Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

Allergy

POSITION PAPER

Practical guide to skin prick tests in allergy to aeroallergens

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To cite this article: Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG, Canonica GW, Carlsen KH, Cox L, Haahtela T, Lodrup Carlsen KC, Price D, Samolinski B, Simons FER, Wickman M, Annesi-Maesano I, Baena-Cagnani CE, Bergmann KC, Bindslev-Jensen C, Casale TB, Chiriac A, Cruz AA, Dubakiene R, Durham SR, Fokkens WJ, Gerth-van-Wijk R, Kalayci O, Kowalski ML, Mari A, Mullol J, Nazamova-Baranova L, O'Hehir RE, Ohta K, Panzner P, Passalacqua G, Ring J, Rogala B, Romano A, Ryan D, Schmid-Grendelmeier P, Todo-Bom A, Valenta R, Woehrl S, Yusuf OM, Zuberbier T, Demoly P. Practical guide to skin prick tests in allergy to aeroallergens. *Allergy* 2012; **67**: 18–24.

Keywords
allergy; asthma; inhalant; rhinitis; skin prick test.

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Accepted for publication 5 September 2011

DOI:10.1111/j.1398-9995.2011.02728.x

Edited by: Thomas Bieber

Abstract

This pocket guide is the result of a consensus reached between members of the Global Allergy and Asthma European Network (GA^{2}LEN) and Allergic Rhinitis and its Impact on Asthma (ARIA). The aim of the current pocket guide is to offer a comprehensive set of recommendations on the use of skin prick tests in allergic rhinitis–conjunctivitis and asthma in daily practice. This pocket guide is meant to give simple answers to the most frequent questions raised by practitioners in Europe, including 'practicing allergists', general practitioners and any other physicians with special interest in the management of allergic diseases. It is not a long or detailed scientific review of the topic. However, the recommendations in this pocket guide were compiled following an in-depth review of existing guidelines and publications, including the 1993 European Academy of Allergy and Clinical Immunology position paper, the 2001 ARIA document and the ARIA update 2008 (prepared in collaboration with GA^{2}LEN). The recommendations cover skin test methodology and interpretation, allergen extracts to be used, as well as indications in a variety of settings including paediatrics and developing countries.

Skin prick tests (SPTs) are widely used to demonstrate an immediate IgE-mediated allergic reaction. They represent a major diagnostic tool in the field of allergy. If properly performed, they yield useful evidence for the diagnosis of specific allergy (1–3). As there are many complexities in their performance and interpretation, they should be carried out by trained health professionals (4).

Skin tests to foods, venoms, occupational agents and drugs will not be considered in this document.

Methods

This guide was prepared by a combined Global Allergy and Asthma European Network (GA^{2}LEN) and Allergic Rhinitis and its Impact on Asthma (ARIA) task force and finally presented to all GA^{2}LEN partners for comments. It follows in the history of the 1993 European Academy of Allergy and Clinical Immunology position paper (5), and the 2001 ARIA document (6). It is also based on the ARIA update 2008 (prepared in collaboration with GA^{2}LEN) (1). The recommendations are compiled from the exhaustive overview of these guidelines.

This guide is not intended to address evidence-based medicine (EBM) issues regarding skin tests. It is written to give clear-cut answers to the most frequent questions raised by practitioners and patients. Certain other papers with a stronger and deeper clinical and scientific EBM background will follow this guide.

Abbreviations
ARIA, Allergic Rhinitis and its Impact on Asthma; EBM, evidence-based medicine; GA^{2}LEN, Global Allergy and Asthma European Network; ID, Intradermal skin test; SPT, skin prick test.

1. What are the indications for skin tests in clinical practice?

Skin tests represent the first diagnostic method in patients with a suggestive clinical history of allergic rhinitis (conjunctivitis) and/or asthma. They can be used from infancy to old age (4).

Repeated testing may only be needed, mainly to detect new sensitizations in children and when changes in symptoms have occurred.

