extracts115,116) and
drugs (penicillin, amoxicillin).117 In a 12-year survey of fatal
reactions (1990-2001), one fatality was confirmed after SPT
with multiple food allergens (90 food prick tests were ap-
plied at one time in a patient with moderately persistent
asthma).118

A retrospective review of medical records concerning SPT
with foods corroborates the low rate of generalised reac-
tions, as previously stated, and points out that all reactions
in infants (n = 6) occurred under 6 months of age and only
with fresh food specimens.119

Special attention should be given to young children and
pregnant women. Skin test duplication should be avoided in
children with suspected food allergy (fresh food or commer-
cial extracts), especially when suffering from extensive ec-
zema.119 As for pregnant women, although SPT is not con-
traindicated, it is prudent to postpone such procedures
and/or propose sIgE assays instead.119

Variability factors
Multiple factors have been found to influence skin test results.
These variability factors include technical issues, biological
determinants and other external factors such as previous
medication or infections (Table I).

Skin reactivity is known to vary according to age: children,
particularly under the age of 2 years, are less reactive than
adults.114 The prevalence of positive skin test results in-
creases until the 2nd decade, with a slow decline above the
age of 60 years.106 In children with manifest allergy, how-
ever, skin has similar reactivity from 1 year of age until puberty.
117 Nevertheless, SPT tests can be used in infants as young
as 1 month, with a high degree of reliability, usually with
more erythema than wheal reaction.117

Test results also depend on anatomic location since skin
reactivity differs from region to region. In decreasing order,
the degrees of reactivity are as follows: mid and upper back
> lower back > upper arm > elbow > forearm (ulnar > radi-
al) > wrist.112

Besides age and anatomic location, other biological and
physiological factors may also influence skin test results,
Table I. False results in skin prick tests

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<th>False negative results</th>
<th>False positive results</th>
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<td>Biological factors</td>
<td>Dermography</td>
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<td>Cross-reactivity</td>
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<td>External factors</td>
<td>Trauma and non-blood-free procedure, extract quality (impure mixtures)</td>
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<td>Technical factors</td>
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<td>SPT diagnostic limitations</td>
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such as histologic qualities of the skin (vasculature, number of histamine receptors, mast cells, and dermal thickness). In one study, UV-B exposure was found to reduce skin reactivity by as much as 48%. Concerning racial factors, dark-skinned patients seem to have larger wheal-and-flare reactions, but some authors found Caucasians to be more reactive than non-Caucasians. Circadian rhythm has no influence on skin reactivity but some data show maximum wheal size during the night. Different studies identified a relevant increase in wheal-and-flare reaction in patients with allergic asthma and rhinitis after pollen season. On the contrary, the reduction in skin reactivity in sensitised subjects is a common finding after specific immunotherapy, either sublingual or subcutaneous.

Concurrent drugs, in particular antihistamines (AH), tricyclic antidepressants and topical corticosteroids may affect the validity of skin testing. Different pharmacodynamic models have been used to evaluate the degree and duration of drug suppression on skin reactivity, making direct comparisons unreliable (Table II).

The histamine-induced wheal and flare model helps to identify the objective effectiveness of AH in humans, as well as their differences in the onset and duration of action. Several studies have employed this model to compare AH and assess their pharmacokinetic properties. When compared to other 2nd generation AH, such as desloratadine, levocetirizine appears to be more effective in inhibiting wheal and flare response. Ebastine, fexofenadine, cetirizine and micizostat rank next and have similar skin effects. Superior efficacy of ebastine (20 mg) was found in comparison to cetirizine (10 mg) or loratadine (10 mg) on the overall skin wheal response after single and multiple doses, with a longer-acting effect than fexofenadine as well.

The general principle concerning first- and second-generation AH is to stop medication 2 to 3 days before SPT, with the exception of cetirizine, hydroxyzine (5 days), clermastine (5 days), loratadine (7 days) and perhaps others not yet studied. For this reason, and as it seems easier for the patient to remember, we suggest a one-week drug-free interval before skin testing. Many patients who require SPT cannot deal with pruritus without taking AH. In a recent work by Danarti et al., topical AH can be used in such circumstances. Because of their short duration of action (< 180 minutes), these drugs can be used in patients who need antihistamines but are scheduled to undergo skin prick testing after a few hours, without influencing the patient’s skin response.

Doxepin, a tricyclic antidepressant, and anti-H2 drugs can also cause false-negative results for as long as 6 days or 24h, respectively. Systemic corticosteroids do not inhibit skin reactivity when used for short term therapy (i.e. 30 mg prednisone a day for 1 week). When used for longer periods, conflicting results have been obtained, recommending a more critical analysis. Topical steroids should be discontinued 2 to 3 weeks before testing as prolonged use (over 3 weeks) can suppress wheal reaction in the application sites.

Bronchodilators, epinephrine and theophylline do not significantly suppress skin reactivity. In the case of cysusteinyl leukotrienes antagonists (e.g. montelukast and zafirlukast) or EMLA cream, no significant effect on wheal-and-flare reaction has been described either. Concerning intranasal topical AH (e.g. azelastine) results are somehow contradictory and discontinuance is recommended for a 48h minimum period.
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Populse size depends as well as on allergen concentration and number of allergens tested for which the patient is sensitised. Some authors have studied these variables and calculated, for example, that the wheal diameter increases 1.5 times (area 2.25 times) if the allergen concentration increases 10 times. In polysensitised individuals, simultaneous prick testing with multiple allergens can induce additive histamine release from cutaneous mast cells. In vivo and in vitro studies suggest an additive effect of multiple proteins (allergens mixture) on histamine release from cutaneous mast cells, causing mean wheal diameters larger than obtained with single allergens.

Future directions

Skin testing remains an essential diagnostic tool in modern allergy practice. Allergen extracts have experienced great progress in recent years but a long way remains ahead. Many allergens have yet to be characterized. The quality of extraction and biological potency assessment. The capacity to differentiate between clinically irrelevant and relevant sensitisations constitutes an important motivation to future investigations. The definition and use of recombinant allergens promises to lead to an improvement in this area, eliminating diagnostic errors due to cross-reactivity phenomena.

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