2. Which skin tests are recommended?

Prick and puncture tests are recommended because there is a high degree of correlation with symptoms. Skin prick tests have a high specificity and sensitivity for the diagnosis of inhalant allergens (4) (Table 1). Common errors in SPTs are listed in Table 2. Skin prick tests with commercial inhalant extracts may exceptionally induce systemic reactions (7, 8).

3. What role do intradermal tests play?

Intradermal (ID) skin tests are not useful for allergy diagnosis with inhalant allergens (4, 9). Although some patients may only have an ID-positive skin test, the clinical value is unknown. They are less safe to perform (10).

4. What is the recommended skin prick test technique?

Table 1 Performance of skin prick tests

1. Use standardized extracts when available.
2. Include a positive and a negative control solution.
3. Perform tests on normal skin.
4. Evaluate the patient for dermographism.
5. Determine and record medications taken by the patient and time of last dose.
6. Record the reactions after 15 min.
7. Measure the longest wheal diameter.

Table 2 Common errors in skin prick tests

1. Tests are placed too close together (<2 cm), and overlapping reactions cannot be separated visually.
2. Induction of bleeding, leading possibly to false-positive results.
3. Insufficient penetration of skin by puncture instrument, leading to false-negative results. This occurs more frequently with plastic devices.
4. Spreading of allergen solutions during the test or when the solution is wiped away.

Prick-to-prick tests are not useful with inhalant allergens.
Adapted from Mansmann HC Jr, Bierman CW, Pearlmman DS, editors. Allergic Diseases in Infancy, Childhood, and Adolescence. Philadelphia: WB Saunders Co, 1980:289 (45).

The modified SPT introduced by Pepys (11), which passes a fine metal needle through a drop of allergen extract after wiping the skin with alcohol with little pressure, is the current reference method. Puncture tests with various devices can decrease SPT variability (12–15). A different needle or puncture test should be used for each test (16). For allergens, the peak of the skin wheal is reached around 10–20 min after the test, and a reading of the largest diameter of the skin wheals after 15 min is recommended.

5. Which treatments suppress skin tests?

Drugs can suppress skin tests, therefore it is always necessary to ask patients about the medications they have taken in the preceding days (Table 3). This is particularly true for oral H_1-antihistamines, but also for other drugs which are not necessarily used for the treatment of allergic diseases (4, 17) such as anxiolytics but not antidepressants (18). Topical skin corticosteroids may alter skin reactivity (4, 17).

Table 3 Inhibitory effect of various treatments on skin prick tests

Treatment	Degree	Duration	Clinical significance
Oral H1-antihistamine	++++	2–7 days	Yes
Intranasal H1-antihistamine			None
H2-antihistamine	0 to +		None
Imipramines	++++	Up to 21 days	Yes
Phenothiazines	+ to ++	Up to 10 days	Yes
Corticosteroids			
Systemic, short term	0		None
Systemic, long term	Possible		None
Inhaled	0		None
Topical skin	+ to ++	Up to 7 days	Yes
Dopamine	+		None
Clonidine	++		None
Montelukast	0		None
Specific immunotherapy	0 to ++		None
UV light treatment systemic depending on light source, most intensive with PUVA	+++	Up to 4 weeks	Yes

6. Which diseases affect skin tests?

Prick testing can only be performed on healthy skin. Patients with widespread urticaria or eczema (e.g. atopic dermatitis) cannot be tested in areas of affected skin.

Neurological disorders as well as infectious disease (e.g. leprosy) can lead to false-negative SPTs.

7. Which allergenic extracts to choose?

The quality of the allergen extract is of key importance (19) as variations in the quality and/or potency of commercially available extracts exist (20, 21), in particular for animal mites, animal danders and moulds, but even pollens (22). When possible, standardized allergens using biological methods and labelled in biological units or micrograms of major allergens should be used (5, 23).

Recombinant DNA technology allows the production of pure biochemically characterized proteins. Skin tests with recombinant allergens were available in the 1990s for pollens (24), moulds such as *Aspergillu*s (25) or mites (26). Skin tests with recombinant and natural allergens have a similar value (27, 28) if the recombinant allergens have been well selected and represent all or most epitopes of the natural allergen (29).

8. Which allergens should be tested?

It is sometimes proposed that the panel of allergens tested depends on the allergen exposure of the area. However, allergic patients are travelling across countries, new sensitizations are being found in relation to climate change (30), and cross-reactivities may be unsuspected. A common standardized allergen battery should be recommended for clinical use and research across Europe (31–34) (Table 4). The Global Allergy

Table 4 Global Allergy and Asthma European Network-suggested panel of allergens to be tested in all patients in Europe

- Pollen
  - Birch (*Betula verucosa*) or mixed Betulaceae
  - Cypress (*Cupressus sempervirens*) or other cypress pollen species
  - Grass: one species or mixed grass pollens
  - Mugwort (*Artemisia vulgaris*)
  - Olive (*Olea europaea*) or ash (*Fraxinus exelsior*)
  - *Parietaria officinalis*
  - Plane (*Platanus occidentalis*)
  - Ragweed (*Ambrosia eliator*)
- Mites
  - *Dermatophagoides pteronyssinus*
  - *Dermatophagoides farinae*
- Animals
  - Cat (*Felix domesticus*)
  - Dog (*Canis familiaris*)
- Moulds
  - *Alternaria alternata*
  - *Cladosporium album*
- Insects
  - Cockroach (*Blatella* sp.)

and Asthma European Network skin test battery is recommended for all adolescents and adults in Europe.

Aspergillus is an important allergen of severe asthma (35), but it is not available in some countries owing to regulatory issues. In preschool children, the number of skin tests to inhalants should be reduced.

In the United States, according to the third National Health and Nutrition Examination Surveys, 10 allergens were used for skin tests and the most common positive skin tests were dust mite (*Dermatophagoides* spp.), perennial rye (*Lolium perenne*), short ragweed (*Ambrosia eliator*), German cockroach (*Blatella germanica*), Bermuda grass (*Cynodon dactylon*), cat (*Felix domesticus*), Russian thistle (*Salsola kati*), white oak (*Quercus alba*), *Alternaria alternata* and peanut (36).

Evaluated panels like those in Europe are very useful but still need to be developed for other areas of the world, for example Japanese cedar (*Cryptomeria japonica*, highly prevalent in Japan and Eastern Asia) (37), mulberry (*Broussonetia papyrifera*, a common allergen in some areas like Pakistan), Russian thistle (*Salsola kali*) or *Chenopodium* (38) (important pollen allergens in Spain and semi-arid areas). One should also consider that the grass pollen mix selected should cover the regionally most dominant grasses [including those which are not cross-reactive such as Bahia grass, *Paspalum notatum* (39), or Bermuda grass, *C. dactylon* (40)].

9. Which area of the body should be chosen and what is the ideal distance between tests?

Usually, skin tests are performed on one or both forearms, depending on the age (size) of the patient. The distance between two prick tests should be 2 cm to avoid cross-contamination (16).

10. Which negative and positive controls are recommended?

Negative (saline) and positive (e.g. 9% histamine hydrochloride solution) controls are required in SPTs to make any interpretation possible. The positive control should optimally show a wheal diameter ≥3 mm.

11. Which results are regarded as positive?

The wheal and erythema have been used to assess the positivity of the skin test. However, only the wheal is needed. The largest size of the wheal is considered to be sufficient (41). Wheal diameters ≥3 mm are considered positive in SPTs. It is considered that small wheals under 3 mm of diameter are not significant in clinical studies (11) whereas they are considered to be positive in epidemiologic studies (42).

Very large reactions are not necessarily associated with more severe disease.

12. How do skin tests compare to serum-specific IgE?

Serum-specific IgE, SPTs and allergen challenge do not have the same biological and clinical relevance and are not interchangeable (43). There may be age-dependent differences, and elderly people may more commonly have negative skin tests (44) or tests of a smaller size. Low levels of serum-specific IgE are less often associated with symptoms than higher levels, but they do not exclude allergic symptoms (45), particularly in very young children. Some allergens exhibit poor allergenic activity and skin testing may be useful to identify such allergens.

13. How to interpret skin test results?

Skin testing represents the primary tool for allergy diagnosis by the trained physician.

False-positive skin tests may result from dermographism or may be caused by 'irritant' reactions or a nonspecific enhancement from a nearby strong reaction.

False-negative skin tests can be caused by the following:

- Extracts of poor initial potency or subsequent loss of potency (46).
- Drugs modulating the allergic reaction.
- Diseases attenuating the skin response.
- Improper technique (no or weak puncture).
- Limited local production of allergen-specific IgE only in the nose (47) or in the eye (48).

14. Which skin tests are recommended in adolescents and adults?

The diagnosis of allergy is based on the correlation between the clinical symptoms, medical history and test results. It cannot be based only on responses to skin tests, *in vitro* tests or even challenge tests (49). The clinical relevance of all identified sensitizations must be evaluated, as determined by the medical history and clinical symptoms.

In longitudinal cohorts, positive skin tests in nonsymptomatic subjects predict the onset of allergic symptoms including asthma (50).

15. Which skin tests are recommended in the elderly?

Although skin test size is usually smaller in elderly patients (51), SPTs can be used in this age group for the diagnosis of allergy. In patients with atrophic skin, skin tests may be difficult to interpret.

16. Which skin tests are recommended in young children?

Allergy to inhalant allergens is common from early childhood; SPTs can be performed and interpreted in infants (52). Usually, the size of the lower arm limits the number of allergens that can be tested. The back may then be used if needed. In preschool children, it may be difficult to ascribe a positive SPT to symptoms because asthma and rhinitis may be difficult to diagnose (53).

17. What is the role of skin tests in primary care?

Allergic rhinitis is a growing primary care challenge because most patients consult primary care physicians (54–56). General practitioners play a major role in the management of allergic rhinitis as they make the diagnosis, start the treatment, give relevant information and monitor most of the patients (57). In some countries, general practitioners perform SPTs. A structured allergy history appears to be insufficient when assessing patients with asthma and rhinitis in general practice (58). However, performing and interpreting skin prick tests requires adequate training.

18. How can skin tests be used in developing countries?

Skin prick tests can be used in developing countries where allergy is booming. Reliable data have been reported from all continents (59). However, local allergens may not necessarily have been identified and therefore cannot be tested. Some important allergens such as *Blomia tropicalis* should be included in the skin test battery of tropical countries (60).

19. Are skin tests needed in allergen immunotherapy follow-up?

Skin test reactivity decreases with allergen-specific immunotherapy to inhalant allergens, but skin tests cannot be used to assess the efficacy of immunotherapy in practice (61). Moreover, skin tests cannot be used to decide on the cessation of immunotherapy (62).

20. Can skin tests be used in research?

Skin prick tests are often used in research, but certain criteria should be met: the same allergen should be used throughout and the shelf-life of the allergen should be known. In multicentre trials, the reproducibility of the test within and between centres should be ascertained.

Skin tests have been largely used in epidemiologic studies in populations and birth cohorts (45, 47, 48), but unfortunately, the method of performing the tests is not always clearly described. Moreover, results of SPTs and serum-specific IgE are not interchangeable (42).

21. What are the future needs?

We are entering the third decade of the allergenic molecule era (63, 64). However, there are critical issues with these novel techniques because their clinical relevance has not yet been established and they may unnecessarily increase the complexity and costs of diagnosis procedures.

Nevertheless, allergy is facing more basic challenges. In many areas, we do not yet have pollen counts, indoor allergen loads are unknown and there is little knowledge about relevant allergens. Even in Europe, sensitization rates are rapidly changing, thus active surveillance for these trends is required.

Acknowledgments

We thank Ms Anna Bedbrook for her technical assistance.

Conflict of interest

The following authors declare to have no conflicts of interest: I Annesi-Maesano, C Bachert, CE Baena-Cagnani, KC Bergmann, C Bindslev-Jensen, PJ Bousquet, P Burney, GW Canonica, KH Carlsen, TB Casale, A Chiriac, AA Cruz, R Dubakiene, Durham, WJ Fokkens, T Haahtela, L Heinzerling, O Kalayci, ML Kowalski, A Mari, RE O'Hehir, K Ohta, P Panzner, NG Papadopoulos, G Passalacqua, B Rogala, A Romano, D Ryan, P Schmid-Grendelmeier, A Todo-Bom, M Wickman, S Woehrl, OM Yusuf.

Author contributions

J.B. has received honoraria for scientific and advisory boards, lectures during meetings, press conferences from Stallergènes, Actelion, Almirall, AstraZeneca, Chiesi, GSK, Merck, MSD, Novartis, OM Pharma, Sanofi-Aventis, Schering Plough, Teva, Uriach. L.C. has received Phadia-speaker's fees < $5000. For this work, P.D. is the EAACI vice-president for Education & Specialty and acts occasionally as a consultant and a speaker for the allergen companies Stallergenes and ALK. R.G.W. has received fees for lectures, expert panel participation and consultancy and research support from Allergopharma, Allmiral, Alcon, Crucell, Hal, Merck Sharp & Dome, Novartis, Stallargenes, Artu Biologicals and UCB. K.C.L.-C. has received reagents from Phadia for s-IgE analyses in the birth cohort of the ECA-study. J.M. has been a member of National and International Scientific Advisory Boards (consulting), has received fees for lectures and grants for research projects from Boheringer-Ingelheim, Esteve, FAES, Hartington Pharmaceuticals, MSD, Novartis. Schering Plough, UCB, Uriach SA, Zambon, GSK. L.N.-B's research was supported by Astellas, MSD; research on vaccines was funded by Glaxo SmithKline, Pfizer; clinical trial on cystic fibrosis: Novartis; research on children's toilet behaviour was funded by Procter and Gamble. D.P. has consultant arrangements with Boehringer Ingelheim, GlaxoSmithKline, Merck, Mundipharma, Novartis and Teva. He or his research team have received grants and support for research in respiratory disease from the following organisations in the last 5 years: UK National Health Service, Aerocrine, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck, Mundipharma, Novartis, Nycomed, Pfizer and Teva. He has spoken for: Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Mundipharma, Pfizer and Teva. He has shares in AKL Ltd which produces phytopharmaceuticals. He is the sole owner of Research in Real Life Ltd. J.R. has been involved in clinical trials with: ALK Abelló, Allergopharma, Almirall-Hermal, Astellas, Bavarian Nordic, Bencard, Galderma, Glaxo SmithKline – Stiefel, Leo, Novartis, Stallergenes. He has also been involved in research with: Biogen-Idec, MSD, Phadia, PLS Design, Procter and Gamble, Sanofi Aventis. B.S. has participated in research sponsored by Allergopharma. F.E.R.S. has been a consultant for Uriach. R.V. has received grant support from: The Austrian Science Fund, FWF, the Christian Doppler Association Austria, Biomay, Vienna and Phadia, Uppsala. He is consulting with Phadia regarding allergy diagnosis and Biomay regarding allergy therapy. T.Z. has received research grants and/or honoraria and has consultant arrangements with the following companies: AnseIl, Bayer Schering, DST, Fujisawa, HAL, Henkel, Kryolan, Leti, MSD, Novartis, Procter and Gamble, Sanofi-Aventis, Schering Plough, Stallergenes, UCB.

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